Surgical strategies in MEN1 related pancreatic neuroendocrine tumors

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Contents

Management of MEN1 related non-functioning pancreatic NETs: a shifting paradigm. Results from the DutchMEN1 Study Group

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Abstract

Objective: To assess if surgery for Multiple Endocrine Neoplasia type 1 (MEN1) related non-functioning pancreatic neuroendocrine tumors (NF-pNETs) is effective for improving overall survival and preventing liver metastasis.

Background: MEN1 leads to multiple early-onset NF-pNETs. The evidence base for guiding the difficult decision who and when to operate is meager.

Methods: MEN1 Patients diagnosed with NF-pNETs between 1990-2014 were selected from the DutchMEN1 study group database, including >90% of the Dutch MEN1 population. The effect of surgery was estimated using time-dependent Cox analysis with propensity score restriction and adjustment.

Results: Of the 152 patients, 53 underwent surgery and 99 were managed by watchful waiting. In the surgery group, tumors were larger and faster-growing, patients were younger, more often male and were more often treated in centers that operated more frequently. Surgery for NF-pNETs was not associated with a significantly lower risk of liver metastases or death, (adjusted Hazard Ratio (HR) = 0.73 (0.25 - 2.11). Adjusted HR's after stratification by tumor size were: NF-pNETs <2cm = 2.04 (0.31 - 13.59) and NF-pNETs 2-3cm = 1.38 (0.09 - 20.31). Five out of the six patients with NF-pNETs >3cm managed by watchful waiting developed liver metastases or died compared with six out of the 16 patients who underwent surgery.

Conclusions: MEN1 patients with NF-pNETs <2cm can be managed by watchful waiting, hereby avoiding major surgery without loss of oncological safety. The beneficial effect of a surgery in NF-pNETs 2-3cm requires further research. In patients with NF-pNETs >3cm, watchful waiting seems not advisable.

No Association of Blood Type O with Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1

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Abstract

Context: An association between ABO blood type and the development of cancer, in particular, pancreatic cancer, has been reported in the literature. An association between blood type O and neuroendocrine tumors in multiple endocrine neoplasia type 1 (MEN1) patients was recently suggested. Therefore, blood type O was proposed as an additional factor to personalize screening criteria for neuroendocrine tumors in MEN1 patients.

Objective: The aim of this study was to assess the association between blood type O and the occurrence of neuroendocrine tumors in the national Dutch MEN1 cohort.

Design: Cohort study using the Dutch National MEN1 database, which includes >90% of the Dutch MEN1 population. Demographic and clinical data were analyzed by blood type. Chi-square tests and Fisher exact tests were used to determine the association between blood type O and occurrence of neuroendocrine tumors. A cumulative incidence analysis (Gray's test) was performed to assess the equality of cumulative incidence of neuroendocrine tumors in blood type groups, taking death as a competing risk into account.

Results: ABO blood type of 200 of 322 MEN1 patients was known. Demographic and clinical characteristics were similar amongst blood type O and non-O type cohorts. The occurrence of neuroendocrine tumors of the lung, thymus, pancreas and the gastrointestinal tract was equally distributed across the blood type O and non-O type cohorts (Grays's test for equality; $P = 0.72$). Furthermore, we found no association between blood type O and the occurrence of metastatic disease or survival.

Conclusions: An association between blood type O and the occurrence of neuroendocrine tumors in MEN1 patients was not confirmed. Addition of the blood type to screening and surveillance practice seems for this reason not of additional value for identifying MEN1 patients at risk for the development of neuroendocrine tumors, metastatic disease or a shortened survival.

Robot-assisted spleen preserving pancreatic surgery in MEN1 patients

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Abstract

Background: Multiple Endocrine Neoplasia type 1 (MEN1) patients often undergo multiple pancreatic operations at a young age.

Objective: To describe robot-assisted and laparoscopic spleen-preserving pancreatic surgery in MEN1 patients, and to compare both techniques.

Methods: Robot-assisted pancreatectomies of the DutchMEN1 study group and the Université de Lorraine, Nancy, France were compared to a historical cohort of laparoscopic treated MEN1 patients. Perioperative outcomes were compared.

