Prognostic Features in Surgically Resected Well-Differentiated Pancreatic Neuroendocrine Tumors: An Analysis of 904 Patients with 7882 Person-Years of Follow-Up

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Key Points

Question: Does subdividing grade 2 well-differentiated pancreatic neuroendocrine tumors (PanNETs) into grade 2a (Ki-67 3- <10%), and grade 2b (Ki-67 10%- ≤20%) improve patient prognostication after surgery?

Findings: In this single-institution cohort study of 904 adults, patients with grade 2a and patients with grade 2b PanNETs had distinct outcomes. Furthermore, the magnitude of the risk associated with metastases, perineural invasion, positive margins, tumor size, vascular invasion, sclerosing variant and cystic variant was refined.

Meaning: This study supports classifying PanNETs into four grades (G1, G2a, G2b, and G3), and provides a basis for accurate prognostic assessments of patients.

Abstract

Importance: The clinical behavior of well-differentiated pancreatic neuroendocrine tumors (PanNETs) is difficult to predict.

Objective: To define more accurately prognosticators for patients with a surgically resected PanNET.

Design: The pathology and Ki-67 immunolabeling index of PanNETs resected from 904 patients was correlated with patient outcome.

Setting: Academic tertiary care hospital.

Participants: Consecutive patients who had a PanNET resected between 1985 and 2025.

Results: The mean patient age at surgery was 56.6 years (SD 14.0), 477 were male (52.8%), and 7882 person-years of follow-up were obtained (mean 8.8 years, SD 6.5). The 10-year survival was 81% (95% CI: 77,86%) for patients with G1 PanNETs (Ki-67 <3%), 68% (95% CI: 61,76%) for patients with G2a PanNETs (Ki-67 3- <10%), 44% (95% CI: 29,66%) for patients with G2b PanNETs (Ki-67 of 10%- ≤20%), and 23% (95% CI: 8,61%) for patients with G3 PanNETs. Metastases (HR 4.7, p <0.0001), vascular invasion (HR 3.0, p <0.0001), tumor size ≥ 2 cm (HR 2.88, p <0.0001), perineural invasion (HR 2.42, p<0.0001), and positive margins (HR 2.18, p <0.0001) were associated with worse overall survival. Insulinoma (HR 0.34, p=3e-04), sclerosing variant (HR 0.47, p=0.05), and cystic variant (HR 0.61, p=0.05) were associated with improved overall survival. T stage and N stage were all statistically significant classifiers of overall survival. Similar associations were found with respect to disease relapse. There was a significant (P<0.001) increase in the proportion of patients diagnosed with stage I vs stage IV disease over time.

Conclusions and relevance: This study supports the classification of PanNETs into four grades (G1, G2a, G2b, and G3) based on Ki-67 labeling, which allows a more accurate prognostic assessments of patients.

Key words: Well-differentiated pancreatic neuroendocrine tumor, PanNET, Ki 67, grade, vascular invasion, stage, prognosis

Introduction

The incidence of well-differentiated pancreatic neuroendocrine tumors (PanNETs), the most prevalent non-ductal neoplasms of the pancreas, is increasing with increasing use of abdominal imaging.[1-7] Clinical management of the growing numbers of patients with PanNETs is challenging.[8] A number of new medical therapies are available for patients with advanced disease, and expert opinions vary on the optimal use of surgery, complicating the selection of the best therapy for patients.[8-10] These challenges are perhaps greatest for patients with small, <2 cm, PanNETs, as prognostic classification of these relatively indolent tumors is imperfect, and the risks of surgery are not trivial.[11-14] For example, Partelli and colleagues concluded, from the results of the ASPEN trial, that active surveillance is safe for patients with a small PanNET, while Lin and Huang, in an analysis of 1,102 patients, concluded that surgical resection is recommended for these patients.[12,14] As a result of this uncertainty, guidelines vary, and the treatment of a significant proportion of patients is not based on any guidelines.[10,11]

A number of clinical, pathological and genetic prognostic markers for patients with a PanNET have been identified.[4,7] Male sex and increasing age are both associated with shorter survival.[4,15] Clinically, insulinomas and cystic PanNETs have been reported to be associated with improved survival.[7,16-20] The pathological factors associated with survival include tumor size, lymph node status, metastasis, proliferation rate of the neoplastic cells, vascular invasion, and perineural invasion.[21-26] Margin status, necrosis, a sclerotic growth pattern with serotonin expression, an invasive growth pattern, and the type and intensity of any associated immune infiltrates have also been reported as significant prognosticators.[21,27-34] The genes *DAXX* and *ATRX* are frequently inactivated in PanNETs and inactivation of either one of these genes is associated with the alternative lengthening of telomeres (ALT) phenotype.[35] The ALT phenotype and inactivation of *DAXX* or *ATRX* are also poor prognosticators.[36-39] Despite these predictive features, prognostication remains imperfect, and there is still room for improvement.[7]

Recently, several studies have proposed refinements to prognostic features.[40,41] Currently, PanNETs are divided into three grades based on proliferation rate of the neoplastic cells: G1 (Ki-67 <2%), G2 (Ki-67 3-20%) and G3 (Ki-67 >20%).[7,42] Adsay and colleagues suggested that grade 2 PanNETs should be subdivided into two grades (G2a for Ki-67 3- <10%, and G2b for Ki-67 of 10%- ≤20%), and that G2b PanNETs have a prognosis similar to G3 (Ki-67 >20%) PanNETs.[40] For small tumors, <2 cm, Pawlik and colleagues suggested that vascular invasion may be a particularly useful prognosticator.[41]

To further refine the prognosticators for surgically resected PanNETs, particularly T1N0M0 tumors, and to specifically examine the most appropriate cut-off for proliferation rate, we reviewed the pathology of a large single-institution series of surgically resected PanNETs with up to three decades of follow-up and correlated findings with patient outcome. As it has been suggested that the incidence of clinically recognized PanNETs is increasing because of the incidental detection of asymptomatic lower-stage PanNETs, we also examined trends in age and stage at diagnosis over time.[1,43]

Methods

Study Population

This study was approved by the Institutional Review Board of the Johns Hopkins Hospital. The pathology and surgery files of the Johns Hopkins Hospital were searched for surgically resected PanNETs from January 1984 to January 2025. All available medical records were reviewed, as were all available microscope slides.

Pathology Review

Five of the authors (ALK, EDY, GK, AK and RHH), as a group, reviewed all available slides. Neuroendocrine neoplasms metastatic to the pancreas, and neoplasms not meeting diagnostic definitions outlined in the 5th edition of the World Health Organization (WHO) Classification of Tumours of the Digestive System were excluded, l904 patients.[42] Histologic slides were available from 883 of these 904 cases (Mean of 26, and median of 25 slides per case). Cystic PanNETs were defined by imaging and confirmed by gross appearance. Insulinoma was defined as a PanNET with associated clinical findings of hyperinsulinemic hypoglycemia.[7] Patients had the classical "Whipple triad" of symptoms of hypoglycemia, low blood glucose levels (below 3.0 mmol per liter), and relief of symptoms when given glucose.[7,44] Margins and size were recorded as reported in the pathology report. The sclerosing variant of PanNET was defined as a PanNET composed of cords of cells embedded in dense stromal fibrosis, centered on a large pancreatic duct, often with upstream ductal dilatation, and frequent expression of serotonin by immunolabeling.[32-34,45-47]

Proliferation Rate

Tumor Ki-67 labeling index was available for 820 of the 904 patients. Ki-67 labeling was determined by one of two methods. For 302 of the cases, a labeling "hot spot" with the highest density of Ki-67

labeling cells was photographed, the photo printed and at least 500 neoplastic cells were manually counted.[48] For 534 of the cases the percentage of neoplastic cells labeling in a "hot spot" was determined by the pathologist.[48]

Statistics

The primary endpoint of this study was overall survival (OS), defined as the time from surgery to last follow-up or death and was estimated using the Kaplan-Meier method. Eleven of the 904 patients had more than one pancreas surgery. In these instances, we included their first surgery in the analyses. Twenty-nine of the 904 patients had <30 days of follow-up information and were excluded from recurrence and survival analyses. Hazard ratios (HR) for differences in OS according to patient subgroups were estimated with Cox proportional hazards models. Cause-specific survival was estimated similarly, except patients who died without relapse were censored on their date of death. Time to relapse was calculated as the time from surgery to date of relapse (event), death (competing event) or last follow-up, whichever came first. Patients with unknown disease status at last follow-up were excluded. The impact of margin status on outcome was calculated for the entire cohort and separately after excluding patients who had an enucleation procedure. Estimates of cumulative incidence of relapse at 2, 5, and 10 years and differences in time to relapse according to patient subgroups defined at the time of surgery were estimated using proportional sub-distribution hazards regression models.[49]

A multivariable model selection approach for OS was performed using a Least Absolute Shrinkage and Selection Operator (LASSO) method. LASSO, a regularization procedure, selects optimal covariates by applying a penalty factor through cross-validation. It performs both variable selection and shrinkage, reducing some coefficients to zero and improving model generalization by controlling overfitting.[50] Age (per 5 years), gender, year of surgery, tumor size (per 1cm), Ki-67, TNM staging, and presence of insulinoma, sclerosing variant, cystic variant, vascular invasion, perineural invasion and

margins were offered as candidates to the model selection. Estimates, 95% confidence intervals, and p-values were bias-corrected using the selective Inference package in R.[51]

Restricted cubic splines were used to assess the potential non-linear association between Ki-67 and tumor size with OS. To estimate changes in the prevalence of stage I disease over time, a multinomial regression model with stage (I, II, III, or IV) was fit with year of surgery included as the main independent variable, adjusting for age and gender. Due to the relatively small number of patients represented in some years, year of diagnosis was grouped into quintiles for this analysis. Predicted probabilities of being diagnosed with stage I disease were estimated from the model using the MNLpred package in R. Changes in age at surgery over time were estimated with a simple linear regression model. Analyses were completed with R version 4.4.1.[52]

Results

Patient Characteristics and Follow-Up

Patient characteristics are shown in Table 1. A total of 7882 person-years of follow-up were obtained (mean 8.8 years, SD 6.5) on the 875 patients followed for > 1 month. Of the 875 patients, 251 were followed until death. Disease status at last follow-up was known on 822 (94%) of the 875 patients.

