

# Prognosis following surgery for pancreatic neuroendocrine tumors linked to multiple endocrine neoplasia type 1

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### ABSTRACT

Patients with Multiple Endocrine Neoplasia Type 1 most commonly die from metastatic pancreatic neuroendocrine tumors. Prognostic factors for pancreatic neuroendocrine tumors are mainly unclear, except from tumor size. The purpose of the current study was to examine potential differences in prognosis between patients with resected multiple endocrine neoplasia type 1 related nonfunctioning pancreatic neuroendocrine tumors and those with resected multiple endocrine neoplasia type 1 related insulinomas.

Databases were searched for patients who had multiple endocrine neoplasia type 1-related pancreatic neuroendocrine tumors removed. Regression was used to evaluate the liver metastases-free survival between patients with insulinomas and non-functioning pancreatic neuroendocrine tumors, as well as to determine the risk variables for this survival.

**Key Words:** *Surgical care; Virtual reality; Neuro surgery; Endocrine.*

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### INTRODUCTION

An inherited cancer syndrome known as Multiple Endocrine Neoplasia type 1 (MEN1) is caused by a germline mutation in the MEN1 tumor suppressor gene, which is located on the chromosome that codes for the protein men in. 2 to 3 people out of every 100,000 have the characteristic. Pancreatic neuroendocrine tumors (pNETs), which have a prevalence of, are one of the disease's defining symptoms. By the time a person reaches the age of 80, pNETs' age-related penetrance has also increased to over 80%. The greatest cause of death in MEN1 patients and the major predictor of shorter life spans are metastatic pNETs. According to the presence of a specific clinical illness brought on by excessive hormone synthesis, pNETs are clinically categorized as functioning or nonfunctioning tumors. Insulinomas are the most common functioning pancreatic neuroendocrine tumors, but non-functioning pancreatic neuroendocrine tumors (NF-pNETs) are more common. PNETs, micro adenomas, and clusters of mono-hormonal endocrine cells are examples of lesions where loss of heterozygosity of the wild-type MEN1 allele results in tumor formation.

11 Despite the pNETs' presumed common origin, patients with MEN1-related NF-pNETs and functional pNETs have reported varied survival rates. A minority of pNETs in MEN1 metastasis to the liver, which reduces survival even if the majority of pNETs in MEN1 have a very passive natural course. The goal of treatment should be to prevent liver metastases and to relieve symptoms brought on by excessive hormone production in order to preserve a high quality of life. The prognostic variables of MEN1-related pNETs are mainly unknown, other than tumor size as a predictor of liver metastasis. Insulinomas in MEN1 are generally thought to have a better prognosis than NF-pNETs due to smaller tumor size, earlier symptomatology with subsequent treatment, or changes in grade. Given the high age-related prevalence of pNETs, comprehensive lifelong screening programs, and extensive patient counseling, patient counseling is unavoidable in MEN1 everyday clinical management. Nevertheless, knowledge of the prognosis of MEN1-related pNETs is the main unmet need for proper patient counseling. The customization of surgical indications, timing, and ex-

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-tent of the operation, and postoperative follow-up schedules in each patient will benefit from the knowledge of variances in prognostic variables. In order to determine if individuals with a resected MEN1-related NF-pNET have a different prognosis than those with a resected MEN1-related insulinoma, this study compared the two groups of patients. To make informed recommendations on postoperative counseling and follow-up specifically for NF-pNETs and insulinomas, survival and variables linked to liver metastases-free survival were also evaluated. From the cohort of the Dutchmen Investigation Group, individuals with NF-pNETs and insulinomas were chosen for this observational study. Patients with MEN1-related insulinomas were additionally found through a MEN1 partnership involving European and North American hospitals, which is important given the rarity of MEN1-related insulinomas. Patients were considered eligible if they underwent surgery between 1990 and 2016 to remove an NF-pNET or an insulinoma, had that surgery confirmed by histopathology, and were monitored for at least a year afterward. The most recent practice recommendations were used to determine the MEN1 diagnosis. Patients who had undergone surgery for a pNET or who were diagnosed with distant metastases were not included. Due to the rarity of glucagonomas, vasoactive intestinal peptidomics, and somatostatinoma, those patients were excluded. Medical ethics commissions or institutional review boards gave their approval to the study protocol. Patients with MEN1 who are 16 years of age or older and receiving treatment at Dutch University Medical Centers are included in the Dutchmen Study Group database. By looking through the hospital's diagnosis databases, patients were located. The database contains information on all MEN1 people in the Netherlands. Every month, clinical and demographic data were gathered using a systematic method for reviewing medical records in accordance with a predetermined protocol. The partnership includes seven MEN1 expert centers, including hospitals across Europe and North America, as well as the population-based database from the Dutchmen Study Group and the national database from the French Grouped detruides des Tumeurs Endocrines. MEN1-related insulinomas in patients were found by searching hospital databases using codes from the International Classification of Diseases. Investigators collected clinical and demographic information from each hospital in accordance with the same predefined protocol. A pNET was deemed to be NF-pNET in the lack of excessive hormone production causing a specific clinical tumor syndrome and in the presence of positive histology, computed tomography, magnetic resonance imaging, and/or endoscopic ultrasonography diagnostic of a pNET. The first imaging test that was positive or the date of the pathology were used to determine the diagnosis. An hour-supervised fast test result that was positive indicated the presence of an insulinoma. According to clinical practice standards, the diagnosis of an insulinoma was made based on clinical criteria, symptoms, or signs of hypoglycemia with concurrent biochemical endogenous hyperinsulinemia hypoglycemia in the absence of an hour-supervised fast test. In the insulinoma group, patients who also had concomitant NF-pNETs were examined if they had an insulinoma.