Results: A total of twenty-one MEN1 patients underwent minimally invasive pancreatic surgery for pancreatic neuroendocrine tumors, seven patients were subjected to robot-assisted surgery, and fourteen patients underwent laparoscopic surgery. Demographics and clinical characteristics did not differ between the cohorts and no significant differences in operative outcomes were found. A high number of ISGPS grade B/C pancreatic fistulas were observed in both cohorts (38%), and no conversions were seen in the robot-assisted cohort (respectively 0% versus 43%, $P = 0.06$). In one laparoscopic and one robot-assisted case the primary tumor was not resected.

Conclusions: Minimally invasive spleen-preserving surgery in MEN1 patients is safe and feasible. Patients who underwent robot-assisted surgery did not require conversion to open surgery.

Insulinoma in Multiple Endocrine Neoplasia Type 1

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Minimal risk of persistent or recurrent hypoglycemia after MEN1-related insulinoma surgery. A large international cohort study.

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Abstract

Objective To determine the optimal surgical strategy in treating patients with Multiple Endocrine Neoplasia type 1 (MEN1)-related insulinomas.

Background Current literature states that 15-30% of MEN1 patients have persistent or recurrent hypoglycemia after insulinoma surgery, depending on the surgical procedure. The current European Neuroendocrine Tumor Society (ENETS) and the MEN1 clinical practice guidelines lack well-grounded recommendations with regards to which surgical strategy is preferred due to limited evidence.

Methods A total of 96 MEN1 patients with insulinomas underwent surgery between 1990-2015 at one of the 46 participating hospitals from Europe and North America. Post-operative hypoglycemia, complications, and pancreatic insufficiency were captured.

Results Seven percent of the patients had persistent or recurrent hypoglycemia. None of the nine patients who were operated for a solitary proximal insulinoma developed hypoglycemia. Of the 54 patients with a solitary distal insulinoma, one patient had persistent disease after a distal pancreatectomy (1/41), and one patient developed a new insulinoma after a distal enucleation (1/13). Of the 33 patients operated for multiple insulinomas, 1/26 patients developed an insulin producing liver metastasis after a distal pancreatectomy combined with surgery of the pancreatic head. Four out of seven patients developed recurrent disease after other surgical approaches for multiple insulinomas. Patients who underwent an enucleation did not develop pancreatic insufficiency.

Conclusions MEN1-related insulinoma surgery is more successful than previously thought. In MEN1 patients with a solitary insulinoma, enucleation is recommended, if surgically feasible. A distal pancreatectomy combined with enucleation of the pancreatic head lesions is favorable for MEN1 patients with multiple insulinomas.

Early and late complications after surgery for MEN1 related non-functioning pancreatic neuroendocrine tumors

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Abstract

Objective: To estimate short- and long-term morbidity after pancreatic surgery for Multiple Endocrine Neoplasia type 1 (MEN1) related non-functioning pancreatic neuroendocrine tumors (NF-pNETs).

Background: Fifty percent of the MEN1 patients harbor multiple NF-pNETs. The decision to proceed to NF-pNET surgery is a balance between the risk of disease progression versus the risk of surgery-related morbidity. Currently, there are insufficient data on the surgical complications after MEN1 NF-pNET surgery.

Methods: MEN1 Patients diagnosed with a NF-pNET who underwent surgery were selected from the DutchMEN1 study group database, including >90% of the Dutch MEN1 population. Early postoperative complications, new-onset diabetes mellitus, and exocrine pancreatic insufficiency were captured.

Results: Sixty-one patients underwent NF-pNET surgery at one of the eight Dutch academic centers. Patients were young (median age; 41 years) with low ASA scores. Median NF-pNET size on imaging was 22 mm [3-157]. Thirty-three percent (19/58) of the patients developed major early - Clavien-Dindo grade III-IV – complications mainly consisting ISGPS grade B/C pancreatic fistulas. Twenty-three percent of the patients (14/61) developed endo- or exocrine pancreas insufficiency. The development of major early postoperative complications was independent of the NF-pNET tumor size. Twenty-one percent of the patients (12/58) developed multiple major early complications.

Conclusions: MEN1 NF-pNET surgery is associated with high rates of major short- and long-term complications. Current findings should be taken into account in the shared decision-making process when MEN1 NF-pNET surgery is considered.

