LONG-TERM MORBIDITY AND MORTALITY IN PATIENTS DIAGNOSED WITH AN
INSULINOMA

Elina Peltola¹,², Päivi Hannula¹,³, Heini Huhtala⁴, Saara Metso¹,³, Juhani Sand⁵, Johanna Laukari⁶, Mirja Tiikkainen⁶, Jukka Siren⁷,⁸, Minna Soinio⁹, Pirjo Nuutila¹⁰,¹¹, Leena Moilanen¹², David E. Laaksonen¹², Tapani Ebeling¹³,¹⁴, Johanna Arola¹⁵,¹⁶, Camilla Schalin-Jäntti¹⁶,¹⁷, and Pia Jaatinen¹,²,³

¹Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland, ²Division of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland, ³Endocrinology, Department of Internal Medicine, Tampere University Hospital, Tampere, Finland, ⁴Faculty of Social Sciences, Tampere University, Tampere, Finland, ⁵Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland, ⁶Endocrinology, Abdominal Center, Helsinki University Hospital, Helsinki, Finland, ⁷Surgery, Abdominal Center, Helsinki University Hospital, Helsinki, Finland, ⁸Surgery, Abdominal Center, University of Helsinki, Helsinki, Finland, ⁹Department of Endocrinology, Turku University Hospital, Turku, Finland, ¹⁰Department of Endocrinology, Division of Medicine, Turku University Hospital, Turku, Finland, ¹¹Turku PET Centre, University of Turku, Turku, Finland, ¹²Department of Medicine, Kuopio University Hospital, Kuopio, Finland, ¹³Faculty of Medicine, University of Oulu, Oulu, Finland, ¹⁴Endocrinology, Department of Medicine, Oulu University Hospital, Oulu, Finland, ¹⁵Pathology, HUSLAB, Helsinki University Hospital, Helsinki, Finland, ¹⁶Pathology, University of Helsinki, Helsinki, Finland, ¹⁷Endocrinology, Abdominal Center, University of Helsinki, Helsinki, Finland

Corresponding author: Elina Peltola, M.D.
Tampere University
Faculty of Medicine and Health Technology
P. O. Box 100
FIN-33014 Tampere University
Finland
E-mail: elina.peltola@tuni.fi

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ABSTRACT

Objective: Insulinomas are rare functional pancreatic neuroendocrine tumours. As previous data on the long-term prognosis of insulinoma patients are scarce, we studied the morbidity and mortality in the Finnish insulinoma cohort.

Design: Retrospective cohort study

Methods: Incidence of endocrine, cardiovascular, gastrointestinal and psychiatric disorders, and cancers was compared in all the patients diagnosed with an insulinoma in Finland during 1980–2010 (n=79, including two patients with multiple endocrine neoplasia type 1 syndrome), vs. 316 matched controls, using the Mantel-Haenszel method. Overall survival was analysed with Kaplan-Meier and Cox regression analyses.

Results: The median length of follow-up was 10.7 years for the patients and 12.2 years for the controls. The long-term incidence of atrial fibrillation [rate ratio, RR 2.07 (95% CI 1.02–4.22)], intestinal obstruction [18.65 (2.09–166.86)], and possibly breast [4.46 (1.29–15.39] and kidney cancers (RR not applicable) was increased among insulinoma patients vs. controls, p<0.05 for all comparisons. Endocrine disorders and pancreatic diseases were more frequent in the patients during the first year after insulinoma diagnosis, but not later on. The survival of patients with a non-metastatic insulinoma (n=70) was similar to that of controls, but for patients with distant metastases (n=9), the survival was significantly impaired (median 3.4 years).

Conclusions: The long-term prognosis of patients with a non-metastatic insulinoma is similar to the general population, except for an increased incidence of atrial fibrillation, intestinal obstruction, and possibly breast and kidney cancers. These results need to be confirmed in future studies. Metastatic insulinomas entail a markedly decreased survival.
INTRODUCTION

Insulinomas are rare insulin-secreting functional pancreatic neuroendocrine tumours, with an estimated incidence of 1–4 per million per year (1-4). They usually do not show metastatic behaviour and are considered cured after a complete surgical removal of the tumour (3-5). On the other hand, disease recurrence occurs in 7% of the surgically treated patients (4), and in patients with distant metastases the median survival has been reported to be less than 2 years (2).

Despite the improved diagnostic options, the diagnostic delay of insulinomas has remained long, presumably due to the rarity of the disease and the nonspecific clinical picture, as we have shown in our previous study on all adult patients diagnosed with an insulinoma in Finland during 1980–2010 (6). Because previous data on the long-term prognosis of insulinoma patients are scarce, we wanted to study the long-term morbidity and mortality in the Finnish insulinoma cohort (6).

SUBJECTS AND METHODS

The Finnish insulinoma register consists of all adult patients (≥18 years of age) diagnosed with an insulinoma in Finland during 1980–2010 (n=79) (6). For each patient, 4 controls were chosen from the Finnish Population Register Centre. The controls had to be equal by age (±6 months), gender and the place of residence, and alive at the diagnosis of the corresponding patient. The dates of death or emigration were provided by the Finnish Population Register Centre. Personal identification numbers assigned to all Finnish residents were used to link the information from the separate registers described below. The register-based follow-up began on January 1, 1980, and lasted until December 31, 2015, unless death or emigration occurred first.

The morbidity of insulinoma patients vs. controls was analysed before and after the diagnosis of insulinoma, focusing on five distinct disease groups: endocrine, gastrointestinal, cardiovascular, cancer and psychiatric diseases, to evaluate the potential comorbidity and long-term effects of
insulinoma on the development of these diseases. Cancer morbidity was evaluated based on the
cancer diagnoses registered at the Finnish Cancer Registry, where Finnish health care organizations
statutorily provide information on all new cancer cases. Insulinoma-related notifications were
excluded from the analyses.

Morbidity due to endocrine, cardiovascular, gastrointestinal and psychiatric disorders was evaluated
on the basis of the diagnoses registered at the National Hospital Discharge Register, the Care
Register for Health Care. This register, maintained by the Finnish Institute of Health and Welfare,
collects the statutory data on all Finnish residents discharged from inpatient care in any Finnish
hospital since 1969, and on outpatient visits in specialized health care since 1998. The diagnoses are
coded according to the Finnish version of the 10th revision of the International Classification of
Diseases (ICD-10) since 1996, ICD-9 during 1987–1995, and ICD-8 during 1980–1986. These
classifications were reviewed, and the diagnoses of interest were grouped into corresponding
disease categories and subcategories (Supplementary Table 1). Both the primary and the secondary
diagnoses were included in the analyses, and the diagnosis codes for hyperinsulinism and
hypoglycaemia were excluded from the analysis of endocrine disorders.

