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Comparison of benign and malignant insulinoma

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ABSTRACT

Background: How malignant insulinomas present relative to benign insulinomas is unknown.
Methods: A single-institution retrospective study identified patients with insulinoma. Malignancy was defined by distant metastases, positive lymph node(s), T stage of 4, direct invasion into surrounding peripancreatic tissue, or presence of lymphovascular invasion. Wilcoxon Rank Sum tests and Kaplan-Meier analysis were used.
Results: A total of 311 patients were identified: 51 malignant and 260 benign. Patients with malignant insulinoma presented with higher levels of insulin, proinsulin, and c-peptide. Malignant lesions were larger: 4.2 ± 3.2 vs 1.8 ± 0.8 cm in benign lesions, $p < 0.01$. Overall survival at 5 years was 66.8% vs 95.4% for malignant and benign insulinoma respectively, $p < 0.01$.
Conclusions: Larger size of insulinoma and increased serum β-cell polypeptide concentrations were associated with malignancy. Malignant insulinoma has poorer survival. Further work-up to rule out malignancy may be indicated for larger pancreatic lesions and for patients with higher pre-operative insulin and pro-insulin.

Introduction

Insulinoma is a rare neoplasm with an estimated incidence of 4 cases per 1 million person-years, yet it is the most common type of functional pancreatic neuroendocrine tumor.[1–3] While, the first documented case of insulinoma was malignant, the majority of insulinomas are benign.[4] According to a Mayo Clinic study that assessed this disease over a 60-year period, the incidence of malignant insulinoma is estimated to be around 6% of all insulinoma.[1]

As malignant insulinoma is extremely rare, there is still a paucity of literature describing its clinical manifestations and outcomes. More importantly, the differences between benign and malignant insulinoma are not well studied with regard to the presenting characteristics that may help identify patients at risk of having malignant lesions preoperatively. Therefore, we aimed to analyze our institutional experience with this rare disease with the goal of comparing benign and malignant insulinoma in terms of presenting characteristics, work-up, management, and outcomes.

Methods

This is a retrospective cohort study that assessed patients who presented to any of the Mayo Clinic facilities with malignant insulinoma (between January 1, 1990 and May 6, 2019) and benign insulinoma (between January 1, 1999 and May 6, 2019). Patients were identified from our institutional databases using International Classification of Diseases (ICD) 9th Revision codes: 211.7 and 157.4 for insulinoma and code 258.01 for multiple endocrine neoplasia type 1 syndrome (MEN1) in addition to using the ICD 10th Revision codes: D13.7 and C25.4 for insulinoma and E31.2 for MEN1. Patients' charts were reviewed to confirm the diagnosis and collect

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Table 1
Baseline characteristics.

	All patients	Benign	Malignant	*P*-value
	N = 311	N = 260	N = 51	
Age at diagnosis				
Mean (SD)	52.6 (16.4)	52.5 (16.0)	53.1 (18.2)	0.80[a]
Range	(12.7–86.9)	(12.7–86.9	(17.9–83.6)	
Sex				
Male	126 (40.5%)	100 (38.5%)	26 (50.9%)	0.12[b]
Female	185 (59.5%)	160 (61.5%)	25 (49.1%)	
Race/Ethnicity				
White	254 (81.7%)	209 (80.4%)	45 (88.2%)	N/A
African American	6 (1.9%)	6 (2.3%)	0 (0%)	
Asian	4 (1.3%)	2 (0.8%)	2 (3.9%)	
American Indian/Alaskan Native	2 (0.6%)	2 (0.8%)	0 (0%)	
Indian	1 (0.3%)	1 (0.4%)	0 (0%)	
Unknown	44 (14.2%)	40 (15.4%)	4 (7.8%)	
Multiple endocrine neoplasia, type 1				
Yes	22 (7.1%)	18 (6.9%)	4 (7.8%)	0.76[b]
No	289 (92.9%)	242 (93.1%)	47 (92.2%)	

[a] Wilcoxon rank sum test.
[b] Fisher's Exact Test.