Prognostic factors for survival of MEN1 patients with duodenopancreatic tumors metastatic to the liver: results from the DMSG

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Abstract

Objective Duodenopancreatic neuroendocrine tumors (DP-NETs) develop in a majority of patients with Multiple Endocrine Neoplasia Type 1 (MEN1) and are the leading cause of death. Overall survival (OS) and prognostic factors for patients with liver metastases from DP-NETs are not known.

Design and Methods Cohort study using the Dutch National MEN1 database, which includes >90% of the Dutch MEN1 population between 1990-2014. OS was assessed with time to event analysis, and prognostic factors were evaluated.

Results A total of 56% of the MEN1 patients (n=220) were diagnosed with a DP-NET of whom 34 (15%) developed DP-NET liver metastases. Median age at liver metastases diagnosis was 53 years [range 31-74]. Of those patients, after a median follow-up of 4 years [range 0.3-12.3] 16 patients (47%) had died. After 2, 5, 10 years OS was respectively 91%, 65%, and 50%. A trend towards worse survival was seen in males compared to females (5-year OS 58% versus 75%, p = 0.07) and also in patients with multiple liver metastases compared to patients with solitary liver metastasis (59 versus 83%, p = 0.09).

Conclusions Despite the fairly indolent course of DP-NET liver metastases in MEN1 patients, half of the population was deceased after 10 years. Gender and tumor load at diagnosis of liver metastases are possible prognostic factors for worse survival.

General Discussion

This thesis investigated the optimal strategy for MEN1 related pNETs in which the benefits of surgery to prevent metastasis and premature death is weighed against the risk of unintended potential harm. Identifying patients at highest risk for an adverse course of the disease in terms of metastasis could lead to clearer surgical indications and even help to indicate the extent of duodenopancreatic surgery. Consequently, evidence-based recommendations can be made to improve morbidity and mortality in this patient group. This will result in improvement of personalized cancer care and life expectancy among MEN1 patients.

When to operate a MEN1 patient with a non-functioning pancreatic neuroendocrine tumor?

In chapter 2 we assess if surgery for MEN1 related nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) is effective for improving overall survival and preventing liver metastasis. Evidence-based treatment guidelines are lacking, and clinician are faced with the difficult decision of who and when to operate MEN1 patients with NF-pNET. We studied 152 MEN1 patients with NF- pNETs and estimated the effect of surgery on the development of liver metastases and overall survival. The outcomes of this study results suggest that the majority of patients can safely be managed by watchful waiting, hereby avoiding major surgery without increasing the risk of metastases or death. Furthermore, the decision to operate patients with NF-pNETs between 2 to 3 cm is debatable on the basis of our results.

Up to now, based on the available studies, clinical decision making for MEN1 patients with NF-pNETs was hampered by non-comparable study groups because of issues of confounding by indication and possibly selected populations. Current evidence is mainly based on two important papers from the Groupe d'Etude des Tumeurs Endocrines in France. 4, 5 In the first study, 50 MEN1 patients with NF-pNETs of ≤2 cm managed non-operatively were compared to 15 surgically treated patients and it appeared that surgery did not decrease mortality or disease progression since more patients died in the surgically treated group.4 In the second study of 108 MEN1 patients with NF-pNETs, the importance of tumor size, as it correlated with metastasis, was highlighted.5 In both studies

(time dependent) confounders were not taken into account. Furthermore, although both studies were the largest yet available MEN1 studies, selection bias cannot be ruled out. Based on these findings the authors recommended not to perform routine surgery for NF-pNETs of <2 cm.4, 5 Given the paucity of evidence, current MEN1 clinical practice guidelines are more conservative and advise to consider surgery for NF-pNETs >1 cm based on the same studies.6 To adjust for known confounders, we used a propensity score for the differences between patients.7, 8 Propensity score analysis is accepted as a valid alternative when a randomized controlled trial is not feasible.9 Changing the surgical strategy from operating patients with NF-pNETs ≥1 cm to operating patients with NF-pNETs ≥ 2 cm would lead to a reduction of 59% of the pancreatic procedures in our population. Shifting the cut-off point from ≥ 2 cm to > 3 cm would further reduce the number of pancreatic surgical procedures with 37%. Indicating that changing the cut-off point for surgical resection of the NF-pNET has a substantial impact on the MEN1 population.