For the mortality analyses, the causes of death were obtained from Statistics Finland, which
collects the dates and causes of death of all Finnish citizens deceased since 1971. The causes of
death are classified according to the ICD, as well as with a national time series classification,
including 54 categories. In the analyses, we used the underlying cause of death, defined as the
disease that has initiated the series of illnesses directly leading to death.

This study was conducted in accordance with the Declaration of Helsinki. The Regional Ethics
Committee of the Tampere University Hospital catchment area reviewed and approved the study
protocol. Informed consent was waived because of the retrospective, register-based nature of the
study, and the fact that many of the study subjects died before data collection for the study. The
Finnish Institute for Health and Welfare, the University Hospitals of Tampere, Helsinki, Kuopio, Oulu and Turku, Statistics Finland, and the Finnish Population Register Centre yielded permission for the use of data from their registers. Research data are not shared for ethical reasons, to protect the anonymity of patients with a rare disease.

**Statistical analysis**

The analyses were conducted with the IBM SPSS Statistics for Windows, Versions 25.0 and 27.0 (IBM Corp., Armonk, NY, USA), the STATA Statistical Software, Release 13 (StataCorp LP, College Station, TX, USA) and the OpenEPI Collection of Epidemiologic Calculators, Version 3.01. The data are presented as mean (standard deviation) for normally distributed variables, median (minimum–maximum) for other numerical variables, and number (%) for categorical variables.

In the morbidity analyses, the prevalence of diseases diagnosed before the diagnosis of insulinoma was first compared between the patients and the controls with the Fisher’s exact test and conditional logistic regression. Then, the incidence rates of these disease groups after the diagnosis of insulinoma were compared by analysing the incidence rate ratios (RR) and 95% Confidence Intervals (95% CI), using the Mantel-Haenszel method. Because only the first notification of each disease category per person was included in the analyses, the patients with a disease registered before the diagnosis of insulinoma were excluded from the incidence calculations of that disease category, together with their controls. The controls with a given disease diagnosed before the index date were excluded from the analyses individually. For diseases with a statistically significant difference in the patients vs. controls, a sensitivity analysis was performed, excluding the MEN1 patients and their controls, as well as the persons with each disease diagnosed within the first year after insulinoma diagnosis, to eliminate detection bias. The Bonferroni correction was applied to define the level of significance for multiple comparisons.
The overall survival of the patients vs. controls was compared using Kaplan-Meier analysis with the log-rank test. Insulinomas were retrospectively classified according to their highest diameter (≥ vs. <2 cm) and staged according to the most recent TNM classification system (7). Cox regression analyses were used to calculate the hazard ratios (HR), to identify factors associated with mortality among the patients. The distribution of the causes of death was compared with the Fisher’s exact test. For the patients who underwent curative-intent surgery, disease-free survival was calculated from the date of primary surgery to the date of disease progression or relapse. In the survival analyses, a two-sided p value below 0.05 was considered statistically significant.

RESULTS

Follow-up data of all the 79 patients and their 316 controls were included in the study. The mean age at the insulinoma diagnosis was 51.7 (15.6) years in the patients and 51.7 (15.5) years in the controls. The median duration of symptoms before the diagnosis was 13.0 (0.1–243.5) months. The median duration of the register-based follow-up between January 1, 1980, and the date of diagnosis of insulinoma was 22.7 (0.5–30.8) years for both the patients and the controls, and the median duration of follow-up after the diagnosis of insulinoma was 10.7 (0.2–32.6) years for the patients and 12.2 (1.2–35.5) years for the controls. A metastatic insulinoma was detected in 9 (11%) patients. Multiple endocrine neoplasia type 1 (MEN1) syndrome was diagnosed in two patients, both associated with a non-metastatic, solitary insulinoma.

Long-term morbidity

Before the diagnosis of insulinoma, there was no statistically significant difference in morbidity between the patients and the controls (Supplementary Table 2). After the diagnosis of insulinoma, the overall incidence of any cardiovascular disease and the incidence of atrial fibrillation were increased in the patients vs. controls, although the increase was not significant after the Bonferroni
correction (Table 1, Figure 1A). In the Kaplan-Meier analysis, the difference in the cumulative incidence of atrial fibrillation in the patients vs. controls increased gradually after the diagnosis of insulinoma (Figure 1B). A sensitivity analysis excluding the first year after insulinoma diagnosis showed a trend towards increased incidence of atrial fibrillation in the insulinoma patients, but this difference was not statistically significant (Table 2).

Regarding endocrine morbidity (Figure 1C), the overall incidence of endocrine and thyroid disorders was higher in the patients than in the controls (Table 1, Figure 1C). The thyroid diagnoses included hypothyroidism in 3 (4%), hyperthyroidism in 2 (3%) and goitre in 1 (1%) of the patients, compared to 6 (2%), 2 (1%) and 2 (1%) of the controls, respectively. In the Kaplan-Meier analysis, the cumulative incidence of thyroid disorders in the patients vs. controls started to increase right from the diagnosis of insulinoma (Figure 1D). After excluding the first post-diagnostic year, no difference was found in the incidence of endocrine or thyroid disorders between the patients and the controls (Table 2). A parathyroid disorder (hyperparathyroidism) was diagnosed in only 2 (3%) patients, one of them having a confirmed MEN1 syndrome.

As for gastrointestinal diagnoses, the incidence of pancreatic diseases, and bowel diseases other than IBD, hernias and appendiceal diseases, were increased among the insulinoma patients (Table 1). The increased incidence of pancreatic diseases was explained by acute pancreatitis, usually diagnosed during the first 2 months after the primary pancreatic surgery. In the subgroup analysis of bowel diseases, the only statistically significant difference was an increased incidence of intestinal obstruction, diagnosed in 5% of the surgically treated patients, a median of 5.9 (2.1–11.3) years after primary pancreatic surgery [RR 18.7 (95% CI 2.1–166.9), \( p < 0.001 \)].