Prognosticators in the Entire Cohort

OS for the entire cohort is shown in Figure 1A (sub-analysis of OS by stage in Supplemental Figure 1). Metastases (HR 4.71, 95% CI: 3.53, 6.28, p<0.0001), vascular invasion (HR 3.00, 95% CI: 2.31, 3.91, p<0.0001), tumor size ≥ 2 cm (HR 2.88, 95% CI: 2.10, 3.93, p<0.0001), perineural invasion (HR 2.42, 95% CI: 1.88, 3.12, p<0.0001), positive margins (HR 2.18, 95% CI: 1.56, 3.04, p<0.001 for the overall cohort and HR 3.1, 95% CI: 2.18,4.43, P≤0.0001 excluding enucleations), age ≥60 years (HR 2.08, 95% CI: 1.62, 2.68, p <0.0001), Ki-67 ≥ 2% (HR 1.74, 95% CI: 1.31, 2.30, p<0.0001) and male gender (HR 1.46, 95% CI: 1.14, 1.89, p=0.003) were all associated with worse OS (Table 2). Insulinoma (HR 0.34, 95% CI: 0.19, 0.62 p<0.001), sclerosing variant (HR 0.47, 95% CI: 0.22, 1.00, p=0.05), and cystic variant (HR 0.61, 95% CI: 0.38, 0.99 p=0.05) were associated with improved OS. Grade, T stage and N stage, as defined by the WHO, were also all statistically significant classifiers of outcome.[7,42]

Non-linear models for the association between tumor size and survival revealed a stronger positive association between 0 and 4 cm that reduces but remains positive without an additional inflection point for tumors >4 cm (Figure 1B).

Subdividing Grade 2 PanNETs

We found that patients with G1 PanNETs had 10-year OS of 81% (95% CI: 77, 86%), G2a PanNETs 68% (95% CI: 61, 76%), G2b PanNETs 44% (95% CI: 29, 66%), and G3 PanNETs 23% (95% CI: 8, 61%) (Figure 1C

and Table 2). Plotting Ki-67 versus the HR (Figure 1D) revealed a slight change to the slope of the curve at around a Ki-67 of 10%, supporting the introduction of a 10% threshold in the grading system.

Prognosticators in M0, N0M0 and T1N0M0 Cohorts

As the most significant surgical decisions present in patients free of metastases at diagnosis, we estimated OS in lower stage subgroups, including patients who were M0 at surgery (Supplemental Table 1) , N0M0 at surgery (Supplemental Table 2) and T1N0M0 at surgery (Table 3).

Multivariate Analyses

Multivariate analyses of OS was performed on four cohorts (all patients, patients with M0 disease, patients with N0M0 disease, and patients with T1N0M0 disease) (Supplemental Table 3) using the LASSO method. For the whole cohort, M stage (M1 vs M0, HR 2.46, 95% CI: 1.85, 3.3, p<0.001), perineural invasion (HR 1.62, 95% CI: 1.24, 2.09, p=0.002), N stage (N1 vs N0, HR 1.56, 95% CI: 1.19, 2.02, p=0.005), age (per 5 years) (HR 1.26, 95% CI: 1.2, 1.32, p <0.001), Ki-67 (HR 1.06, 95% CI: 1.04, 1.09, p <0.001), tumor size (per 1cm) (HR 1.04, 95% CI: 1.01, 1.12, p=0.023), and year of surgery (per 1 year) (HR 0.96, 95% CI: 0.93, 0.97, p,0.001) were selected by the LASSO. Gender, vascular invasion and positive margins were also retained but not statistically significant. For the T1N0M0 cohort, age (HR 1.38, 95% CI: 1.18,1.59, p<0.001), year of surgery (HR 0.97, 95% CI: 0.91, 1.25, p = 0.556) and Ki-67 labeling (HR 1.15, 95% CI: 1.08,1.23, p<0.001) were retained.

Cause-Specific Survival

Information on cause-specific survival for patients with M0 disease and M0N0 disease are presented in Supplemental Tables 4 and 5 respectively. With the exception of patient age (HR 1.29, 95% CI: 0.79, 2.11, p=0.31) and patient gender (HR 1.30, 95% CI: 0.80,2.10, p=0.30), all variables identified as statistically associated with OS remained significant. These results suggest that the patient age and

gender findings observed with OS were due to the long follow-up obtained in this study, and not tumor-specific biological drivers.

Cumulative Incidence of Relapse

Next, we estimated the cumulative probabilities of disease relapse at 2, 5, and 10 years after surgery for the M0, M0N0 and M0N0T1 cohorts (Table 4 and Supplemental Tables 6 and 7). In the M0 cohort, tumor size (HR 6.19, 95% CI: 3.9, 9.85, p<0.001), vascular invasion (HR 4.41, 95% CI: 3.18, 6.12, p<0.001), Ki-67 (HR 4.14, 95% CI: 2.65, 6.48, p<0.001), and perineural invasion (HR 3.17, 95% CI: 2.31, 4.35, p<0.001) remained poor prognosticators, while insulinoma (HR 0.26, 95% CI: 0.11, 0.63, p=0.003), sclerosing variant (HR 0.27, 95% CI: 0.09, 0.84, p=0.02), and cystic variant (HR 0.29, 95% CI: 0.13, 0.65, p=0.003) were associated with improved outcome. T stage and N stage were also significantly associated with relapse.

As with OS, the cumulative incidence of relapse was associated with refined tumor grade. Patients with G1 PanNETs had 5-year cumulative incidence of relapse of 8% (95% CI: 5,11%), those with G2a PanNETs 25% (95% CI: 19, 32%), those with G2b PanNETs 62% (95% CI: 43, 80%), and those with G3 PanNETs 69% (95% CI: 44, 94%) (Table 4). These results again support adding a 10% threshold in the grading system.

Year and Age of Surgery

A comparison of the distribution of patients diagnosed with stage I, II, III, or IV disease by year of surgery grouped into quintiles revealed a down shift in stage at diagnosis over time (Figure 1E). Over the study period, patients were more likely to be diagnosed with stage I (Odds Ratio (OR) 1.61, 95% CI: 1.34, 1.93, p <0.001), stage II (OR 1.30, 95% CI: 1.08, 1.55, p =0.005), or stage III disease (OR 1.2, 95% CI: 1.00, 1.45, p=0.054) compared to stage IV disease.

Hypothesizing that a down shift in stage over time would be associated with an earlier age at diagnosis, we next examined trends in age at surgery by year of surgery (Supplemental Figure 2). Surprisingly, and perhaps reflecting regional referral practices, we observed a slight increase in the mean age at diagnosis over time, with mean age increasing 1.08 years every five years (95% CI: 0.51, 1.65, $p<0.001$).

Discussion

The incidence of PanNETs is increasing.[1-7] Fortunately, new therapeutic options beyond surgery are available. As clinical trials are designed to define the impact of novel therapies and as clinicians struggle to determine the best therapy for their individual patients, it is important that prognosticators are identified and that their impact on patient survival is quantified accurately.

In this single-institution series of 904 patients with surgically resected PanNETs and extensive follow-up, we provide support for the proposed separation of G2 PanNETs (Ki-67 of 3-≤ 20%) into two grades (G2a for Ki-67 3- <10%, and G2b for Ki-67 of 10%- ≤20%).[40] Here, the proposed grading system clearly stratified the patients for both cumulative incidence of relapse and OS (Figure 1C). Furthermore, analysis of the non-linear relationship between Ki-67 and OS (Figure 1D) revealed a subtle inflection point near a Ki-67 labeling index of 10%. While the separation of patients is clear, we should emphasize that the relationship between Ki-67 and recurrence and OS is generally fairly linear, and all cut-offs are somewhat arbitrary. Furthermore, the division of G2 tumors into two grades (G2a and G2b) may not currently have immediate therapeutic implications.

We also confirm the major prognosticators and refine the magnitude of risk associated with each. The highest HRs for recurrence and OS were associated with metastases at surgery, T stage, N stage, vascular invasion, perineural invasion, and positive margins. Separately analyzing the influence of margin status in a cohort excluding enucleations, as these are performed on low-risk tumors, demonstrates an even greater impact of margin status on prognosis.

Here we show that the serotonin-positive duct-centric sclerosing variant of PanNET comprises 6% of surgically resected PanNETs, and, as has been reported, that patients with this tumor type have an excellent prognosis with a five-year cumulative incidence of relapse of 5% (95% CI: 0%, 11%) and a 10-year OS of 91% (95% CI: 83%, 100%).[32-34,45-47] This finding has clinical implications as these tumors often

involve and stricture the main pancreatic duct causing ductal dilatation and can therefore be detected on imaging as ductal dilatation abruptly ending at a small enhancing mass lesion on computed tomography.[32-34,45-47] We confirm that insulinomas and cystic PanNETs are associated with a lower risk of recurrence and improved OS.[7,16-20] Further, in a finding that will improve risk stratification we confirm that that grade, vascular invasion and positive margins are important prognosticators of recurrence and OS in the critical group of patients with T1N0M0 disease.[41]

Finally, we examined changes in stage at diagnosis and patient age at diagnosis over time (Figure 1E and Supplemental Figure 1). The trend towards a lower stage at diagnosis supports the hypothesis that a growing number of asymptomatic patients are being diagnosed incidentally on imaging performed for another indication.[1,43] However, we did not observe a trend towards younger age at the time of diagnosis over time. In interpreting these trends, one should note that the patients included in this study, who underwent surgery at a high-volume tertiary care center, may not be representative of the entire population of patients with a PanNET.

Weaknesses of the study include the use of two methods to determine the Ki-67 labeling indexes of tumors, although both methods have been used in previous studies.[22,48,53,54] Finally, OS was used in our initial analyses as it provided, compared to disease-specific survival, the most complete dataset and the exact date of death was clear, while accuracy of the date of recurrence depends on the frequency of surveillance. Because the follow-up on many of the patients was so long, as demonstrated in the cause-specific survival analyses, caution should be taken in interpreting the risk associated with age and gender in OS, as these could be attributable to gender- and age-based differences in mortality in the general population.

Accurate risk stratification of PanNETs will help predict the clinical behavior of these tumors and increase the precision with which future treatment efficacy is assessed. The prognostic significance of

grade (Ki-67 index) will help inform the design and interpretation of clinical trials, while other prognostic factors reported here such as histologic subtype or invasive behavior may inform future basic science inquiry into these increasingly common pancreatic tumors.

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Table 1: Descriptive summary of patient characteristics at the time of surgery and in follow-up.