Based on the outcomes of this study it can be concluded that MEN1 patients with NF-pNETs <2 cm can be managed by watchful waiting and the group of MEN1 patients with NF-pNETs 2 to 3 cm requires further research. Based on the outcomes of other studies and our study, setting up a randomized controlled trial on surgical resection of NF-pNETs between 2 and 3 cm seems justified at this point. Although the propensity score method accounts for the known confounders measured in the study, unknown confounders (residual confounding) may still have occurred. A randomized controlled trial could overcome the issue of potential residual confounding. This trial would have to take place in the context of a broad international collaboration and needs a long-term follow-up, because of the rarity and fairly indolent course of the disease. Alternatively, a well-designed international large long-term prospective cohort study could be the subsequent step to investigate the surgical indications for MEN1 related NF-pNETs. A prospective cohort study is easier to set up, compared to a randomized controlled trial. Selection bias is a potential disadvantage of such a study since it would be impossible to set up a prospective international population-based cohort study.

Until a well-designed randomized controlled trial is available, the decision to proceed to surgery in MEN1 patients with NF-pNETs between 2-3 cm should be a balance between the risk of disease progression versus the risk of surgery-related morbidity. We suppose that the clinician, should inform MEN1 patients with NF-pNETs between 2-

3 cm about the risk of development of liver metastases, and the debatable effect of surgery on overall survival and development of liver metastases. Further, tumor size and growth rate should be taken into account in the decision to proceed to surgery in this subgroup since larger and faster-growing tumors have a greater potential to metastasize to the liver. Additionally, the age, overall condition of the patient, tumor relation to the pancreatic duct, the risk of postoperative complications, and the patient's preference should be taken into account when deciding to operate MEN1 related NF-pNETs between 2-3 cm.

Which MEN1 patient gets a neuroendocrine tumor?

An association between ABO blood type and the development of cancer, in particular, pancreatic cancer, was recently reported in the literature. The addition of other prognostic factors to the current MEN1 neuroendocrine screening program are important because prognostic factors for neuroendocrine tumor development in MEN1 patients remain largely unknown. In the American National Institute of Health (NIH) cohort of 105 MEN1 patients, a significant association was found between blood type O and neuroendocrine tumors of the lung, thymus, pancreas, and GI tract; therefore, the possible addition of blood type criterion to the current screening and surveillance practices of MEN1 patients was proposed.6

In the study described in chapter 3, the previous found association was validated in 200 Dutch MEN1 patients. In our cohort the occurrence of neuroendocrine tumors of the lung, thymus, pancreas, and gastrointestinal tract was equally distributed across the blood type O and non-O type cohorts (Grays's test for equality; P = 0.72). Furthermore, we didn't find an association between blood type O and the occurrence of metastatic disease or survival.10 In the initial NIH study, no neuroendocrine tumors in blood type AB patients were found, further supporting the assumption that blood type O was associated with the occurrence of neuroendocrine tumors.11 However, in our population 6 out of 10 patients with blood type AB developed a neuroendocrine tumor. Differences in the study populations might be an explanation for the contradictory results. In the initial report, the blood type distribution of the studied population was not corresponding to the general population of the United States.11 In our population-based cohort, there was no selection of a particular blood type since the allocation of

blood types did not differ from the distribution of the general Dutch population. This difference could explain the contradictory results, and underpins the essence of independent validation of screening criteria before using them in daily clinical practice. Based on our study, blood type screening seems of no additional value for identifying patients at higher risk for the development of neuroendocrine tumors and metastatic disease in clinical practice. Therefore blood type is no additional tool for MEN1 liver metastases risk stratification and does not contribute to the main goal of this thesis. Further research should focus on new factors for identifying MEN1 patients at higher risk for the development of neuroendocrine tumors and metastatic disease.

Minimally invasive pancreatic surgery to treat MEN1 related pancreatic neuroendocrine tumors.