The incidence of dementia or all mental and behavioural disorders did not significantly differ between the patients and the controls (Table 1). Regarding cancer morbidity, 14 cancers were diagnosed in the patients and 42 in the controls (Table 23, Figure 1E), after the diagnosis of
insulinoma. Of specific cancer types, the incidence of breast and kidney cancers was increased in insulinoma patients vs. controls (Table 23). After the exclusion of the 2 MEN1 patients and their controls, however, no statistically significant increase was found in breast cancer incidence [RR 2.64 (0.63–11.04), \( p=0.167 \)]. The breast cancers occurred 4.7–24.3 years after the diagnosis of insulinoma. The three kidney cancers in the patients were diagnosed 2.7, 16.9 and 20.5 years after the diagnosis of a sporadic, non-metastatic insulinoma. Only one of the kidney cancers was detected before the end of insulinoma follow-up at the University Hospital.

**Long-term survival**

With the three disease progressions and three recurrences detected in the 71 patients treated with curative-intent surgery (6), the five-, 10- and 15-years disease-free survival rates were 94, 93 and 90%, respectively. During the follow-up, 25 (32%) patients and 63 (20%) controls deceased. The Kaplan-Meier survival curves of the patients with a non-metastatic or a metastatic insulinoma and their controls are shown in Figure 2. In a Cox regression analysis, the median overall survival of 27.5 (95% CI 24.1–30.8) years in the patients with a non-metastatic insulinoma did not significantly differ from the 33.2 (29.8–36.7) years in their controls [HR 1.5 (0.9–2.6), \( p=0.128 \)]. In the patients with a metastatic insulinoma, the survival was significantly impaired, with a median of 3.4 (2.9–4.0) years vs. not reached in the controls [HR 5.1 (1.9–13.3), \( p=0.001 \)]. Three of the patients with a metastatic insulinoma (33%), however, showed a remarkably long survival time of 6–30 years.

In univariate analyses, older age, distant metastases, tumour size \( \geq 2 \) cm, higher preoperative serum insulin concentration, lack of curative-intent surgery, and the need of postoperative medication for the insulinoma, were all associated with a significantly decreased overall survival among insulinoma patients (Supplementary Table 3). The occurrence of major surgical complications, classified as grades III–V of the Clavien-Dindo classification (8, 9), was associated with a
decreased survival, due to the early postoperative mortality. After the exclusion of postoperative deaths (grade V complication), no significant difference was found in the survival of patients with major vs. no or minor surgical complications [HR 2.28 (0.77–6.71), \( p=0.136 \)]. The association of laparoscopic vs. open surgery with the survival could not be assessed, as only two patients underwent laparoscopic insulinoma surgery. In the multivariate analyses, older age and distant metastases were associated with decreased survival (Table 4, Supplementary Table 4).

**Causes of death**

Nine of the 25 insulinoma patients who deceased during the study period (36%), died due to an insulinoma-related cause: 6 patients died of metastatic insulinoma, 2 patients died of surgical complications, and 1 patient died due to complications of invasive diagnostics, as previously described (6). With the two deaths due to surgical complications, the perioperative mortality, defined as any death occurring within 30 days after surgery, was 2.7%. The causes of death of the patients and controls are presented in Table 5. During the follow-up, 16 non-insulinoma-related deaths occurred in the patients and 54 in the controls. Of these 16 deaths among the patients, 8 (50%) were due to diseases of the circulatory system, 4 (25%) due to cancer and 4 (25%) due to other causes, compared to 24 (44%), 12 (22%) and 18 (33%) in the controls, respectively \( (p=0.765) \). The distribution of the causes of death did not significantly differ between the patients and the controls \( (p=0.363) \), analysed according to the national time series classification of Statistics Finland.

**DISCUSSION**

This study suggests an increased long-term morbidity in insulinoma patients, due to atrial fibrillation, intestinal obstruction, and possibly breast and kidney cancers. Endocrine and pancreatic
diseases were more frequent within the first year after the diagnosis, likely due to a detection bias and the occurrence of short-term surgical complications, respectively. Despite the increased long-term morbidity, the overall survival of patients with a non-metastatic insulinoma is similar to the general population. In patients with a metastatic insulinoma, the prognosis is significantly impaired.

The long-term morbidity due to any cardiovascular disease, or due to atrial fibrillation was increased among the patients previously diagnosed with an insulinoma. The reason for the increased cardiovascular morbidity in insulinoma patients is unclear. Previous studies have found no association between insulinoma and hypertension (10, 11), but the incidence of atrial fibrillation in insulinoma patients has, to our knowledge, not been studied before. Hypoglycaemia has been shown to induce cardiac arrhythmias in persons with diabetes, but the potential effect of hypoglycaemia on the cardiovascular morbidity of insulinoma patients is unclear (12, 13). Unfortunately, the total burden of hyperinsulinaemia and hypoglycaemia could not be quantified retrospectively in the present study, nor in the previous ones. In our study, the follow-up due to insulinoma may have contributed to the early diagnoses of atrial fibrillation in the patients, as the difference between the patients and the controls was no longer statistically significant after excluding the first year after diagnosis.

Morbidity due to any endocrine or thyroid disorders was increased among the patients during the first year after insulinoma diagnosis, but not later on. Although the diagnosis codes for hyperinsulinism and hypoglycaemia were excluded, the substantial number of other or unspecified endocrine disorders diagnosed near the time of diagnosis of insulinoma indicate that these codes may have been used instead of the specific diagnoses for insulinoma. A possible explanation for the increased thyroid morbidity is the careful examination and follow-up of these patients by endocrinologists, contributing to a prompt diagnosis of disorders that may partly remain undiagnosed in the general population.
The incidence of acute pancreatitis and intestinal obstruction was increased among the insulinoma patients vs. controls. Most cases of pancreatitis occurred as early postoperative complications, with a rate of 10% in the surgically treated patients, as described previously (6). Intestinal obstruction occurred in 5% of the surgically treated patients, likely as a late postoperative complication of insulinoma surgery. Previous studies on surgically treated insulinomas have mainly focused on the short-term complications and have not reported the incidence of late intestinal obstruction in insulinoma patients. In accordance with this study, previous studies have reported similar rates of intestinal obstruction after pancreatic and other abdominal surgery (14-16).