	N = 904		N = 904
Age at Surgery, years		**Ki-67**	
Mean (SD)	56.6 (14.0)	Mean (SD)	4.5 (6.6)
Median (Min, Max)	58.0 [12.3, 93.3]	Median (Min, Max)	2.0 [0.1, 58.6]
No. observations	904	No. observations	820
Age at Surgery - no. (%)		**Ki-67 - no. (%)**	
< 60	509 (56.3)	< 2	289 (35.2)
60+	395 (43.7)	2+	531 (64.8)
		No. Missing	84
Gender - no. (%)			
Female	427 (47.2)	**Grade - no. (%)**	
Male	477 (52.8)	G1	461 (56.2)
		G2	335 (40.9)
Year of Surgery - no. (%)		G3	24 (2.9)
1984 - 2000	106 (11.7)	No. Missing	84
2001 - 2010	306 (33.8)		
2011 - 2020	390 (43.1)	**Grade, Proposed - no. (%)**	
2020 - 2024	102 (11.3)	G1	461 (56.2)
		G2a	282 (34.4)
Years of Follow-Up		G2b	53 (6.5)
Mean (SD)	8.8 (6.5)	G3	24 (2.9)
Median (Min, Max)	7.7 [0.0, 40.2]	No. Missing	84
No. observations	900		
		Insulinoma - no. (%)	
Death or LFU < 30d of surgery - no. (%)		No	805 (89.0)
Alive at 30d	875 (97.2)	Yes	99 (11.0)
Death or LFU < 30d	25 (2.8)		
No. Missing	4	**Functional - no. (%)**	
		ACTH	1 (0.8)
Type of Surgery - no. (%)		Gastrinoma	15 (11.8)
Whipple	324 (35.8)	Glucagonoma	3 (2.4)
Total Pancreatectomy	19 (2.1)	Insulinoma	99 (78.0)
Central Pancreatectomy	13 (1.4)	Pancreatic Polypeptide	1 (0.8)
Distal Pancreatectomy	471 (52.1)	VIPoma	8 (6.3)
Enucleation	76 (8.4)	No. Missing	777
Hepatectomy	0 (0.0)		
Biopsy Only	0 (0.0)	**Sclerosing Variant - no. (%)**	
No Surgery/Missing	1 (0.1)	No	853 (94.4)
		Yes	51 (5.6)
Tumor Size, cm			
Mean (SD)	3.4 (3.0)	**Cystic Variant - no. (%)**	
Median (Min, Max)	2.5 [0.1, 27.0]	No	813 (89.9)
No. observations	904	Yes	91 (10.1)
Tumor Size - no. (%)		**Vascular Invasion - no. (%)**	
< 2cm	338 (37.4)	No	667 (75.4)
2cm +	566 (62.6)	Yes	218 (24.6)

		No. Missing	19
T Stage - no. (%)			
		Perineural Invasion - no. (%)	
T1	338 (37.4)		
T2	330 (36.5)	No	601 (67.5)
T3	214 (23.7)	Yes	290 (32.5)
T4	22 (2.4)	No. Missing	13
N Stage - no. (%)		**Margins - no. (%)**	
N0	552 (61.1)	Negative	814 (90.7)
Nx or Unknown	83 (9.2)	Positive	83 (9.3)
N1	269 (29.8)	No. Missing	7
M Stage - no. (%)		**Margins (Excluding Enucleations) - no. (%)**	
M0	796 (88.1)	Negative	768 (93.1)
M1a	99 (11.0)	Positive	57 (6.9)
M1b	3 (0.3)	No. Missing	79
M1c	6 (0.7)		
Stage Grouping - no. (%)			
I	255 (28.2)		
II	263 (29.1)		
III	193 (21.3)		
IV	108 (11.9)		
Unstaged	85 (9.4)		

Cm=centimeter, d=days, max=maximum, min=minimum, no=number, SD=standard deviation

Table 2: Overall Survival: Estimates of survival after surgery for the whole cohort and according to patient subgroups defined at the time of surgery.

	N	Follow-Up, PY	Median [95% CI]	10-year OS	20-year OS	HR	95% CI	P
Whole Cohort	875	7882	19.7 [16.8, 23.9]	74 [70, 77]	49 [44, 55]			
Age, years								
< 60	493	4882	26.51 [23.03, 40.23+]	81 [77, 85]	60 [53, 67]	1.0 (ref)	-	
60+	382	2999	14.25 [12.08, 16.04]	64 [58, 70]	32 [24, 43]	2.08	[1.62, 2.68]	< 0.0001
Gender								
Female	409	3894	26.51 [21.4, 40.23+]	76 [71, 81]	60 [53, 68]	1.0 (ref)	-	
Male	466	3987	15.98 [14.56, 18.96]	72 [67, 77]	38 [30, 48]	1.46	[1.14, 1.89]	0.003
Tumor Size								
< 2cm	326	3222	27.05 [22.46, 40.23+]	88 [84, 92]	66 [57, 77]	1.0 (ref)	-	
2cm +	549	4659	14.88 [12.55, 18.07]	65 [61, 70]	40 [34, 47]	2.88	[2.1, 3.93]	< 0.0001
T Stage								
T1	326	3222	27.05 [22.46, 40.23+]	88 [84, 92]	66 [57, 77]	1.0 (ref)	-	
T2	319	2793	18.07 [15.45, 40.23+]	72 [66, 78]	48 [40, 58]	2.27	[1.61, 3.21]	< 0.0001
T3	208	1730	12.08 [10.17, 15.06]	58 [51, 66]	31 [23, 43]	3.68	[2.6, 5.2]	< 0.0001
T4	22	134	9.88 [6.9, 40.23+]	46 [26, 81]	0 [5, 81]	5.81	[3.01, 11.21]	< 0.0001
N Stage								
N0	536	4988	23.03 [21.16, 40.23+]	81 [77, 85]	58 [50, 67]	1.0 (ref)	-	
Nx or Unknown	78	869	31.23 [26.51, 40.23+]	90 [82, 99]	78 [66, 93]	0.54	[0.29, 1.01]	0.05
N1	261	2023	10.49 [8.94, 12.38]	54 [48, 62]	25 [18, 34]	3	[2.32, 3.86]	< 0.0001
M Stage								
M0	767	7235	22.46 [19.66, 27.05]	80 [76, 83]	54 [48, 61]	1.0 (ref)	-	
M1	108	646	6.61 [5.09, 8.94]	35 [26, 47]	15 [8, 30]	4.71	[3.53, 6.28]	< 0.0001
Ki-67								
< 2	279	2947	22.46 [19.66, 32.15+]	81 [76, 86]	55 [47, 66]	1.0 (ref)	-	
2+	514	3858	15.45 [12.97, 21.16]	69 [64, 74]	40 [31, 50]	1.74	[1.31, 2.3]	0.0001
Grade								
G1	448	4383	23.03 [19.66, 32.15+]	81 [77, 86]	55 [48, 64]	1.0 (ref)	-	
G2	321	2325	12.97 [12.08, 18.07]	64 [58, 71]	35 [25, 48]	2.07	[1.57, 2.72]	< 0.0001
G3	24	96	3.04 [1.67, 32.15+]	23 [8, 61]	23 [8, 61]	9.31	[5.42, 15.99]	< 0.0001
Grade, Proposed								
G1	448	4383	23.03 [19.66, 32.15+]	81 [77, 86]	55 [48, 64]	1.0 (ref)	-	
G2a	270	2060	16.81 [12.38, 21.4]	68 [61, 76]	38 [28, 52]	1.78	[1.33, 2.39]	0.0001
G2b	51	264	7.88 [5.93, 32.15+]	44 [29, 66]	11 [2, 63]	5.09	[3.21, 8.06]	< 0.0001
G3	24	96	3.04 [1.67, 32.15+]	23 [8, 61]	23 [8, 61]	9.7	[5.64, 16.7]	< 0.0001

Insulinoma								
No	781	6923	17.89 [15.45, 21.52]	72 [68, 76]	45 [39, 52]	1.0 (ref)	-	
Yes	94	957	27.05 [23.03, 40.23+]	92 [85, 99]	80 [69, 94]	0.34	[0.19, 0.62]	0.0003
Sclerosing Variant								
No	824	7423	18.96 [16.65, 23.03]	73 [69, 77]	48 [43, 54]	1.0 (ref)	-	
Yes	51	458	31.23 [14.56, 40.23+]	91 [83, 100]	72 [50, 100]	0.47	[0.22, 1]	0.05
Cystic Variant								
No	786	7018	18.14 [15.63, 23.89]	72 [69, 76]	48 [42, 54]	1.0 (ref)	-	
Yes	89	863	NR	86 [78, 94]	64 [48, 85]	0.61	[0.38, 0.99]	0.05
Vascular Invasion								
No	646	6288	23.03 [19.69, 40.23+]	80 [76, 83]	56 [50, 63]	1.0 (ref)	-	
Yes	211	1316	10.28 [8.26, 14.25]	51 [43, 60]	19 [10, 35]	3	[2.31, 3.91]	< 0.0001
Perineural Invasion								
No	577	5526	23.89 [21.52, 40.23+]	80 [76, 84]	58 [51, 65]	1.0 (ref)	-	
Yes	286	2150	12.18 [10.42, 15.45]	61 [54, 68]	26 [17, 40]	2.42	[1.88, 3.12]	< 0.0001
Margins								
Negative	787	7130	21.4 [18.07, 27.05]	76 [72, 80]	52 [46, 59]	1.0 (ref)	-	
Positive	82	661	11.02 [8.48, 15.48]	52 [41, 66]	27 [17, 45]	2.18	[1.56, 3.04]	< 0.0001
Margins*								
Negative	744	6755	19.69 [17.24, 23.9]	75 [72, 79]	50 [43, 57]	1.0 (ref)	-	
Positive	56	390	8.68 [5.59, 12.08]	39 [26, 57]	15 [6, 35]	3.1	[2.18, 4.43]	< 0.0001

*Excludes patients who had an enucleation procedure. Abbreviations: Median survival is shown in 10- and 20-year OS are the respective survival probabilities from the Kaplan-Meier estimate for each subgroup, HR=Hazard Ratio, estimated from univariate Cox proportional hazards regression models, NR=Median survival not reached Median OS is shown in years, OS=Overall survival; Calculated from the date of surgery to last follow-up or death, PY=Person-years.

Table 3: Overall Survival in Patients with T1N0M0 Disease: Estimates of survival after surgery for patients with M0, N0, and T1 disease, overall and according to patient subgroups defined at the time of surgery.