MEN1 patients often undergo multiple pancreatic operations at a young age, with a high risk of surgery-related morbidity. Minimally invasive pancreatic surgery could reduce surgical morbidity in MEN1 patients, since, minimally invasive pancreatic surgery is associated with a shorter hospital stay, less blood loss, and less pain compared to open pancreatic surgery.12-14 Possible advantages and disadvantages of robot-assisted and laparoscopic spleen-preserving pancreatic surgery remain largely unknown in MEN1 patients. In chapter 4 we showed our first experience of minimally invasive, spleen-preserving, pancreatic surgery in MEN1 patients and compared the outcomes of techniques in MEN1 patients. A substantial part of the MEN1 patients underwent minimally invasive pancreatic surgery in the Netherlands and Nancy, France between 1990–2014. We demonstrate the safety and feasibility of both techniques in a small number of selected patients. Patients who underwent robot-assisted surgery did not require conversion to open surgery.

Benefits of minimally invasive pancreatic MEN1 surgery were also observed in a recent German series comparing 21 patients who underwent open pancreatic surgery to patients who underwent laparoscopically (n = 8) or robot-assisted (n = 4) surgery.15 This study showed a shorter operation time, less intraoperative blood loss and shorter hospital stay in the minimally invasive treated group. Surprisingly more spleen preservations were seen in the openly treated group, a finding that is inconsistent with current literature on minimally invasive pancreatic.14 Challenges finding the primary tumor were not reported.15 Pancreas fistulas are a major complication of minimally

invasive pancreatic surgery 12, 13, and seems to be a significant complication in MEN1 related pancreatic surgery. A minimally invasive approach could potentially lead to improved accessibility in the future, a significant advantage for these patients who have a substantial chance of being operated again.16

A significant disadvantage of minimally invasive pancreatic surgery compared to open surgery in MEN1 patients is the impossibility of digital palpation of the pancreas. In contrast to pancreatic surgery for adenocarcinomas or sporadic pNETs, MEN1 related pNETs are multiple and difficult to localize. In our study, in four patients it was challenging to localize the primary tumor, and in two patients the primary tumor was not resected. We consider the lack of digital palpation as the primary cause for unsuccessful procedures. The probability of not resecting the primary tumor is essential to take into account when planning minimally invasive surgery in MEN1 patients. The use of intraoperative pancreatic ultrasound, frozen section of the specimen, careful postoperative examination of the pathologic specimen and imaging are, therefore, in our opinion, essential in minimally invasive MEN1 surgery in clinical practice.

Setting up a prospective cohort comparing robot-assisted spleen-preserving pancreatic surgery to laparoscopic pancreatic surgery in MEN1 patients could be the next step to evaluate the effect of minimally invasive pancreatic surgery on short-term postoperative complications. Data collection and correction for potential confounders, such as tumor size, location and the overall condition of the patient, would be important when setting up such a study.

In conclusion, minimally invasive spleen-preserving pancreatic surgery in MEN1 patients is safe and feasible. Further research is needed to assess whether minimally invasive pancreatic surgery could reduce surgery-related morbidity in MEN1 patients.

How to operate a MEN1 patient with an insulinoma?

About 10%-15% of MEN1 patients develop insulin-producing pNETs.6, 17 Insulinomas originate from pancreatic islets, resulting in an overproduction of insulin that can lead to symptoms of hypoglycemia.18 A minority of the insulinomas metastasize to the liver. In chapter 5 & 6 we investigated the optimal surgical strategy to reduce

surgery-related morbidity for this separate and symptomatic group of MEN1 related pNETs. In chapter 5 we reviewed the literature and gave an overview of current strategies and evidence for different surgical approaches to treat MEN1 related insulinomas. We found that the literature about the extent of pancreatic surgery for MEN1 related insulinomas is limited, and no particular procedure is recommended in the MEN1 guidelines.6, 19 To provide a scientific surgical treatment guideline for MEN1 patients with an insulinoma we set up a large international cohort study. The results of this study are described in chapter 6. This study was an international collaboration between 40 hospitals from Europe and six hospitals from North America, including the Mayo Clinic, MD Anderson, Weill Cornell Medical Center, the National Institutes of Health, and the French Endocrine Tumor Study Group. This study shows that only 7% of MEN1 patients who underwent surgery for an insulinoma had postoperative hypoglycemia, due to the development of de novo insulinomas or insulin-producing liver metastases rather than persistent disease. This percentage was much lower than we expected to find based on current literature.20-23 Due to the absence of long-term complications and high rate of symptom resolution, enucleation appears to be the favorable surgical strategy to treat solitary MEN1-related insulinoma. In patients with multifocal disease, distal pancreatectomy combined with enucleation of tumors in the head of the pancreas is preferable. Due to high disease recurrence, enucleation of the head and body/tail seems not recommendable to treat multifocal pancreatic insulinomas.