Morbidity due to breast and kidney cancers also seemed to increase among the insulinoma patients. To our knowledge, increased incidence of breast or kidney cancers in insulinoma patients has not been reported before, apart from an increased risk for breast cancer in MEN1 patients (17). The breast and kidney cancers of the patients were diagnosed 2.7–24.3 years after the diagnosis of insulinoma. The MEN1 syndrome explained at least part of the increased morbidity due to breast cancer, and no statistically significant difference was found in the breast cancer incidence of the patients vs. controls after the exclusion of MEN1 patients from the analysis. As renal cancers are often discovered incidentally in abdominal imaging (18, 19), we cannot exclude neither a true association of kidney cancer with insulinoma nor an effect of frequent CT scanning. As these results were based on a small number of patients diagnosed with breast or kidney cancer, larger studies are needed to confirm these preliminary findings.

No significant difference was detected in the incidence of dementia or other psychiatric disorders between insulinoma patients and controls. The sample size and the follow-up time in our study may, however, have been insufficient to detect a possible difference. A recent prospective study reported cognitive impairment in 18 of 34 insulinoma patients, measured with the Montreal Cognitive Assessment questionnaire prior to the pancreatic surgery, with improvement detected in most patients at one year after surgery (20).
In the present study, the overall survival of patients with a non-metastatic insulinoma did not significantly differ from the general population. The 10-year survival of 87% for non-metastatic and 33% for metastatic insulinomas in this study was similar to the 91% and 29%, respectively, reported previously (1). Similarly to previous studies, older age and metastases were the most important factors associated with an impaired survival (1, 21, 22). In fact, recent evidence suggests that metastatic and non-metastatic insulinomas differ in their origin and pathogenesis and should be regarded as two different diseases (23). An increased risk of insulinoma recurrence and an impaired survival has been reported in MEN1 patients (1). In our study, however, no recurrences were detected during the follow-up of the two MEN1 patients.

Among the surgically treated insulinoma patients, the surgical method or the period of surgery was not associated with the overall survival. The postoperative mortality of 2.7% was slightly lower than the 3.7% reported previously for an open approach (4). Except for the postoperative deaths, no significant association was found between surgical complications and overall survival, which is in line with a recent series of 105 surgically managed pancreatic neuroendocrine tumour patients (23-24). A recent study of 198 insulinoma patients, however, reported a higher reoperation rate after tumour enucleations compared to pancreatic resections (24-25). To minimise the complication risks and need for reoperations, the invasive diagnostics and surgical treatment of insulinomas, like all pancreatic tumours, should be performed in centres with adequate expertise (2, 26-31).

In this study, the median overall survival of 3.4 years in patients with a metastatic insulinoma was similar to the 40 months (3.3 years) reported recently in 31 patients with metastatic insulinomas (32). This is better than the median survival of 29 months (2.4 years) reported earlier (22). Despite the poor overall survival, one third of the patients with a metastatic insulinoma had a remarkably long survival time. Previous studies have shown that palliative debulking surgery, and newer treatment options, such as peptide receptor radionuclide therapy and everolimus, may improve survival and relieve symptoms in patients with a metastatic disease (26, 32-36). Because of the
small number of metastatic insulinomas, we were not able to assess the effect of treatment on the survival of patients with a metastatic insulinoma.

The major strengths of this study are the nationwide, unselected study cohort, including all the patients diagnosed with an insulinoma in Finland over a three-decade period, and the long-term follow-up data of the patients and controls, matched for age, gender, and the place of residence. In Finland, it is mandatory to report the underlying causes of death to the Population Information System, and the hospital discharge diagnoses to the National Hospital Discharge Register, contributing to the complete, comprehensive, and high-quality data in these registers (37, 38).

The relatively small sample size, due to the rarity of insulinomas, is the major limitation of this study. In addition, the prognosis of the subgroups of patients with metastatic, recurrent or MEN1-related insulinomas could not be evaluated comprehensively. Due to the retrospective, register-based study design we were not able to specify the causative factors of the long-term morbidity in insulinoma patients. Another limitation is that the National Hospital Discharge Register only includes information on the hospital visits in the specialized health care system, which may lead to underestimation of the incidence of non-severe diseases, treated mainly in the primary health care. On the other hand, detection bias probably contributed to the high incidence of non-severe endocrine disorders near the time of diagnosis of insulinoma in the patients.

In conclusion, the long-term prognosis of patients with a non-metastatic insulinoma seems to be similar to the general population, except for an increased incidence of atrial fibrillation, intestinal obstruction, and possibly breast and kidney cancers. Metastatic insulinomas are rare but generally entail a markedly decreased survival. To our knowledge, this is the first study to report findings of increased long-term morbidity in insulinoma patients. In the future, larger studies are needed to confirm these results.
DISCLOSURE

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Caption : Figure 1 (A–E). Cumulative incidence of cardiovascular, endocrine and cancer diseases in the patients (solid line) diagnosed with an insulinoma Finland during 1980–2010, compared with controls (dashed line) matched for age, gender, and the place of residence (log rank test).

A. Cardiovascular diseases (<i>p</i>=0.048)

B. Atrial fibrillation (<i>p</i>=0.024)
C. Endocrine disorders (<i>p</i>&lt;0.001)

E. Cancers (<i>p</i>=0.061)

Figure 2 (A–B). Survival of the patients diagnosed with a non-metastatic (2A) or a metastatic insulinoma (2B) in Finland during 1980–2010, compared with controls matched for age, gender, and the place of residence (log rank test).

A. Patients with non-metastatic insulinoma vs. controls (<i>p</i>&lt;0.125)

B. Patients with metastatic insulinoma vs. controls (<i>p</i>&lt;0.001)
Table 1. Incidence of endocrine, cardiovascular, gastrointestinal, and psychiatric disorders in the 79 patients diagnosed with an insulinoma in Finland during 1980–2010, and in 316 matched controls, after the diagnosis of insulinoma.