In MEN1, gastronomes are primarily of duodenal origin and seldom develop in the pancreas. As a result, patients with hypergastrinemi-

-a and a pNET were considered to have a duodenal gastronomie concurrently. Combination resections included multiple enucleations, a distal pancreatectomy plus enucleation, Whipple plus enucleation, and Whipple plus distal pancreatectomy. The number of pNETs and the size of the greatest pNET were analyzed in pancreatic specimens. The greatest planet's size was selected for analysis. Positive insulin immunohistochemistry identified insulinomas in patients who had their tumors surgically removed. The size of the biggest pNET was employed for analysis if insulin staining was negative or if comprehensive information on immunohistochemical staining was lacking.

Lymph node metastases were looked for in the specimens. Regardless of hormone expression, any peripancreatic lymph node containing neuroendocrine tumor cells was regarded as lymph node metastasis. When performing an inspection, it was considered that no lymph nodes had been removed if none were visible.

Tumors had their mitotic rate and Ki67 staining analyzed. Tumor features from the first resection were analyzed for individuals who had multiple pancreatic resections for pNETs. Since it is expected that the largest tumor was present at the time of the first operation and likely determines prognosis, characteristics of the largest tumor were gathered if the interval between resections was shorter than months. The occurrence of liver metastases associated with pNET during follow-up and overall survival were the primary outcomes. It was calculated to measure a composite endpoint (pNET liver metastases and/or overall survival). There are two ways to categorize liver metastases: radiologically confirmed or pathologically proven. Radiology was recorded as positive if at least successive CT/MRI reports indicated lesions that might represent liver metastases. During the study period, the pre-and postoperative liver assessment was carried out using conventional imaging (CT or MRI), depending on the local availability of imaging modalities. The preference of each surgeon guided the intraoperative evaluation of the liver, which may have involved intraoperative ultrasonography or bimanual palpation. A multidisciplinary team discussion was used to determine the most likely reason for liver metastases. Medical records were consulted to determine the cause of death. MEN1-related deaths were those brought on by MEN1-related symptoms or treatment. Other reasons of mortality were considered unrelated to MEN1. Categorical variables were represented as counts, whereas continuous variables were reported as median range or interquartile range. Continuous variables were compared using Mann-Whitney U tests, while categorical variables were compared using  $\chi^2$  or Fisher exact tests. The period of follow-up was calculated from the date of surgery to the date of liver metastases related to pNET diagnosis, death, or last follow-up. Estimates of the survival probability were derived and Kaplan-Meier curves were displayed. For the comparison of univariable survival, the log-rank test was utilized. The time to pNET-related liver metastases or death was the outcome of univariable and multivariable Cox proportional hazard regression analysis. Covariates could be incorporated into the multivariable analysis, which was chosen based on clinical judgment and prior research, given the relatively low number of outcomes. Scaled Schoenfeld residuals were used to formally test and graphically evaluate the Cox

proportional hazard regression assumptions, and no assumptions were broken. The same procedure was followed for handling tied occurrences. The pNET functionality (NF-pNET versus insulinoma), pNET size in mm, and lymph node status (metastases versus none removed versus no metastases) were all taken into account in the sensitivity analysis. When missing data were found for variables used in the Cox regression, they were treated as missing at random and were therefore imputed using multiple imputations when constructing datasets using the iterative Markov chain Monte Carlo approach. Along with the primary outcome (known for all patients) and the Nelson-Aalen estimate, the factors mentioned in employed as predictor variables for multiple imputations. The censoring time and the event should coincide for repeated imputations of time-to-event data. In the insulinoma group, three patients with negative insulin immunohistochemistry underwent successful treatment. Patients with excised insulinomas tended to die more frequently without NF-pNET-related liver metastases, whereas patients with NF-pNETs developed liver metastases at greater rates across the board for all tumor sizes. Compared to patients with a resected insulinoma, patients with NF-pNET had a noticeably lower chance of avoiding liver metastases. Individuals with a resected NF-pNET had a considerably higher risk for liver metastases or mortality compared to patients with a resected insulin-

-oma, even after accounting for age at surgery, pNET size, and WHO grade. Additionally, the WHO grade, age at surgery, and pNET type were not related to the pNET size per mm increase in patients with LMFS. When lymph node status was taken into account, sensitivity analysis revealed identical HRs for pNET functionality and size. Regardless of the patient's age at surgery, the size, and the WHO grade of the tumor, this study demonstrates that patients with a resected MEN1-related NF-pNET had a lower LMFS than those with a resected MEN1-related insulinoma. These findings point to distinct MEN1-related pNET tumor origins, developments, or biological characteristics. Consequently, postoperative counseling and patient monitoring throughout follow-up should be tumor-type specific and at the very least include tumor size and WHO grade. Previous research proposed that the improved prognosis of individuals with MEN1-related insulinomas was due to modest tumor size, early symptomatology with subsequent treatment, or changes in grade. In fact, compared to individuals with NF-pNETs, patients with insulinomas in this study were younger, underwent surgery sooner after diagnosis, and had smaller pNETs. There were no distinctions in WHO grade between NF-pNETs and insulinomas. However, the risk of liver metastases or mortality was double for patients with a resected NF-pNET compared to those with a resected insulinoma after adjusting for age at surgery, size, and WHO grade. This suggests that NF-pNETs' pathogenesis is probably more aggressive.