	N	Follow-Up, PY	Median [95% CI]	10-year OS	20-year OS	HR	95% CI	P
Whole Cohort	251	2443	27 [22.5, 36.78+]	88 [83, 93]	65 [52, 80]			
Age, years								
< 60	143	1504	27.05 [23.03, 36.78+]	93 [89, 98]	69 [54, 90]	1.0 (ref)	-	
60+	108	938	22.46 [15.63, 36.78+]	79 [70, 90]	58 [41, 82]	2.63	[1.34, 5.15]	0.005
Gender								
Female	129	1254	NR	87 [80, 94]	64 [47, 87]	1.0 (ref)	-	
Male	122	1189	22.46 [17.02, 36.78+]	89 [82, 96]	65 [50, 86]	1.05	[0.55, 2]	0.89
Ki-67								
< 2	110	1138	23.03 [19.66, 27.05+]	88 [81, 95]	64 [48, 85]	1.0 (ref)	-	
2+	114	918	NR	85 [77, 95]	52 [27, 94]	1.09	[0.52, 2.26]	0.82
Grade								
G1	175	1682	23.03 [22.46, 27.05+]	88 [83, 94]	66 [51, 85]	1.0 (ref)	-	
G2	48	367	17.02 [14.42, 27.05+]	83 [69, 100]	33 [8, 100]	1.38	[0.56, 3.44]	0.49
Grade, Proposed								
G1	175	1682	23.03 [22.46, 27.05+]	88 [83, 94]	66 [51, 85]	1.0 (ref)	-	
G2a	46	360	17.02 [14.42, 27.05+]	89 [75, 100]	35 [8, 100]	0.94	[0.32, 2.76]	0.92
G2b	2	6	3.41 [0.89, 27.05+]	0 [13, 100]	0 [13, 100]	35.66	[7.56, 168.11]	< 0.0001
Insulinoma								
No	216	2021	22.46 [18.14, 36.78+]	86 [80, 92]	55 [39, 77]	1.0 (ref)	-	
Yes	35	422	27.05 [23.03, 36.78+]	100 [100, 100]	94 [83, 100]	0.22	[0.05, 0.93]	0.04
Sclerosing Variant								
No	214	2120	23.03 [22.46, 36.78+]	87 [82, 93]	64 [51, 80]	1.0 (ref)	-	
Yes	37	322	NR	91 [82, 100]	80 [60, 100]	0.92	[0.32, 2.61]	0.88
Cystic Variant								
No	219	2099	23.03 [22.46, 36.78+]	89 [83, 94]	64 [51, 82]	1.0 (ref)	-	
Yes	32	343	NR	82 [68, 98]	69 [52, 93]	1.4	[0.61, 3.2]	0.42
Vascular Invasion								
No	231	2240	23.03 [22.46, 31.52+]	88 [83, 94]	65 [51, 82]	1.0 (ref)	-	
Yes	12	64	NR	55 [26, 100]	55 [26, 100]	5.7	[1.65, 19.78]	0.006

Perineural Invasion								
No	200	1896	23.03 [22.46, 31.52+]	86 [80, 92]	64 [50, 83]	1.0 (ref)	-	
Yes	44	417	NR	91 [83, 100]	57 [33, 97]	1.13	[0.49, 2.6]	0.77
Margins								
Negative	242	2367	23.03 [22.46, 36.78+]	89 [84, 94]	65 [52, 81]	1.0 (ref)	-	
Positive	8	44	9.22 [5.59, 36.78+]	33 [7, 100]	33 [7, 100]	6.62	[1.98, 22.07]	0.002
Margins*								
Negative	233	2295	23.03 [22.46, 36.78+]	89 [84, 94]	64 [51, 80]	1.0 (ref)	-	
Positive	4	19	5.59 [0.89, 36.78+]	0 [8, 100]	0 [8, 100]	19.15	[5.49, 66.78]	< 0.0001

*Excludes patients who had an enucleation procedure. Abbreviations: Median survival is in years 10-and 20-year OS are the respective survival probabilities from the Kaplan-Meier estimate for each subgroup, HR=Hazard Ratio, estimated from univariate Cox proportional hazards regression models, NR=Median survival not reached Median OS is shown in years, OS=Overall survival; Calculated from the date of surgery to last follow-up or death, PY=Person-years.

Table 4: Cumulative Incidence of Relapse: Estimates of cumulative probability of relapse at 2, 5 and 10 years after surgery, accounting for death before relapse as a competing event, for the M0 cohort and according to patient subgroups defined at the time of surgery.

	N	N Relapses	N Deaths	CIR, 2y	CIR, 5y	CIR, 10y	HR (95% CI)	P
Whole Cohort	767	154	91	0.07 (0.05, 0.08)	0.17 (0.14, 0.2)	0.23 (0.19, 0.26)		
Age, years								
< 60	409	88	35	0.06 (0.04, 0.08)	0.17 (0.13, 0.21)	0.23 (0.19, 0.28)	1.0 (ref)	
60+	314	66	56	0.07 (0.04, 0.1)	0.18 (0.13, 0.22)	0.22 (0.17, 0.27)	1.01 (0.74, 1.39)	0.93
Gender								
Female	349	73	36	0.06 (0.03, 0.09)	0.17 (0.12, 0.21)	0.22 (0.17, 0.27)	1.0 (ref)	
Male	374	81	55	0.07 (0.04, 0.1)	0.18 (0.14, 0.22)	0.24 (0.19, 0.28)	1.06 (0.78, 1.46)	0.7
Tumor Size								
< 2cm	308	20	37	0.01 (0, 0.02)	0.05 (0.02, 0.07)	0.07 (0.04, 0.1)	1.0 (ref)	
2cm +	415	134	54	0.11 (0.08, 0.14)	0.27 (0.22, 0.32)	0.35 (0.3, 0.4)	6.19 (3.9, 9.85)	< 0.001
T Stage								
T1	308	20	37	0.01 (0, 0.02)	0.05 (0.02, 0.07)	0.07 (0.04, 0.1)	1.0 (ref)	
T2	265	69	35	0.08 (0.05, 0.12)	0.22 (0.16, 0.27)	0.29 (0.23, 0.35)	4.87 (2.98, 7.95)	< 0.001
T3	139	60	17	0.16 (0.09, 0.22)	0.34 (0.26, 0.43)	0.45 (0.36, 0.54)	8.66 (5.24, 14.31)	< 0.001
T4	11	5	2	0.1 (0, 0.3)	0.51 (0.17, 0.84)	0.51 (0.17, 0.84)	9.97 (3.73, 26.66)	< 0.001
N Stage								
N0	481	71	57	0.03 (0.01, 0.05)	0.11 (0.08, 0.14)	0.16 (0.13, 0.2)	1.0 (ref)	
Nx or Unknown	70	2	8	0 (0, 0)	0 (0, 0)	0.02 (0, 0.06)	0.18 (0.05, 0.71)	0.01
N1	172	81	26	0.19 (0.13, 0.25)	0.41 (0.33, 0.48)	0.49 (0.4, 0.57)	4.1 (2.99, 5.64)	< 0.001
Ki-67								
< 2	243	23	42	0.03 (0.01, 0.05)	0.05 (0.02, 0.08)	0.1 (0.06, 0.14)	1.0 (ref)	
2+	416	118	39	0.08 (0.06, 0.11)	0.25 (0.21, 0.3)	0.32 (0.27, 0.38)	4.14 (2.65, 6.48)	< 0.001
Grade								
G1	397	44	51	0.03 (0.01, 0.05)	0.08 (0.05, 0.11)	0.11 (0.08, 0.14)	1.0 (ref)	
G2	246	86	26	0.1 (0.06, 0.14)	0.31 (0.24, 0.37)	0.44 (0.36, 0.51)	4.5 (3.13, 6.48)	< 0.001
G3	16	11	4	0.25 (0.03, 0.47)	0.69 (0.44, 0.94)	0.69 (0.44, 0.94)	11 (5.24, 23.07)	< 0.001
Grade, Proposed								
G1	397	44	51	0.03 (0.01, 0.05)	0.08 (0.05, 0.11)	0.11 (0.08, 0.14)	1.0 (ref)	
G2a	213	65	24	0.08 (0.04, 0.12)	0.25 (0.19, 0.32)	0.39 (0.31, 0.47)	3.81 (2.6, 5.58)	< 0.001
G2b	33	21	2	0.23 (0.08, 0.38)	0.62 (0.43, 0.8)	0.75 (0.53, 0.97)	10.82 (6.37, 18.36)	< 0.001
G3	16	11	4	0.25 (0.03, 0.47)	0.69 (0.44, 0.94)	0.69 (0.44, 0.94)	11.07 (5.25, 23.35)	< 0.001

Insulinoma								
No	642	149	83	0.07 (0.05, 0.09)	0.18 (0.15, 0.22)	0.24 (0.21, 0.28)	1.0 (ref)	
Yes	81	5	8	0.01 (0, 0.04)	0.07 (0, 0.13)	0.09 (0.01, 0.16)	0.26 (0.11, 0.63)	0.003
Sclerosing Variant								
No	677	151	86	0.07 (0.05, 0.09)	0.18 (0.15, 0.21)	0.24 (0.2, 0.27)	1.0 (ref)	
Yes	46	3	5	0 (0, 0)	0.05 (0, 0.11)	0.08 (0, 0.18)	0.27 (0.09, 0.84)	0.02
Cystic Variant								
No	642	148	81	0.07 (0.05, 0.09)	0.19 (0.16, 0.22)	0.25 (0.21, 0.29)	1.0 (ref)	
Yes	81	6	10	0.01 (0, 0.04)	0.04 (0, 0.09)	0.06 (0, 0.12)	0.29 (0.13, 0.65)	0.003
Vascular Invasion								
No	558	86	69	0.03 (0.02, 0.05)	0.1 (0.08, 0.13)	0.16 (0.12, 0.19)	1.0 (ref)	
Yes	151	65	20	0.18 (0.12, 0.25)	0.45 (0.36, 0.54)	0.53 (0.43, 0.62)	4.41 (3.18, 6.12)	< 0.001
Perineural Invasion								
No	500	73	61	0.03 (0.02, 0.05)	0.11 (0.08, 0.14)	0.16 (0.12, 0.19)	1.0 (ref)	
Yes	211	80	29	0.14 (0.09, 0.19)	0.33 (0.26, 0.4)	0.4 (0.33, 0.48)	3.17 (2.31, 4.35)	< 0.001
Margins								
Negative	662	137	78	0.06 (0.04, 0.08)	0.17 (0.14, 0.2)	0.22 (0.19, 0.26)	1.0 (ref)	
Positive	55	16	12	0.13 (0.04, 0.23)	0.26 (0.14, 0.38)	0.31 (0.18, 0.45)	1.47 (0.85, 2.54)	0.17
Margins*								
Negative	619	137	76	0.06 (0.04, 0.08)	0.18 (0.14, 0.21)	0.23 (0.2, 0.27)	1.0 (ref)	
Positive	30	15	7	0.21 (0.06, 0.36)	0.42 (0.24, 0.61)	0.51 (0.31, 0.71)	2.78 (1.58, 4.88)	< 0.001

*Excludes patients who had an enucleation procedure. Abbreviations: CIR = Cumulative Incidence of Relapse; Calculated from the date of surgery to last follow-up, date of relapse or death HR =Hazard Ratio, estimated from univariate competing risks regression models.