| Disease                               | Patients | Control | Patients vs Controls |
|---------------------------------------|----------|---------|---------------------|
|                                       | n/n at risk  | Incidence Rate/10000/y | 95% CI   | n/n at risk  | Incidence Rate/10000/y | 95% CI   | Rate Ratio | 95% CI       | P value   |
| Endocrine disorders                   |          |         |                     |          |         |                     |          |            |             |          |
| Diabetes                              | 21/72    | 295.37  | 192.58–453.01       | 32/273   | 84.58    | 59.81–119.60         | 3.49     | 2.01–6.06  | <0.001     |
| Other endocrine disorders             | 11/76    | 130.00  | 70.65–230.00        | 1/301    | 2.27     | 0.32–16.14           | 56.12    | 7.25–434.67| <0.001     |
| Cardiovascular diseases               |          |         |                     |          |         |                     |          |            |             |          |
| Coronary artery disease               | 11/77    | 119.17  | 66.00–215.19        | 36/297   | 87.03    | 62.77–120.65         | 1.37     | 0.70–2.69  | 0.360      |
| Diseases of the arteries and veins    | 7/73     | 78.92   | 37.62–165.54        | 30/259   | 81.56    | 57.02–116.64         | 0.97     | 0.43–2.00  | 0.938      |
| Valvular diseases and cardiomyopathies| 4/76     | 42.12   | 15.81–112.23        | 12/302   | 27.24    | 15.47–47.96          | 1.55     | 0.50–4.80  | 0.447      |
| Heart failure                         | 4/77     | 40.03   | 15.02–106.66        | 19/304   | 42.87    | 27.34–67.21          | 0.93     | 0.32–2.75  | 0.901      |
| Diseases of the pulmonary circulation | 2/79     | 19.72   | 4.93–78.84          | 4/316    | 8.77     | 3.29–23.36           | 2.25     | 0.41–12.28 | 0.336      |
| Gastrointestinal diseases             |          |         |                     |          |         |                     |          |            |             |          |
| Diseases of the oesophagus, stomach, |          |         |                     |          |         |                     |          |            |             |          |
| and duodenum                          | 6/76     | 63.83   | 28.68–142.07        | 22/298   | 51.70    | 34.04–78.52          | 1.24     | 0.50–3.05  | 0.647      |
| Abdominal hernias                     | 8/73     | 91.32   | 45.67–182.61        | 19/282   | 45.96    | 29.31–72.05          | 1.99     | 0.87–4.54  | 0.097      |
| Chronic inflammatory bowel diseases   | 0/79     | 0.00    | 0.00–35.85          | 3/315    | 6.58     | 2.12–20.39           | 0.00     | 0.412      |
| Diseases of the appendix              | 2/78     | 20.46   | 5.12–81.79          | 8/304    | 18.32    | 9.16–36.63           | 1.12     | 0.24–5.26  | 0.889      |
| Other bowel diseases                  | 14/77    | 156.41  | 92.63–264.09        | 30/296   | 71.68    | 50.11–102.51         | 2.18     | 1.16–4.12  | 0.013      |
| Diseases of the liver, biliary tract,| 6/77     | 65.02   | 29.21–144.72        | 20/292   | 48.18    | 31.08–74.68          | 1.35     | 0.54–3.36  | 0.518      |
| and gallbladder                       | 8/78     | 85.62   | 42.82–171.20        | 3/311    | 6.66     | 2.15–20.64           | 12.86    | 3.41–48.49 | <0.001     |
| Diseases of the pancreas              |          |         |                     |          |         |                     |          |            |             |          |
| Mental and behavioural disorders      | 12/71    | 148.85  | 84.54–262.11        | 36/265   | 98.09    | 70.76–135.99         | 1.52     | 0.79–2.92  | 0.208      |
| Dementia                              | 4/79     | 39.64   | 14.88–105.61        | 14/312   | 30.86    | 18.28–52.11          | 1.28     | 0.42–3.90  | 0.658      |

Excluding hyperinsulinism and hypoglycaemia. aOther endocrine disorders in the patients included a polyglandular endocrine disorder (n=1) and other or unspecified endocrine disorders (n=10). bAbdominal hernias in the patients included seven ventral hernias and one inguinal hernia. cPancreatic diseases in the patients included acute pancreatitis (n=6), pancreatic pseudocyst (n=1) and other/undefined pancreatic disease (n=1).

CI: Confidence Interval. NA: not applicable. Bold text indicates a statistically significant difference between the patients and the controls (p<0.05, Mantel-Haenszel method). When the Bonferroni correction for multiple comparisons is applied, a p value <0.002 (<0.05/25) is considered statistically significant.
Table 2. Sensitivity analysis of the incidence of endocrine, cardiovascular, gastrointestinal, and psychiatric disorders in the 77 patients diagnosed with a sporadic insulinoma in Finland during 1980–2010, and in 308 matched controls, after the diagnosis of insulinoma, excluding the first year after diagnosis.

| Disease                    | Patients $a$ | Controls | Patients vs controls | P-value |
|----------------------------|--------------|----------|----------------------|---------|
|                            | n/n at risk $a$ | Incidence Rate/10000/y | 95% CI | n/n at risk $ab$ | Incidence Rate/10000/y | 95% CI | Rate Ratio | 95% CI |
| Endocrine disorders$bc$    | 7/52         | 107.19   | 51.10–224.85         | 27/219  | 91.76   | 62.93–133.80   | 1.17 | 0.51–2.68 | 0.714 |
| Thyroid disorders          | 3/69         | 34.88    | 11.25–108.13         | 9/296   | 22.87   | 11.90–43.96    | 1.53 | 0.41–5.63 | 0.524 |
| Parathyroid disorders      | 1/72         | 11.07    | 1.56–78.59           | 0/308   | 0.00    | NA             | 2.09 | 0.98–4.46 | 0.052 |
| Other endocrine disorders  | 1/61         | 12.56    | 1.77–89.13           | 1/262   | 2.74    | 0.39–19.43     | 4.59 | 0.29–73.34 | 0.236 |
| Cardiovascular diseases    | 12/44        | 220.51   | 125.23–388.29        | 44/147  | 227.49  | 169.29–305.69  | 0.97 | 0.51–1.84 | 0.924 |
| Atrial fibrillation and flutter | 10/70    | 121.66   | 65.46–226.11         | 20/274  | 58.34   | 37.64–90.42    | 2.09 | 0.98–4.46 | 0.052 |
| Gastrointestinal diseases  | 13/46        | 273.71   | 162.10–462.15        | 38/175  | 169.19  | 123.11–232.51  | 1.55 | 0.83–2.91 | 0.170 |
|                            | 262.06       | 152.16–451.31         |        |         |        |                |      |            |      |
| Other bowel diseases       | 11/68        | 138.54   | 76.72–250.16         | 26/279  | 70.39   | 47.93–103.38   | 1.97 | 0.97–3.98 | 0.055 |
| Intestinal obstruction     | 4/72         | 46.07    | 17.29–120.00         | 1/315   | 2.43    | 0.34–17.25     | 18.96 | 2.12–169.64 | <0.001 |
|                            |              |         | 1/307                |         |         |                |      |            |      |
| Diseases of the pancreas   | 1/66         | 11.99    | 1.69–85.09           | 3/271   | 9.04    | 2.91–28.02     | 1.33 | 0.14–12.75 | 0.806 |
|                            |              |         | 3/263                |         |         |                |      |            |      |

$^a$Two patients with a MEN1 syndrome were excluded from the analyses, together with their corresponding controls. $^b$Patients with a disease diagnosed before or within one year after the diagnosis of insulinoma were excluded from the incidence calculations of that disease category, together with their corresponding controls. Controls with a given disease diagnosed before or within one year after the diagnosis of insulinoma of the corresponding patient, as well as patients and controls with an insufficient follow-up time (less than a year after the diagnosis of insulinoma) were excluded individually. $^c$Excluding hyperinsulinism and hypoglycaemia.