The lack of detailed information about the diagnostic tools to localize the insulinoma is a disadvantage of the current study. Setting up a prospective cohort study could be the next step in evaluating the optimal surgical strategy for treating MEN1 related insulinomas. This study should collect detailed information on the preoperative diagnostic workup of the insulinoma, tumor location, relation to the pancreatic duct and the considerations of the surgeon to opt for an enucleation or a larger pancreas resection.

Complications after surgery for MEN1 related non-functioning pancreatic neuroendocrine tumors

Although we performed a small study on minimally invasive pancreatic surgery in MEN1 patients, no large comprehensive series on surgical morbidity after MEN1 NF-pNET surgery existed when writing this thesis. Most

MEN1 NF-pNET studies focus on the oncological outcome after MEN1 related NF-pNET surgery without describing postoperative complications.[4, 5, 24] Others do describe postoperative complications but only report small and selected study populations (<20 NF-pNET procedures), emphasizing the rarity of the disorder.[4, 25, 26]

Few studies describe complications after MEN1 NF-pNET surgery but were only able to represent a small numbers of patients. A recent series about minimally invasive and open pancreatic surgery in MEN1 patients describes 33 pancreatic resections for either insulinomas (n = 9) or NF-pNETs (n = 24). This study observed a high number of pancreatic fistulas as well. Sixty-three percent of the patients developed an ISGPS grade B/C pancreatic fistula. The high rates of pancreatic fistulas were explained by the very soft texture of the MEN1 pancreas.[15]

To improve current evidence and to facilitate the decision-making process we investigated the short- and long-term complications of surgical resection of MEN1 related NF-pNETs in chapter 7. We found that 33% of the patients developed major early - Clavien-Dindo grade III-IV – complications, meaning that 33% of the patients need at least one surgical or radiological intervention to treat postoperative complications. Most complications were International Study Group of Pancreatic Surgery grade B/C pancreatic fistulas. Twenty-three percent of the patients (14/61) developed endo- or exocrine pancreas insufficiency. The development of major early postoperative complications was independent of the NF-pNET tumor size. Twenty-one percent of the patients (12/58) developed multiple major early complications, one patient died 30 days after surgery and 2 patients became permanently disabled. Current findings provide insight into the complication rate after MEN1 pNET surgery and could, therefore, support a shared decision-making process when MEN1 NF-pNET surgery is considered. We could not determine from current data if the high incidence of fistulas were directly MEN1 related or if they are secondary to the MEN1 related soft pancreas. We expected to find more early complications in operations for larger tumors (i.e. NF-pNETs > 2cm) or more extended operations such as liver resections, but could not identify such factors. The relatively low power could be the reason we did not find an association. The major early complication rate appeared higher in patients who underwent secondary pancreatic surgery (45%) and lower in patients who underwent tertiary pancreatic surgery (0%) compared to MEN1 patients who underwent primary pancreatic surgery (33%). These groups were too small to come to reliable conclusions about early complication

rates after secondary or tertiary pancreatic surgery in MEN1 patients. Fifteen percent of the patients in our cohort developed new-onset diabetes, and 20% developed exocrine pancreatic insufficiency.

The high rate of major short and long-term complications described in chapter 7 underpins the recommendation to manage NF-pNETs <2cm by watchful waiting as proposed in chapter 2. In the 2-3 cm group, clinicians should be reluctant to operate, since surgery does not seem to prevent liver metastases nor it improves the survival however, it could harm the patient. In patients with NF-pNETs >3 cm, surgery seems indicated, the clinician and the patient should, therefore, be informed by number and kind of postoperative complications in preparation for surgery. We suppose that further research on this topic should examine risk factors for the development of short- and long-term complications after MEN1 related NF-pNET surgery to ultimately improve the postoperative course. Also, evidence on how to diagnose and manage postoperative pancreatic fistula is lacking. Further research is needed to evaluate the detection and management of postoperative pancreatic fistula to reduce major complications and death after pancreatic resection.