Supplemental Table 1: Overall Survival, Patients with M0 Disease: Estimates of survival after surgery for patients with M0 disease, overall and according to patient subgroups defined at the time of surgery.

	N	Follow-Up, PY	Median [95% CI]	10-year OS	20-year OS	HR	95% CI	P
Whole Cohort	767	7235	22.5 [19.7, 31.2]	80 [76, 83]	54 [48, 61]			
Age, years								
< 60	428	4473	27.05 [23.89, 40.23+]	87 [83, 91]	65 [58, 73]	1.0 (ref)	-	
60+	339	2762	15.63 [13.77, 19.69]	69 [63, 76]	36 [27, 49]	2.36	[1.75, 3.18]	< 0.0001
Gender								
Female	367	3603	26.51 [23.03, 40.23+]	80 [75, 85]	65 [58, 73]	1.0 (ref)	-	
Male	400	3631	17.89 [15.63, 23.89]	80 [75, 84]	43 [34, 54]	1.44	[1.07, 1.93]	0.02
Tumor Size								
< 2cm	322	3193	27.05 [23.03, 40.23+]	88 [84, 93]	67 [57, 78]	1.0 (ref)	-	
2cm +	445	4042	18.07 [15.1, 23.89]	73 [68, 78]	46 [39, 54]	2.28	[1.64, 3.18]	< 0.0001
T Stage								
T1	322	3193	27.05 [23.03, 40.23+]	88 [84, 93]	67 [57, 78]	1.0 (ref)	-	
T2	280	2557	21.16 [17.24, 40.23+]	77 [71, 83]	52 [43, 63]	1.95	[1.35, 2.81]	0.0003
T3	152	1399	15.06 [12.16, 40.23+]	69 [61, 78]	39 [28, 53]	2.73	[1.85, 4.03]	< 0.0001
T4	13	85	9.88 [6.9, 40.23+]	45 [21, 98]	0 [21, 98]	5.4	[2.3, 12.68]	0.0001
N Stage								
N0	507	4813	23.03 [21.16, 40.23+]	83 [79, 87]	59 [51, 69]	1.0 (ref)	-	
Nx or Unknown	75	860	31.23 [26.51, 40.23+]	93 [86, 100]	81 [68, 95]	0.48	[0.24, 0.95]	0.03
N1	185	1561	12.97 [11.81, 15.98]	63 [56, 72]	31 [22, 43]	2.6	[1.93, 3.5]	< 0.0001
Ki-67								
< 2	261	2811	23.03 [19.69, 32.15+]	84 [79, 89]	58 [49, 69]	1.0 (ref)	-	
2+	432	3393	17.24 [15.45, 32.15+]	76 [71, 81]	45 [35, 57]	1.55	[1.12, 2.14]	0.007
Grade								
G1	423	4202	23.03 [19.69, 32.15+]	84 [80, 88]	58 [50, 67]	1.0 (ref)	-	
G2	254	1917	17.02 [12.97, 23.89]	72 [65, 80]	40 [28, 55]	1.8	[1.31, 2.48]	0.0003
G3	16	84	7.24 [2.84, 32.15+]	32 [12, 82]	32 [12, 82]	7.2	[3.57, 14.53]	< 0.0001
Grade, Proposed								
G1	423	4202	23.03 [19.69, 32.15+]	84 [80, 88]	58 [50, 67]	1.0 (ref)	-	
G2a	221	1720	17.24 [14.42, 23.9]	75 [67, 83]	43 [31, 60]	1.62	[1.15, 2.27]	0.006
G2b	33	197	10.28 [7.88, 32.15+]	56 [37, 85]	14 [2, 80]	4.02	[2.17, 7.46]	< 0.0001
G3	16	84	7.24 [2.84, 32.15+]	32 [12, 82]	32 [12, 82]	7.41	[3.66, 14.97]	< 0.0001
Insulinoma								
No	677	6301	21.16 [17.89, 40.23+]	78 [74, 82]	50 [44, 58]	1.0 (ref)	-	

Yes	90	933	27.05 [23.03, 40.23+]	94 [88, 100]	82 [71, 96]	0.36	[0.19, 0.68]	0.002
Sclerosing Variant								
No	718	6786	21.52 [18.96, 27.05]	79 [75, 83]	53 [47, 60]	1.0 (ref)	-	
Yes	49	449	31.23 [14.56, 40.23+]	91 [83, 100]	71 [50, 100]	0.62	[0.29, 1.33]	0.22
Cystic Variant								
No	681	6401	21.4 [18.07, 27.05]	79 [75, 82]	52 [46, 60]	1.0 (ref)	-	
Yes	86	833	NR	87 [79, 95]	68 [52, 89]	0.67	[0.39, 1.13]	0.13
Vascular Invasion								
No	594	5900	23.9 [22.46, 40.23+]	83 [79, 86]	60 [53, 67]	1.0 (ref)	-	
Yes	157	1062	14.25 [10.91, 17.24]	63 [53, 74]	22 [11, 43]	2.73	[1.98, 3.76]	< 0.0001
Perineural Invasion								
No	534	5242	23.9 [22.46, 40.23+]	83 [79, 87]	61 [54, 69]	1.0 (ref)	-	
Yes	221	1787	15.1 [12.18, 18.22]	70 [63, 78]	31 [21, 48]	2.32	[1.73, 3.12]	< 0.0001
Margins								
Negative	700	6567	23.03 [21.16, 40.23+]	81 [77, 84]	57 [51, 64]	1.0 (ref)	-	
Positive	61	577	12.55 [11.02, 40.23+]	64 [51, 80]	32 [19, 53]	2.01	[1.34, 3]	0.0007
Margins*								
Negative	657	6192	22.46 [19.66, 40.23+]	80 [77, 84]	54 [48, 62]	1.0 (ref)	-	
Positive	36	310	9.88 [8.26, 16.65]	49 [34, 72]	16 [6, 43]	3.03	[1.95, 4.71]	< 0.0001

*Excludes patients who had an enucleation procedure. Abbreviations: Median survival is in years, 10- and 20-year OS are the respective survival probabilities from the Kaplan-Meier estimate for each subgroup, HR=Hazard Ratio, estimated from univariate Cox proportional hazards regression models, CSS=Cause-specific survival, Calculated from the date of surgery to last follow-up-or death, NR=Median survival not reached Median OS is shown in years, OS=Overall survival; Calculated from the date of surgery to last follow-up or death, PY=Person-years.

Supplemental Table 2: Overall Survival, Patients with M0 and N0 Disease: Estimates of survival after surgery for patients with M0 and N0 disease, overall and according to patient subgroups defined at the time of surgery.

	N	Follow-Up, PY	Median [95% CI]	10-year OS	20-year OS	HR	95% CI	P
Whole Cohort	507	4814	23 [21.2, 36.78+]	83 [79, 87]	59 [51, 69]			
Age, years								
< 60	286	2949	NR	90 [86, 95]	70 [60, 82]	1.0 (ref)	-	
60+	221	1864	16.81 [14.51, 22.46]	74 [67, 82]	42 [29, 60]	2.78	[1.83, 4.22]	< 0.0001
Gender								
Female	249	2387	NR	83 [77, 89]	67 [57, 79]	1.0 (ref)	-	
Male	258	2426	21.52 [17.89, 36.78+]	84 [79, 90]	51 [39, 66]	1.24	[0.83, 1.86]	0.3
Tumor Size								
< 2cm	251	2443	23.03 [22.46, 36.78+]	88 [83, 93]	65 [52, 80]	1.0 (ref)	-	
2cm +	256	2370	21.52 [18.07, 36.78+]	79 [73, 85]	54 [44, 67]	1.58	[1.05, 2.39]	0.03
T Stage								
T1	251	2443	23.03 [22.46, 36.78+]	88 [83, 93]	65 [52, 80]	1.0 (ref)	-	
T2	170	1542	21.52 [18.07, 36.78+]	82 [75, 90]	55 [41, 74]	1.38	[0.86, 2.21]	0.18
T3	81	794	NR	74 [64, 86]	54 [40, 72]	1.88	[1.11, 3.16]	0.02
T4	5	33	14.75 [6.9, 36.78+]	67 [30, 100]	0 [30, 100]	4.53	[1.09, 18.85]	0.04
Ki-67								
< 2	185	1981	23.03 [21.52, 32+]	86 [81, 92]	62 [51, 77]	1.0 (ref)	-	
2+	273	2152	18.07 [14.75, 32+]	81 [75, 87]	45 [30, 67]	1.51	[0.97, 2.35]	0.07
Grade								
G1	305	2977	23.03 [21.52, 32+]	86 [81, 91]	63 [52, 75]	1.0 (ref)	-	
G2	146	1106	16.81 [14.25, 32+]	79 [70, 89]	33 [17, 65]	1.74	[1.1, 2.75]	0.02
G3	7	49	8.68 [7.24, 32+]	34 [8, 100]	34 [8, 100]	5.28	[1.61, 17.3]	0.006
Grade, Proposed								
G1	305	2977	23.03 [21.52, 32+]	86 [81, 91]	63 [52, 75]	1.0 (ref)	-	
G2a	129	1004	17.02 [14.42, 32+]	84 [75, 93]	38 [19, 73]	1.37	[0.83, 2.29]	0.22
G2b	17	102	8.54 [5.93, 32+]	47 [25, 90]	16 [3, 88]	6.42	[2.99, 13.78]	< 0.0001
G3	7	49	8.68 [7.24, 32+]	34 [8, 100]	34 [8, 100]	5.48	[1.67, 18]	0.005
Insulinoma								
No	456	4269	22.46 [19.66, 36.78+]	82 [78, 87]	55 [46, 66]	1.0 (ref)	-	
Yes	51	543	27.05 [23.03, 36.78+]	92 [83, 100]	88 [76, 100]	0.39	[0.16, 0.97]	0.04
Sclerosing Variant								
No	467	4462	23.03 [21.16, 36.78+]	83 [79, 87]	58 [50, 68]	1.0 (ref)	-	

Yes	40	351	NR	91 [83, 100]	81 [63, 100]	0.61	[0.22, 1.67]	0.34
Cystic Variant								
No	436	4102	23.03 [19.66, 36.78+]	83 [78, 87]	58 [49, 68]	1.0 (ref)	-	
Yes	71	711	NR	87 [78, 97]	68 [50, 92]	0.78	[0.43, 1.43]	0.42
Vascular Invasion								
No	428	4154	23.03 [21.52, 32+]	84 [80, 89]	60 [51, 71]	1.0 (ref)	-	
Yes	68	452	14.75 [14.25, 32+]	69 [54, 88]	46 [25, 85]	1.92	[1.08, 3.4]	0.03
Perineural Invasion								
No	390	3699	23.9 [21.52, 32+]	84 [79, 89]	60 [51, 71]	1.0 (ref)	-	
Yes	108	964	21.16 [17.02, 32+]	81 [72, 90]	56 [41, 78]	1.45	[0.9, 2.31]	0.12
Margins								
Negative	483	4625	23.9 [21.16, 36.78+]	85 [81, 89]	61 [52, 70]	1.0 (ref)	-	
Positive	22	151	9.22 [7.49, 36.78+]	50 [28, 87]	25 [8, 77]	3.94	[1.97, 7.89]	0.0001
Margins*								
Negative	469	4510	23.03 [21.16, 36.78+]	84 [80, 88]	60 [51, 70]	1.0 (ref)	-	
Positive	16	115	9.22 [6.9, 36.78+]	46 [23, 90]	15 [3, 87]	4.43	[2.13, 9.2]	< 0.0001

*Excludes patients who had an enucleation procedure. Abbreviations: Median survival is in years, 10- and 20-year OS are the respective survival probabilities from the Kaplan-Meier estimate for each subgroup, HR=Hazard Ratio, estimated from univariate Cox proportional hazards regression models, CSS=Cause-specific survival, Calculated from the date of surgery to last follow-up-or death, NR=Median survival not reached Median OS is shown in years, OS=Overall survival; Calculated from the date of surgery to last follow-up or death, PY=Person-years.