CI Confidence Interval. NA not applicable. Bold text indicates a statistically significant difference between the patients and the controls ($p<0.05$, Mantel-Haenszel method).

When the Bonferroni correction for multiple comparisons is applied, a p value <0.005 (<0.05/10) is considered statistically significant.
Table 3. Cancer incidence in the 79 patients diagnosed with an insulinoma in Finland during 1980–2010, and in 316 matched controls, after the diagnosis of insulinoma.

| Cancer type                   | Patients | Controls | Patients vs controls | P value |
|-------------------------------|----------|----------|---------------------|---------|
|                               | n/n at risk a | Incidence Rate/10000/y | 95% CI | n/n at risk a | Incidence Rate/10000/y | 95% CI | Rate Ratio | 95% CI |         |
| Any cancer                    | 13/77    | 135.66   | 78.77–233.63        | 32/300  | 74.59       | 52.75–105.48          | 1.82 | 0.96–3.47 | 0.065 |
| Breast cancer                 | 5/55     | 71.99    | 29.96–172.95        | 5/216   | 16.15       | 6.72–38.81            | 4.46 | 1.29–15.39 | **0.010** |
| Kidney cancer                 | 3/79     | 29.64    | 9.56–91.90          | 0/315   | 0.00        | 0.00–8.00             | NA  | <0.001     |
| Lymphatic and hematopoietic cancers | 2/79   | 19.74    | 4.94–78.93          | 9/315   | 19.76       | 10.28–37.97           | 1.00 | 0.22–4.62 | 0.999 |
| Prostate cancer b             | 1/23     | 32.75    | 4.61–232.47         | 6/92    | 44.36       | 19.93–98.73           | 0.74 | 0.09–6.13 | 0.778 |
| Colon cancer                  | 0/78     | 0.00     | 0.00–36.06          | 4/312   | 8.74        | 3.28–23.28            | 0.00 | 0.346     |
| Malignant melanoma            | 0/79     | 0.00     | 0.00–35.85          | 3/316   | 6.56        | 2.12–20.34            | 0.00 | 0.413     |
| Gastric cancer                | 0/79     | 0.00     | 0.00–35.85          | 2/315   | 4.36        | 1.09–17.44            | 0.00 | 0.504     |
| Lung and tracheal cancers     | 0/79     | 0.00     | 0.00–35.85          | 2/316   | 4.34        | 1.09–17.36            | 0.00 | 0.505     |
| Ovarian cancer c              | 0/55     | 0.00     | 0.00–51.44          | 2/220   | 6.31        | 1.58–25.21            | 0.00 | 0.502     |
| Skin cancer (other than melanoma) | 0/79  | 0.00     | 0.00–35.85          | 2/316   | 4.35        | 1.09–17.38            | 0.00 | 0.505     |
| Other cancers c               | 3/79     | 29.78    | 9.60–92.33          | 6/315   | 13.12       | 5.90–29.21            | 2.27 | 0.57–9.07 | 0.233 |

*Only females included. **Only males included. ‘Other cancers in the patients included cancers of the thyroid gland, uterus and pancreas (n =1 each).

CI Confidence Interval. NA not applicable. Bold text indicates a statistically significant difference between the patients and the controls (p<0.05, Mantel-Haenszel method). When the Bonferroni correction for multiple comparisons is applied, a p value <0.004 (<0.05/12) is considered statistically significant.
Table 4. Multivariate analysis of factors associated with mortality among patients diagnosed with an insulinoma in Finland during 1980 – 2010 (n = 75a).

| Variable                        | Hazard Ratio | 95% CI       | P value |
|---------------------------------|--------------|--------------|---------|
| Age at diagnosis                | 1.05         | 1.02–1.08    | 0.003   |
| Tumour localization (head/neck vs. body/tail) | 1.90         | 0.72–5.03    | 0.197   |
| Tumour size (≥ 2 cm vs. < 2 cm) | 2.49         | 0.93–6.65    | 0.070   |
| Distant metastases              | 3.71         | 1.18–11.67   | 0.025   |

aFour of the 79 patients in the total cohort were excluded from this multivariate analysis, due to missing data regarding tumour size (n=4) and localization (n=2).

CI Confidence Interval. Bold text indicates a statistically significant hazard ratio (p<0.05, Cox proportional hazards model).
Table 5. Causes of death of the patients diagnosed with an insulinoma in Finland during 1980–2010 and their control group matched for age, gender and the place of residence. Data are presented as n (%).

| Cause of Death                                                      | Patients (n=79) | Controls (n=316) |
|--------------------------------------------------------------------|----------------|-----------------|
| Deaths related to insulinoma                                       | 9 (11.4)       | 0 (0)           |
| Deaths due to metastatic insulinoma                                | 6 (7.6)        | 0 (0)           |
| Deaths due to complications of the invasive diagnostics or pancreatic surgery | 3 (3.8)        | 0 (0)           |
| Deaths due to diseases of the circulatory system                   | 8 (10.1)       | 29 (9.2)        |
| Deaths due to tumours (other than insulinoma)                      | 4 (5.1)        | 13 (4.1)        |
| Deaths due to other causes                                         | 4 (5.1)        | 21 (6.6)        |
| Alive at the end of follow-up                                     | 54 (68.4)      | 253 (80.1)      |
Caption: Figure 1 (A–E). Cumulative incidence of cardiovascular, endocrine and cancer diseases in the patients (solid line) diagnosed with an insulinoma Finland during 1980–2010, compared with controls (dashed line) matched for age, gender, and the place of residence (log rank test). A. Cardiovascular diseases ($p=0.048$)
B. Atrial fibrillation ($p=0.024$)
C. Endocrine disorders ($p<0.001$)
D. Thyroid disorders ($p=0.047$)
E. Cancers ($p=0.061$)
Figure 2 (A–B). Survival of the patients diagnosed with a non-metastatic (2A) or a metastatic insulinoma (2B) in Finland during 1980–2010, compared with controls matched for age, gender, and the place of residence (log rank test).