New techniques such as robot-assisted pancreatic surgery, the use of intra- and postoperative somatostatin treatment or further centralization of MEN1 related pancreatic surgery could potentially decrease the number of postoperative complications. Further research is needed to test these hypotheses.

Which prognosis has a MEN1 patient who developes duodenopancreatic neuroendocrine liver metastases?

A reliable prognosis and prognostic factors for MEN1 patients diagnosed with pancreatic neuroendocrine tumor metastases remained unknown. We investigated 34 MEN1 patients with duodenopancreatic neuroendocrine tumor (dp-NET) metastases and aimed to determine survival and prognostic factors for survival in chapter 8. This study showed a prevalence of 15% dp-NET liver metastases in MEN1 patients. Although progression of liver metastases from DP-NETs in MEN1 can be fairly slow, life expectancy of this relatively young patient group is clearly reduced as the 10-year overall survival rate is only 50%. As far as we know, this is the first study showing

overall survival from the moment of liver metastases diagnosis in a population-based study of MEN1 patients. Gender and tumor load at diagnosis of liver metastases were possible prognostic factors for worse survival. Current findings could be used in the counseling process when an MEN1 patient is diagnosed with dp-NET liver metastases. Prospective clinical studies are warranted to see whether gender and tumor load status are of prognostic value in MEN1 screening and surveillance practices. The apparent survival benefit for MEN1 patients with a solitary liver metastasis compared to patients with multiple lesions is also an important finding. This benefit does not seem to be influenced by locoregional treatment of the solitary lesion (either surgery, radiofrequent ablation or embolization), as only one patient underwent locoregional therapy and seven others did not. However, it is reasonable to argue that resection or other locoregional therapies of the solitary lesions might improve the prognosis of patients with solitary liver metastases. In summary, shows Chapter 8 a shortened survival for MEN1 patients with liver metastases, and underpins the importance of prevention of liver metastases.

Conclusions

With this thesis we investigated MEN1 pNET liver metastases risk stratification to prevent shortened survival, to reduce surgical morbidity, and to ultimately improve personalized cancer care for MEN1 patients with a pNET.

The outcomes of chapter 2 indicate that the majority of MEN1 patients (ie, those with tumors <2 cm) can safely be managed by watchful waiting; hereby avoiding major surgery without increasing the risk for metastases or death. The preferred strategy in MEN1 patients with NF-pNETs ranging from 2 to 3 cm is debatable, as the subgroup analysis of this patient group showed a smaller effect size compared with the <2 cm subgroup and an even larger confidence interval. The subgroup of patients with NF-pNETs >3 cm watchful waiting appears to be not recommendable on the basis of the relatively high number of events in this group. Based on the results of chapter 3 the addition of the blood type to screening and surveillance practice seems not to be of additional value for

identifying MEN1 patients at risk for the development of neuroendocrine tumors, metastatic disease, or a shortened survival.

In chapter 4 we introduced the utility of minimally invasive pancreatic surgery to treat MEN1 related pNETs, and found that patients who underwent robot-assisted surgery did not require conversion to open surgery. In chapter 5 & 6 we investigated the optimal surgical strategy to reduce surgery-related morbidity in a separate and symptomatic group of MEN1 related pNETs; insulinomas. We found that MEN1-related insulinoma surgery is more successful than previously thought, and in MEN1 patients with a solitary insulinoma, enucleation is recommended, if surgically feasible. A distal pancreatectomy combined with enucleation of the pancreatic head lesions is favorable for patients with multiple insulinomas.

Surgery could also harm the patient. In chapter 7 we investigated the short and long-term morbidity after pancreatic surgery for MEN1-related NF-pNETs and found that MEN1 NF-pNET surgery is associated with high rates of major short and long-term complications. We believe that current findings should be taken into account in the shared decision-making process when MEN1 NF-pNET surgery is considered. In chapter 8 investigated overall survival and prognostic factors for patients with liver metastases, and found that despite the fairly indolent course of dp-NET liver metastases in MEN1 patients, half of the population was deceased after 10 years. Gender and tumor load at diagnosis of liver metastases are possible prognostic factors for worse survival.

In conclusion, we improved MEN1 liver metastases risk stratification. The outcomes of this thesis could potentially reduce premature death and surgical morbidity for MEN1 patients with a pNET in the future.