Supplemental Table 3: Multivariable Models for Overall Survival: Estimated hazard ratios from multivariable models for overall survival, among patients alive at 30 days after surgery.

	Whole Cohort		M0 Cohort		N0, M0 Cohort		T1, N0, M0 Cohort	
	HR [95% CI]	**P**	**HR [95% CI]**	**P**	**HR [95% CI]**	**P**	**HR [95% CI]**	**P**
Age (per 5y)	1.26 [1.2, 1.32]	< 0.001	1.26 [1.23, 3.04]	< 0.001	1.3 [1.2, 1.4]	1.4E-08	1.38 [1.18, 1.59]	< 0.001
Gender (M v F)	1.25 [0.39, 1.52]	0.46						
Year of Surgery (per 1y)	0.96 [0.93, 0.97]	< 0.001	0.95 [0.95, 1.3]	0.616	0.95 [0.93, 0.99]	0.013	0.97 [0.91, 1.25]	0.556
Tumor Size (per 1 cm)	1.04 [1.01, 1.12]	0.023	1.05 [1.07, 6.31]	0.003	1.08 [1.01, 1.14]	0.023		
Ki-67	1.06 [1.04, 1.09]	< 0.001	1.05 [1.1, Inf]	< 0.001	1.05 [1.03, 1.08]	0.00014	1.15 [1.08, 1.23]	< 0.001
Insulinoma Sclerosing Variant Cystic Variant Vascular Invasion	1.31 [0.79, 1.96]	0.174	1.31 [0, 0.03]	0.995				
Perineural Invasion	1.62 [1.24, 2.09]	0.002	1.67 [2.82, Inf]	< 0.001				
Positive Margins	1.39 [0.01, 1.72]	0.755						
T2 v T1 T3 v T1 T4 v T1								
N1 v N0	1.56 [1.19, 2.02]	0.005	1.5 [2.47, Inf]	0.003				
M1 v M0	2.46 [1.85, 3.3]	< 0.001						

Variables were selected using a LASSO (Least Absolute Shrinkage and Selection Operator) method. LASSO is a regularization technique that enhances model accuracy and interpretability by applying a penalty factor to the regression coefficients. It performs both variable selection and shrinkage, reducing some coefficients to zero and improving model generalization by controlling overfitting. The method involves selecting an optimal penalty factor through cross-validation. All variables shown in the table were offered as candidates to the model selection, and those shown with hazard ratios were selected by the LASSO approach. Estimates, confidence intervals, and p-values were bias-corrected using the selective Inference package in R.

Supplemental Table 4: Cause-Specific Survival, Patients with M0 Disease: Estimates of survival after surgery for patients with M0 disease, overall and according to patient subgroups defined at the time of surgery.

	N	Follow-Up, PY	Median [95% CI]	10-year CSS	20-year CSS	HR	95% CI	P
Whole Cohort	767	7235	NR	91 [89, 94]	80 [75, 86]			
Age, years								
< 60	428	4473	NR	93 [90, 96]	79 [73, 86]	1.0 (ref)	-	
60+	339	2762	NR	89 [85, 93]	84 [78, 91]	1.29	[0.79, 2.11]	0.31
Gender								
Female	367	3603	NR	91 [87, 94]	85 [80, 91]	1.0 (ref)	-	
Male	400	3631	NR	92 [88, 95]	73 [64, 84]	1.3	[0.8, 2.1]	0.3
Tumor Size								
< 2cm	322	3193	NR	98 [96, 100]	96 [93, 100]	1.0 (ref)	-	
2cm +	445	4042	NR	86 [82, 90]	69 [62, 78]	9.84	[3.96, 24.48]	< 0.0001
T Stage								
T1	322	3193	NR	98 [96, 100]	96 [93, 100]	1.0 (ref)	-	
T2	280	2557	NR	89 [85, 94]	77 [68, 86]	7.37	[2.86, 19.01]	< 0.0001
T3	152	1399	23.89 [18.96, 40.23+]	80 [72, 88]	59 [46, 75]	14.09	[5.47, 36.32]	< 0.0001
T4	13	85	14.75 [NA, 40.23+]	80 [52, 100]	0 [52, 100]	17.62	[3.41, 91.09]	0.0006
N Stage								
N0	507	4813	NR	95 [93, 98]	90 [85, 95]	1.0 (ref)	-	
Nx or Unknown	75	860	NR	100 [100, 100]	100 [100, 100]	0	[0, Inf]	0.99
N1	185	1561	18.96 [15.1, 40.23+]	75 [67, 84]	49 [37, 65]	5.59	[3.39, 9.22]	< 0.0001
Ki-67								
< 2	261	2811	NR	97 [94, 100]	93 [88, 98]	1.0 (ref)	-	
2+	432	3393	23.89 [21.16, 32.15+]	86 [81, 90]	64 [53, 77]	5.42	[2.66, 11.04]	< 0.0001
Grade								
G1	423	4202	NR	95 [92, 97]	88 [82, 94]	1.0 (ref)	-	
G2	254	1917	23.89 [18.96, 32.15+]	84 [78, 91]	61 [48, 78]	3.78	[2.22, 6.44]	< 0.0001
G3	16	84	8.68 [4.05, 32.15+]	47 [20, 100]	47 [20, 100]	14.11	[5.22, 38.16]	< 0.0001
Grade, Proposed								
G1	423	4202	NR	95 [92, 97]	88 [82, 94]	1.0 (ref)	-	
G2a	221	1720	23.89 [21.16, 32.15+]	88 [82, 94]	67 [53, 85]	3.03	[1.71, 5.35]	0.0001
G2b	33	197	10.28 [8.54, 32.15+]	61 [41, 91]	15 [3, 87]	12.39	[5.7, 26.96]	< 0.0001
G3	16	84	8.68 [4.05, 32.15+]	47 [20, 100]	47 [20, 100]	15.12	[5.55, 41.16]	< 0.0001
Insulinoma								

No	677	6301	NR	90 [88, 93]	77 [71, 84]	1.0 (ref)	-	
Yes	90	933	NR	97 [93, 100]	97 [93, 100]	0.1	[0.01, 0.76]	0.03
Sclerosing Variant								
No	718	6786	NR	91 [88, 93]	80 [74, 85]	1.0 (ref)	-	
Yes	49	449	NR	100 [100, 100]	86 [63, 100]	0.24	[0.03, 1.71]	0.15
Cystic Variant								
No	681	6401	NR	90 [88, 93]	78 [72, 84]	1.0 (ref)	-	
Yes	86	833	NR	97 [92, 100]	97 [92, 100]	0.23	[0.06, 0.94]	0.04
Vascular Invasion								
No	594	5900	NR	94 [92, 96]	87 [82, 92]	1.0 (ref)	-	
Yes	157	1062	17.24 [14.25, 40.23+]	75 [65, 85]	38 [22, 66]	5.33	[3.28, 8.65]	< 0.0001
Perineural Invasion								
No	534	5242	NR	96 [93, 98]	89 [85, 94]	1.0 (ref)	-	
Yes	221	1787	21.16 [17.24, 40.23+]	80 [74, 87]	52 [38, 71]	4.97	[3.01, 8.2]	< 0.0001
Margins								
Negative	700	6567	NR	92 [89, 94]	81 [76, 87]	1.0 (ref)	-	
Positive	61	577	23.89 [15.48, 40.23+]	84 [73, 97]	64 [47, 88]	2.26	[1.18, 4.31]	0.01
Margins*								
Negative	657	6192	NR	91 [89, 94]	80 [74, 86]	1.0 (ref)	-	
Positive	36	310	12.55 [12.03, 40.23+]	71 [53, 95]	35 [17, 75]	4.42	[2.31, 8.46]	< 0.0001

*Excludes patients who had an enucleation procedure. Patients who died after relapse were considered to have died of their disease. All other deaths were censored.
Abbreviations: Median survival is in years, 10-and 20-year OS are the respective survival probabilities from the Kaplan-Meier estimate for each subgroup, HR=Hazard Ratio, estimated from univariate Cox proportional hazards regression models, CSS=Cause-specific survival, Calculated from the date of surgery to last follow-up-or death, NR=Median survival not reached Median OS is shown in years, OS=Overall survival; Calculated from the date of surgery to last follow-up or death, PY=Person-years.

Supplemental Table 5: Cause-Specific Survival, Patients with M0 and N0 Disease: Estimates of survival after surgery for patients with M0 and N0 disease, overall and according to patient subgroups defined at the time of surgery.