A. Patients with non-metastatic insulinoma vs. controls ($p=0.125$)
B. Patients with metastatic insulinoma vs. controls ($p<0.001$)
Supplementary Table 1. Classification of endocrine, cardiovascular, gastrointestinal, and mental and behavioural disorders, according to the Finnish version of the ICD-10 since 1996, ICD-9 during 1987–1995, and ICD-8 during 1980–1986.

| Disease category                        | Classification of diseases | ICD-9            | ICD-10          |
|-----------------------------------------|----------------------------|------------------|-----------------|
| **Endocrine disorders**                 |                            |                  |                 |
| Diabetes                                | 240–250, 252–258           | 240–250, 252–259 | E00–E14, E20–E35|
| Thyroid disorders                       | 240–246                    | 240–246          | E00–E07         |
| Parathyroid disorders                   | 252                        | 252              | E20–E21         |
| Other endocrine disorders               | 253–258                    | 253–258          | E22–E29, E31–E35|
| **Cardiovascular diseases**             |                            |                  |                 |
| Cerebrovascular diseases                | 430–438                    | 430–438          | I10–I28, I31, I34–I37, I42–I99 |
| Hypertension                            | 400–404                    | 401–405          | I60–I69         |
| Arrhythmias and conduction disorders    | 427.2–427.98               | 426–427          | I44–I49         |
| Atrial fibrillation and flutter         | 427.92                     | 4273A            | I48             |
| Coronary artery disease                 | 410–414                    | 410–414          | I20–I25         |
| Diseases of the arteries and veins      | 440–448, 451–458           | 440–448, 451–459 | I70–I89        |
| Valvular diseases and cardiomyopathies  | 423–425                    | 423–425          | I31, I34–I37, I42–I43 |
| Heart failure                           | 427.0, 427.1, 428          | 428              | I50             |
| Diseases of the pulmonary circulation   | 426, 450                   | 415–417          | I26–I28         |
| **Gastrointestinal diseases**           |                            |                  |                 |
| Diseases of the oesophagus, stomach, and duodenum | 530–577                     | 530–537          | K20–K93         |
| Abdominal hernias                       | 550–553                    | 550–553          | K40–K46         |
| Chronic inflammatory bowel diseases     | 563                        | 555–556          | K50–K51         |
| Diseases of the appendix                | 540–543                    | 540–543          | K35–K38         |
| Other bowel diseases                    | 560–562, 564–569           | 557–569          | K52–K67, K90–K93|
| Diseases of the liver, biliary tract, and gallbladder | 570–576                     | 570–576          | K70–K83         |
| Diseases of the pancreas                | 577                        | 577              | K85–K87         |
| Mental and behavioural disorders        | 290–315                    | 290–315          | F00–F99         |
| Dementia                                | 290                        | 290              | F00–F03         |
Excluding hyperinsulinism and hypoglycemia, Including pituitary, thymic, adrenal, ovarian, testicular, polyglandular and other or unspecified endocrine disorders, Excluding rheumatic heart diseases and infectious endo-, peri- and myocardial diseases.

ICD International Classification of Diseases
Supplementary Table 2. Prevalence of endocrine, cardiovascular, gastrointestinal, psychiatric disorders and cancers in the 79 insulinoma patients diagnosed with an insulinoma in Finland during 1980–2010, and in 316 matched controls, before the diagnosis of insulinoma.

|                          | Patients (n = 79) | Controls (n = 316) | Patients vs controls |
|--------------------------|------------------|-------------------|---------------------|
|                          | n (%)            | n (%)             | Odds Ratio (95% CI) | Significance |
| **Endocrine disorders**a |                  |                   |                    |              |
| Diabetes                 | 4 5.1            | 6 1.9             | 2.67 (0.75–9.45)   | 0.129        |
| Thyroid disorders        | 0 0.0            | 5 1.6             | 0.00 NA            | NA           |
| Parathyroid disorders    | 0 0.0            | 1 0.3             | 0.00 NA            | NA           |
| Other endocrine disordersb| 3 3.8            | 3 0.9             | 4.00 (0.81–19.82)  | 0.090        |
| **Cardiovascular diseases** |                |                   |                    |              |
| Cerebrovascular diseases | 1 1.3            | 7 2.2             | 0.57 (0.07–4.64)   | 0.601        |
| Hypertension             | 9 11.4           | 18 5.7            | 2.18 (0.92–5.13)   | 0.075        |
| Arrhythmias and conduction disorders | 2 2.5 | 9 2.8 | 0.89 (0.19–4.11) | 0.880 |
| Atrial fibrillation and flutter | 1 1.3 | 5 1.6 | 0.80 (0.09–6.85) | 0.839 |
| Coronary artery disease  | 2 2.5            | 12 3.8            | 0.65 (0.14–3.02)   | 0.582        |
| Disease of the arteries and veins | 6 7.6 | 35 11.1 | 0.65 (0.26–1.63) | 0.362 |
| Valvular diseases and cardiomyopathies | 3 3.8 | 3 0.9 | 7.81 (0.77–78.82) | 0.082 |
| Heart failure            | 2 2.5            | 4 1.3             | 2.17 (0.35–13.47)  | 0.404        |
| Diseases of the pulmonary circulation | 0 0.0 | 0 0.0 | NA | NA |
| **Gastrointestinal diseases** |                |                   |                    |              |
| Diseases of the oesophagus, stomach, and duodenum | 3 3.8 | 6 1.9 | 2.00 (0.50–8.00) | 0.327 |
| Abdominal hernias        | 6 7.6            | 13 4.1            | 2.03 (0.70–5.84)   | 0.190        |
| Chronic inflammatory bowel diseases | 0 0.0 | 1 0.3 | 0.00 NA | NA |
| Diseases of the appendix | 1 1.3            | 8 2.5             | 0.50 (0.06–4.00)   | 0.513        |
| Other bowel diseases      | 2 2.5            | 12 3.8            | 0.66 (0.14–3.00)   | 0.589        |
| Diseases of the liver, biliary tract, and gallbladder | 2 2.5 | 16 5.1 | 0.48 (0.11–2.16) | 0.342 |
| Diseases of the pancreas  | 1 1.3            | 1 0.3             | 4.00 (0.25–63.95)  | 0.327        |
| **Mental and behavioural disorders** |            |                   |                    |              |
| Dementia                 | 0 0.0            | 4 1.3             | 0.00 NA            | NA           |
| Cancers                  | 2 2.5            | 8 2.5             | 1.00 (0.20–4.90)   | 1.000        |
aExcluding hyperinsulinism and hypoglycemia, bOther endocrine disorders in the patient group included a pituitary disorder (n=1), and other or unspecified endocrine disorders (n=2).