	N	Follow-Up, PY	Median [95% CI]	10-year CSS	20-year CSS	HR	95% CI	P
Whole Cohort	507	4814	NR	95 [93, 98]	90 [85, 95]			
Age, years								
< 60	286	2949	NR	95 [92, 98]	90 [84, 96]	1.0 (ref)	-	
60+	221	1864	23.9 [21.16, 36.78+]	96 [92, 99]	89 [81, 99]	1.3	[0.57, 2.95]	0.53
Gender								
Female	249	2387	NR	96 [92, 99]	91 [84, 97]	1.0 (ref)	-	
Male	258	2426	NR	95 [92, 99]	89 [82, 96]	1.08	[0.48, 2.42]	0.86
Tumor Size								
< 2cm	251	2443	NR	99 [97, 100]	96 [92, 100]	1.0 (ref)	-	
2cm +	256	2370	NR	91 [87, 96]	83 [75, 91]	7.18	[2.14, 24.12]	0.001
T Stage								
T1	251	2443	NR	99 [97, 100]	96 [92, 100]	1.0 (ref)	-	
T2	170	1542	NR	95 [90, 99]	93 [87, 99]	4.12	[1.09, 15.56]	0.04
T3	81	794	NR	85 [76, 96]	70 [55, 88]	12.65	[3.56, 44.88]	< 0.0001
T4	5	33	14.75 [NA, 36.78+]	100 [100, 100]	0 [100, 100]	23.12	[2.39, 223.36]	0.007
Ki-67								
< 2	185	1981	NR	98 [96, 100]	97 [94, 100]	1.0 (ref)	-	
2+	273	2152	23.9 [21.16, 32+]	92 [87, 96]	74 [60, 90]	7.85	[2.31, 26.7]	0.001
Grade								
G1	305	2977	NR	96 [94, 99]	93 [89, 98]	1.0 (ref)	-	
G2	146	1106	21.16 [21.16, 32+]	92 [86, 99]	70 [53, 92]	3.95	[1.72, 9.07]	0.001
G3	7	49	8.68 [8.68, 32+]	50 [13, 100]	50 [13, 100]	7.86	[0.97, 63.73]	0.05
Grade, Proposed								
G1	305	2977	NR	96 [94, 99]	93 [89, 98]	1.0 (ref)	-	
G2a	129	1004	23.9 [21.16, 32+]	97 [94, 100]	79 [61, 100]	2.36	[0.89, 6.23]	0.08
G2b	17	102	11.35 [7.88, 32+]	56 [31, 100]	19 [3, 100]	25.42	[8.67, 74.58]	< 0.0001
G3	7	49	8.68 [8.68, 32+]	50 [13, 100]	50 [13, 100]	8.88	[1.08, 73.04]	0.04
Insulinoma								
No	456	4269	NR	95 [93, 98]	89 [84, 94]	1.0 (ref)	-	
Yes	51	543	NR	95 [87, 100]	95 [87, 100]	0.36	[0.05, 2.71]	0.32
Sclerosing Variant								
No	467	4462	NR	95 [92, 98]	89 [84, 94]	1.0 (ref)	-	

Yes	40	351	NR	100 [100, 100]	100 [100, 100]	0	[0, Inf]	> 0.99
Cystic Variant								
No	436	4102	NR	95 [92, 98]	88 [82, 94]	1.0 (ref)	-	
Yes	71	711	NR	98 [94, 100]	98 [94, 100]	0.23	[0.03, 1.73]	0.15
Vascular Invasion								
No	428	4154	NR	96 [94, 99]	92 [88, 97]	1.0 (ref)	-	
Yes	68	452	21.16 [14.25, 32+]	83 [70, 99]	56 [31, 99]	5.19	[2.21, 12.19]	0.0002
Perineural Invasion								
No	390	3699	NR	97 [95, 99]	91 [85, 97]	1.0 (ref)	-	
Yes	108	964	NR	91 [84, 98]	85 [75, 96]	2.46	[1.05, 5.77]	0.04
Margins								
Negative	483	4625	NR	96 [94, 98]	90 [86, 95]	1.0 (ref)	-	
Positive	22	151	NR	82 [62, 100]	55 [23, 100]	5.04	[1.48, 17.19]	0.01
Margins*								
Negative	469	4510	NR	96 [93, 98]	90 [85, 95]	1.0 (ref)	-	
Positive	16	115	12.08 [12.08, 36.78+]	77 [52, 100]	38 [9, 100]	6.42	[1.88, 21.88]	0.003

Table 6: Cumulative Incidence of Relapse: Estimates of cumulative probability of relapse at 2, 5 and 10 years after surgery, accounting for death before relapse as a competing event, for the N0M0 cohort and according to patient subgroups defined at the time of surgery.

	N	N Relapses	N Deaths	CIR, 2y	CIR, 5y	CIR, 10y	HR (95% CI)	P
Whole Cohort	507	71	57	0.03 (0.01, 0.05)	0.11 (0.08, 0.14)	0.16 (0.13, 0.2)		
Age, years								
< 60	276	42	22	0.03 (0.01, 0.06)	0.12 (0.08, 0.16)	0.17 (0.12, 0.22)	1.0 (ref)	
60+	205	29	35	0.02 (0, 0.05)	0.1 (0.06, 0.15)	0.15 (0.1, 0.21)	0.94 (0.59, 1.51)	0.81
Gender								
Female	239	35	25	0.03 (0.01, 0.06)	0.11 (0.06, 0.15)	0.16 (0.1, 0.21)	1.0 (ref)	
Male	242	36	32	0.03 (0.01, 0.05)	0.12 (0.08, 0.16)	0.17 (0.12, 0.22)	1 (0.63, 1.58)	0.99
Tumor Size								
< 2cm	241	15	29	0.01 (0, 0.02)	0.05 (0.02, 0.08)	0.06 (0.03, 0.1)	1.0 (ref)	
2cm +	240	56	28	0.05 (0.02, 0.08)	0.18 (0.13, 0.24)	0.27 (0.2, 0.34)	4.54 (2.58, 7.98)	< 0.001
T Stage								
T1	241	15	29	0.01 (0, 0.02)	0.05 (0.02, 0.08)	0.06 (0.03, 0.1)	1.0 (ref)	
T2	160	27	19	0.04 (0.01, 0.07)	0.13 (0.07, 0.19)	0.2 (0.13, 0.28)	3.25 (1.74, 6.07)	< 0.001
T3	75	27	8	0.08 (0.02, 0.14)	0.27 (0.17, 0.38)	0.38 (0.26, 0.5)	7.04 (3.75, 13.22)	< 0.001
T4	5	2	1	0 (0, 0)	0.5 (0, 1.09)		10.14 (2.15, 47.77)	0.003
Ki-67								
< 2	175	11	28	0.02 (0, 0.04)	0.04 (0.01, 0.07)	0.08 (0.03, 0.12)	1.0 (ref)	
2+	264	53	23	0.03 (0.01, 0.05)	0.17 (0.12, 0.22)	0.24 (0.18, 0.3)	4.19 (2.18, 8.06)	< 0.001
Grade								
G1	290	21	34	0.02 (0, 0.04)	0.06 (0.03, 0.08)	0.08 (0.05, 0.12)	1.0 (ref)	
G2	142	38	15	0.04 (0.01, 0.07)	0.21 (0.13, 0.29)	0.35 (0.25, 0.46)	5.05 (2.94, 8.66)	< 0.001
G3	7	5	2	0 (0, 0)	0.71 (0.3, 1.13)		16.35 (5.77, 46.33)	< 0.001
Grade, Proposed								
G1	290	21	34	0.02 (0, 0.04)	0.06 (0.03, 0.08)	0.08 (0.05, 0.12)	1.0 (ref)	
G2a	125	29	13	0.03 (0, 0.05)	0.17 (0.1, 0.25)	0.3 (0.2, 0.41)	4.24 (2.41, 7.47)	< 0.001
G2b	17	9	2	0.13 (0, 0.31)	0.49 (0.21, 0.76)	0.71 (0.37, 1.05)	13.41 (5.97, 30.14)	< 0.001
G3	7	5	2	0 (0, 0)	0.71 (0.3, 1.13)		16.44 (5.77, 46.82)	< 0.001
Insulinoma								
No	436	67	54	0.03 (0.01, 0.05)	0.11 (0.08, 0.14)	0.17 (0.13, 0.21)	1.0 (ref)	
Yes	45	4	3	0.02 (0, 0.07)	0.11 (0.01, 0.22)	0.11 (0.01, 0.22)	0.59 (0.22, 1.63)	0.31
Sclerosing Variant								
No	443	70	53	0.03 (0.02, 0.05)	0.12 (0.09, 0.16)	0.17 (0.13, 0.21)	1.0 (ref)	

Yes	38	1	4	0 (0, 0)	0 (0, 0)	0.04 (0, 0.13)	0.16 (0.02, 1.11)	0.06
Cystic Variant								
No	414	68	49	0.03 (0.02, 0.05)	0.13 (0.09, 0.16)	0.18 (0.14, 0.23)	1.0 (ref)	
Yes	67	3	8	0 (0, 0)	0.02 (0, 0.05)	0.04 (0, 0.09)	0.25 (0.08, 0.77)	0.02
Vascular Invasion								
No	405	45	50	0.01 (0, 0.02)	0.08 (0.05, 0.1)	0.13 (0.09, 0.16)	1.0 (ref)	
Yes	66	24	5	0.15 (0.06, 0.24)	0.37 (0.24, 0.51)	0.43 (0.28, 0.57)	5.29 (3.21, 8.72)	< 0.001
Perineural Invasion								
No	367	43	42	0.03 (0.01, 0.04)	0.09 (0.06, 0.13)	0.13 (0.09, 0.17)	1.0 (ref)	
Yes	105	27	14	0.05 (0.01, 0.09)	0.18 (0.1, 0.26)	0.28 (0.18, 0.37)	2.27 (1.41, 3.67)	< 0.001
Margins								
Negative	457	65	51	0.03 (0.01, 0.04)	0.11 (0.08, 0.14)	0.16 (0.12, 0.19)	1.0 (ref)	
Positive	22	6	6	0.09 (0, 0.21)	0.25 (0.05, 0.45)	0.32 (0.1, 0.54)	2.32 (0.96, 5.63)	0.06
Margins*								
Negative	443	65	51	0.03 (0.01, 0.04)	0.11 (0.08, 0.14)	0.16 (0.12, 0.2)	1.0 (ref)	
Positive	16	5	5	0.06 (0, 0.18)	0.28 (0.04, 0.53)	0.36 (0.09, 0.63)	2.53 (0.97, 6.6)	0.06

*Excludes patients who had an enucleation procedure. Abbreviations: CIR = Cumulative Incidence of Relapse; Calculated from the date of surgery to last follow-up, date of relapse or death HR =Hazard Ratio, estimated from univariate competing risks regression models.

Table 7: Cumulative Incidence of Relapse: Estimates of cumulative probability of relapse at 2, 5 and 10 years after surgery, accounting for death before relapse as a competing event, for the T1N0M0 cohort and according to patient subgroups defined at the time of surgery.

	N	N Relapses	N Deaths	CIR, 2y	CIR, 5y	CIR, 10y	HR (95% CI)	P
Whole Cohort	251	15	29	0.01 (0, 0.02)	0.05 (0.02, 0.08)	0.06 (0.03, 0.1)		
Age, years								
< 60	138	8	14	0.01 (0, 0.02)	0.03 (0, 0.06)	0.06 (0.02, 0.11)	1.0 (ref)	
60+	103	7	15	0.01 (0, 0.03)	0.07 (0.01, 0.12)	0.07 (0.01, 0.12)	1.26 (0.46, 3.45)	0.66
Gender								
Female	126	10	16	0.01 (0, 0.02)	0.06 (0.01, 0.1)	0.08 (0.03, 0.13)	1.0 (ref)	
Male	115	5	13	0.01 (0, 0.03)	0.04 (0, 0.07)	0.05 (0.01, 0.09)	0.53 (0.18, 1.54)	0.24
Ki-67								
< 2	107	4	18	0.02 (0, 0.04)	0.04 (0, 0.08)	0.04 (0, 0.08)	1.0 (ref)	
2+	109	10	8	0 (0, 0)	0.07 (0.02, 0.12)	0.11 (0.04, 0.18)	2.82 (0.85, 9.34)	0.09
Grade								
G1	169	5	21	0.01 (0, 0.03)	0.03 (0, 0.06)	0.03 (0, 0.06)	1.0 (ref)	
G2	46	9	4	0 (0, 0)	0.15 (0.03, 0.28)	0.27 (0.1, 0.44)	8.75 (2.77, 27.6)	< 0.001
Grade, Proposed								
G1	169	5	21	0.01 (0, 0.03)	0.03 (0, 0.06)	0.03 (0, 0.06)	1.0 (ref)	
G2a	44	8	3	0 (0, 0)	0.13 (0.01, 0.26)	0.26 (0.09, 0.43)	8.05 (2.49, 26.02)	< 0.001
G2b	2	1	1	0 (0, 0)			28.63 (2.35, 348.9)	0.009
Insulinoma								
No	210	13	27	0.01 (0, 0.02)	0.04 (0.01, 0.07)	0.06 (0.03, 0.1)	1.0 (ref)	
Yes	31	2	2	0 (0, 0)	0.08 (0, 0.19)	0.08 (0, 0.19)	1.12 (0.25, 4.94)	0.88
Sclerosing Variant								
No	206	14	25	0.01 (0, 0.02)	0.05 (0.02, 0.09)	0.07 (0.03, 0.1)	1.0 (ref)	
Yes	35	1	4	0 (0, 0)	0 (0, 0)	0.05 (0, 0.14)	0.44 (0.06, 3.32)	0.43
Cystic Variant								
No	209	14	23	0.01 (0, 0.02)	0.05 (0.02, 0.08)	0.07 (0.03, 0.11)	1.0 (ref)	
Yes	32	1	6	0 (0, 0)	0.03 (0, 0.09)	0.03 (0, 0.09)	0.4 (0.05, 3.13)	0.38
Vascular Invasion								
No	221	10	25	0 (0, 0.01)	0.03 (0, 0.05)	0.04 (0.01, 0.07)	1.0 (ref)	
Yes	12	4	3	0.08 (0, 0.25)	0.36 (0.05, 0.67)	0.36 (0.05, 0.67)	10.18 (3.19, 32.49)	< 0.001
Perineural Invasion								

No	190	9	22	0.01 (0, 0.03)	0.04 (0.01, 0.07)	0.05 (0.02, 0.08)	1.0 (ref)	
Yes	44	6	7	0 (0, 0)	0.08 (0, 0.17)	0.15 (0.02, 0.27)	2.89 (1.04, 8)	0.04
Margins								
Negative	232	14	26	0 (0, 0.01)	0.04 (0.02, 0.07)	0.06 (0.03, 0.1)	1.0 (ref)	
Positive	8	1	3	0.12 (0, 0.37)	0.12 (0, 0.37)	0.12 (0, 0.37)	2.53 (0.3, 21.68)	0.4
Margins*								
Negative	223	14	26	0 (0, 0.01)	0.05 (0.02, 0.08)	0.06 (0.03, 0.1)	1.0 (ref)	
Positive	4	0	3	0 (0, 0)	0 (0, 0)		0 (0, 0)	< 0.001

*Excludes patients who had an enucleation procedure. Abbreviations: CIR = Cumulative Incidence of Relapse; Calculated from the date of surgery to last follow-up, date of relapse or death HR =Hazard Ratio, estimated from univariate competing risks regression models.

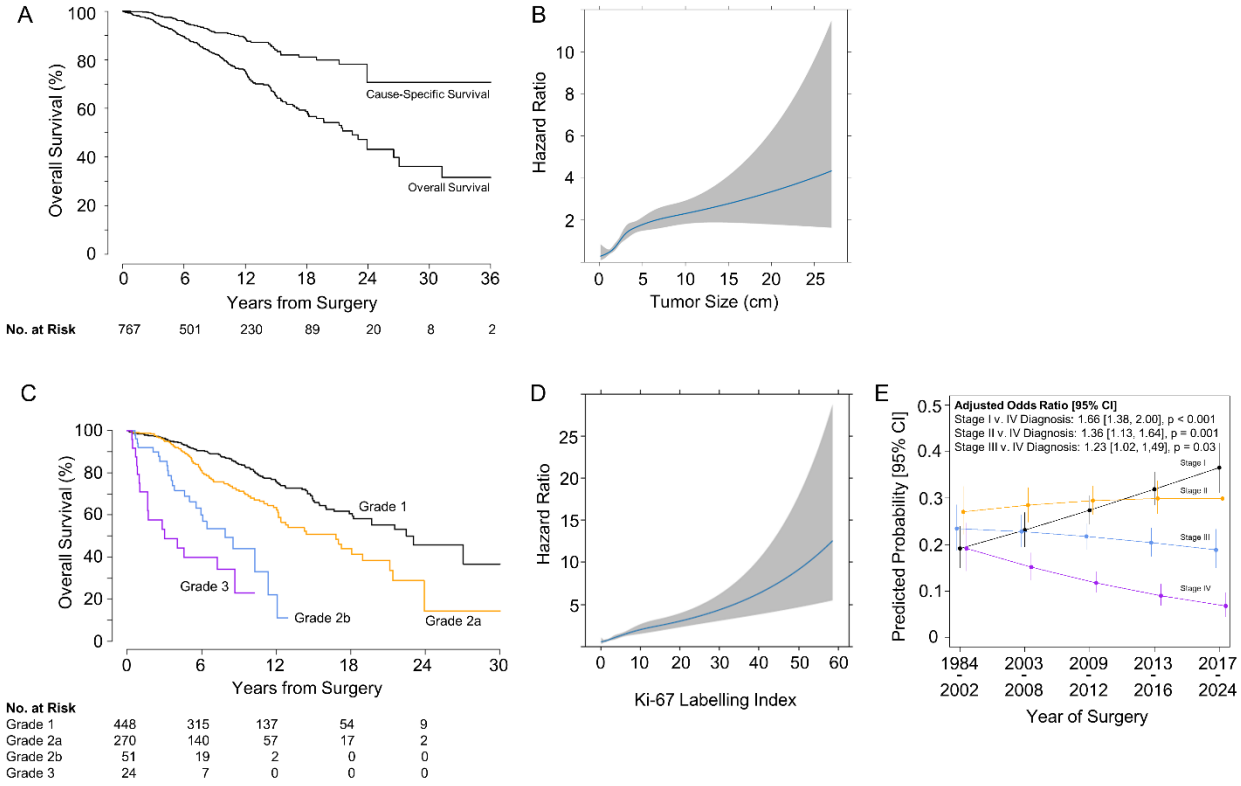
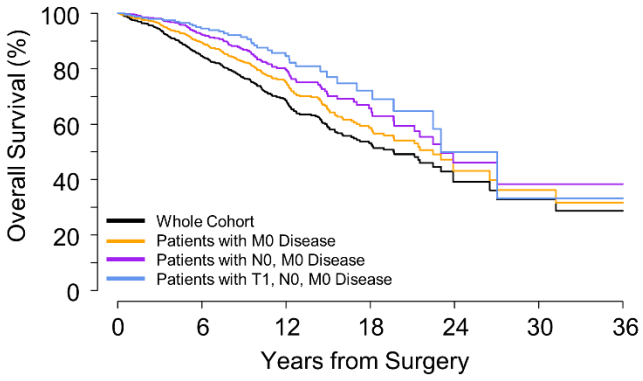
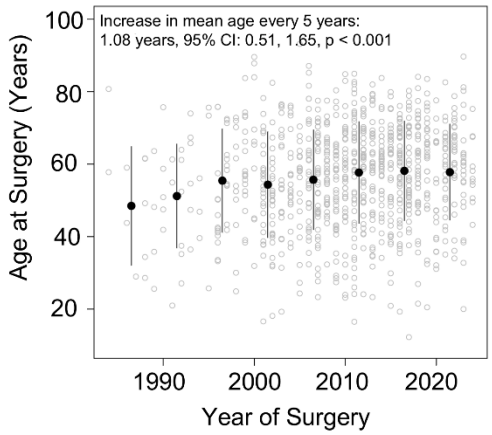


Figure 1: (a) Kaplan-Meier curve for overall survival for the entire cohort. (b) Changes in the hazard ratio for death with increases in tumor size, estimated with restricted cubic splines. The plotted results represent the hazard ratio for different values of the continuous predictor (tumor size), visualizing any non-linear effects captured by the restricted cubic spline. (c) Kaplan-Meier curves for overall survival, separately according to grade. (d) Changes in the hazard ratio for death with increases in Ki-67, estimated with restricted cubic splines. The plotted results represent the hazard ratio for different values of the continuous predictor (Ki-67), visualizing any non-linear effects captured by the restricted cubic spline. (e) Predicted probability [95% CI] of being diagnosed with stage I, II, III, or IV disease (y-axis) by year of surgery grouped into quintiles (x-axis). Probabilities and corresponding odds ratios for the average relative change in the odds of a stage I, II, or III diagnosis compared to stage IV with every increasing quintile of year of surgery, adjusted for age and sex, are estimated from a multinomial regression model.



No. at Risk							
Whole Cohort	875	546	240	92	20	8	2
M0 Patients	767	501	230	89	20	8	2
N0M0 Patients	507	343	145	50	12	4	1
T1N0M0 Patients	251	182	72	23	4	2	1

Supplemental Figure 1: Kaplan Meyer Curve for entire cohort and for the subset of cohort that is M0; N0, M0, and T1, N0, M0.



Supplemental Figure 2: Scatterplot of age at surgery (y-axis) by year of surgery (x-axis). Grey dots represent individual patient data and black points and bars are the mean and standard deviation of age in five-year intervals, starting with 1984 to 1990, 1991 to 1995, and so on. Change in mean age with every five years is estimated from a simple linear regression model.

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