CI Confidence Interval. NA not applicable. Bold text indicates a statistically significant Odds ratio (p<0.05, Conditional logistic regression).
Supplementary Table 3. Univariate Cox regression analysis of factors associated with mortality in the 79 patients diagnosed with an insulinoma in Finland during 1980–2010.

| Clinical factors                                      | Hazard Ratio | 95% CI      | Significance |
|-------------------------------------------------------|--------------|-------------|--------------|
| Age at diagnosis (n = 79)                             | 1.05         | 1.02–1.08   | **0.001**    |
| Male (n = 24) vs. female (n = 55)                     | 1.03         | 0.44–2.39   | 0.955        |
| Symptom duration before diagnosis (n = 75)            | 1.00         | 1.00–1.01   | 0.293        |
| Decade of diagnosis (reference: 2000s, n = 43)        |              |             |              |
| 1990s (n = 17)                                        | 1.58         | 0.55–4.59   | 0.397        |
| 1980s (n = 19)                                        | 1.17         | 0.37–3.67   | 0.793        |

| Preoperative laboratory tests                         |              |             |              |
| Lowest spontaneous plasma glucose, mmol/l (n = 62)    | 2.03         | 0.85–4.82   | 0.111        |
| Highest spontaneous serum insulin, mU/l (n = 49)     | 1.10         | 1.01–1.20   | **0.037**    |
| Highest spontaneous serum C-peptide, nmol/l (n = 39) | 1.74         | 0.99–3.04   | 0.053        |
| Plasma glucose nadir in the fasting test, mmol/l (n = 64) | 1.10     | 0.58–2.11   | 0.770        |
| Corresponding serum insulin in the fasting test, mU/l (n = 55) | 1.01  | 0.99–1.03   | 0.265        |
| Corresponding serum C-peptide in the fasting test, nmol/l (n = 44) | 1.04  | 0.40–2.72   | 0.939        |
| Glycated haemoglobin, HbA1c, % (n = 31)              | 0.97         | 0.23–4.12   | 0.971        |

| Treatment-related factors                              |              |             |              |
| Surgery (reference: curative-intent surgery, n = 71)   |              |             |              |
| Palliative surgery (n = 2)                            | 17.01        | 3.45–83.92  | **0.001**    |
| No surgery (n = 6)                                    | 9.86         | 3.60–27.00  | <0.001       |
| Surgical method (reference: enucleation, n = 31)      |              |             |              |
| Distal resection (n = 33)                             | 1.21         | 0.44–3.30   | 0.717        |
| Pancreatico-duodenectomy (n = 9)                      | 2.11         | 0.54–8.23   | 0.283        |
| Major surgical complicationsb yes (n = 18) vs. no (n = 55) | 3.06      | 1.15–8.12   | **0.025**    |
| Preoperative medicationc yes (n = 55) vs. no (n = 24)  | 0.97         | 0.42–2.24   | 0.934        |
| Postoperative medicationc yes (n = 19) vs. no (n = 53) | 3.09         | 1.23–7.75   | **0.016**    |
| Postoperative diazoxide: yes (n = 8) vs. no (n = 63)   | 4.56         | 1.59–13.03  | **0.005**    |
| Postoperative somatostatin analogue: yes (n = 19) vs. no (n = 54) | 2.04      | 0.84–4.95   | 0.113        |

| Tumour-related factors                                 |              |             |              |
| Tumour size ≥ 2 cm (n = 20) vs. < 2 cm (n = 55)       | 2.79         | 1.19–6.55   | **0.018**    |
| Multiple (n = 5) vs. solitary tumour (n = 73)         | 0.67         | 0.09–5.05   | 0.700        |
| Tumour localization: head/neck (n = 39) vs. body/tail (n = 38) | 0.97    | 0.43–2.21   | 0.949        |
| Distant metastases: yes (n = 9) vs. no (n = 70)       | 5.06         | 2.06–12.41  | <0.001       |
| Clinical TNM staging (7) (reference: Stage I, n = 58) |              |             |              |
| II (n = 10)                                           | 1.88         | 0.53–6.66   | 0.328        |
| III (n = 0)                                           |              |             |              |
| IV (n = 9)                                            | 5.06         | 1.99–12.88  | **0.001**    |

*Hazard Ratio calculated for a 10mU/l rise in plasma insulin concentration, bClassified as grades III–V of the Clavien-Dindo classification (8, 9), cIncluding medical treatment of inoperable patients,
Including diazoxide (n=8), somatostatin analogue (n=19), peroral corticosteroids (n=3), interferon alpha (n=3), 5-fluorouracil-streptozotocin (n=2), streptozotocin (n=1), epirubicin (n=1), doxorubicin (n=1), and sunitinib (n=1).

CI Confidence Interval. Bold text indicates a statistically significant hazard ratio ($p<0.05$, Cox proportional hazards model).
Supplementary Table 4. Multivariate analysis of factors associated with mortality in surgically treated insulinoma patients (n=73).

| Variable                              | Hazard Ratio | 95% CI     | Significance |
|---------------------------------------|--------------|------------|--------------|
| Age at surgery                        | 1.08         | 1.03–1.13  | **0.001**    |
| Surgical method (reference: enucleation) |              |            |              |
| Distal resection                      | 0.81         | 0.27–2.44  | 0.704        |
| Pancreatico-duodenectomy              | 4.07         | 0.80–20.87 | 0.092        |
| Time period of surgery (reference: 1980–1989) |          |            |              |
| 1990–1999                             | 1.20         | 0.35–4.12  | 0.775        |
| 2000–2010                             | 0.39         | 0.09–1.73  | 0.213        |
| Distant metastases                    | 4.58         | 1.29–16.25 | **0.018**    |

CI Confidence Interval. Bold text indicates a statistically significant hazard ratio (p<0.05, Cox proportional hazards model)