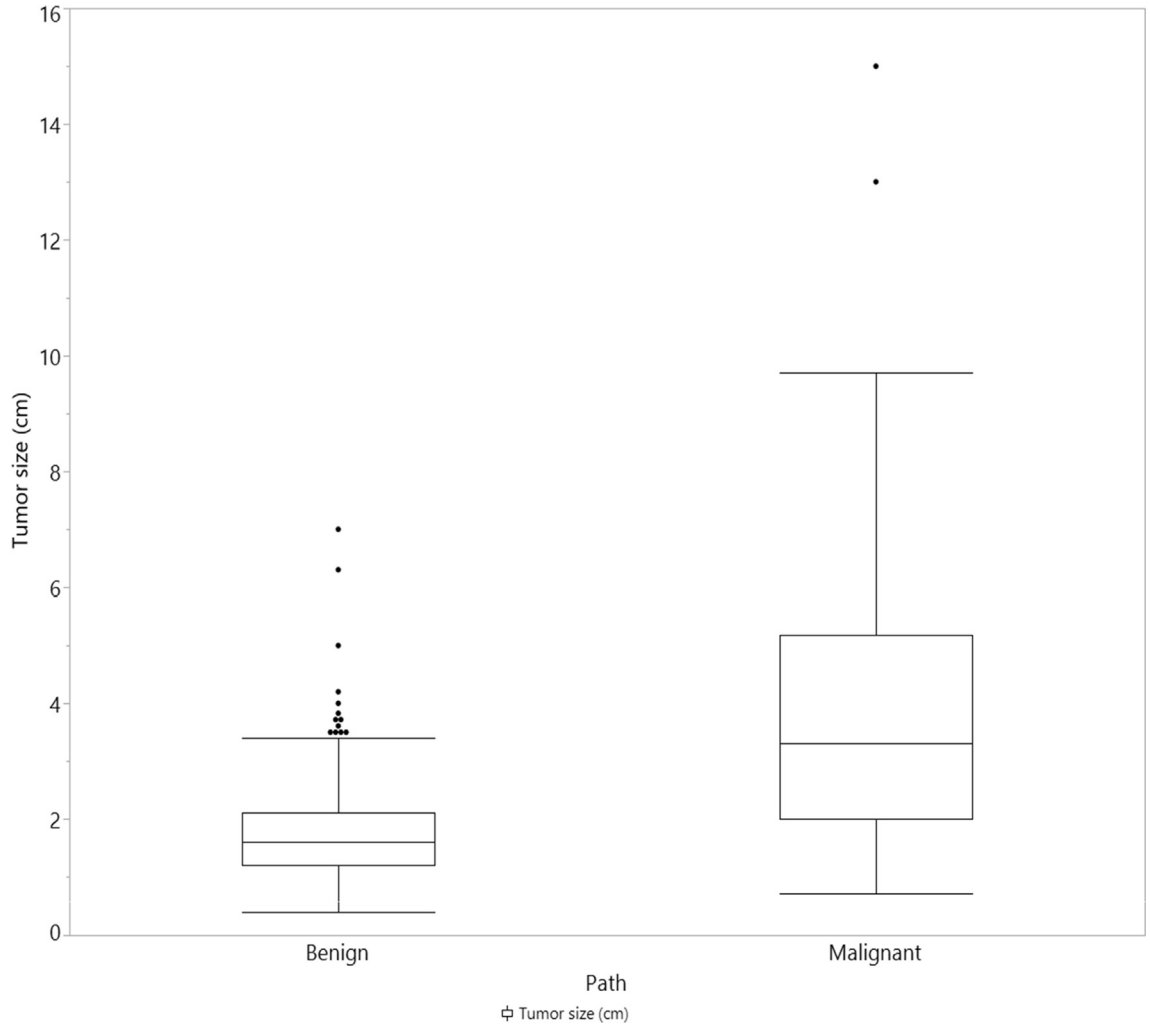

Fig. 1. Tumor sizes.

Table 2
Neoplasm characteristics.

	All patients N = 311	Benign N = 260	Malignant N = 51	*P*-value
Neoplasm size (cm)				
N	292	256	36	<0.01[a]
Mean (SD)	2.1 (1.6)	1.8 (0.8)	4.2 (3.2)	
Median	1.7	1.6	3.3	
Q1, Q3	1.3–2.3	1.2, 2.1	2.0, 5.2	
Range	(0.4–15.0)	(0.4–7.0)	(0.7–15.0)	
Grade				
N	121	89	32	<0.01[b]
I	74 (61.2%)	58 (65.2%)	16 (50.0%)	
II	40 (33.1%)	31 (34.8%)	9 (28.1%)	
III	7 (5.8%)	0 (0%)	7 (21.9%)	
Ki-67%				
N	60	49	11	<0.01[b]
<3	21 (35.0%)	15 (30.6%)	6 (54.5%)	
3–20	36 (60.0%)	34 (69.4%)	2 (18.2%)	
>20	3 (5.0%)	0 (0%)	3 (27.3)	
Location in the pancreas				
N	311	260	51	<0.01[b]
Head/Neck	127 (40.8%)	116 (44.6%)	11 (21.6%)	
Body/tail	172 (55.3%)	136 (52.3%)	36 (70.6%)	
Both locations	7 (2.3%)	6 (2.3%)	1 (1.9%)	
Unknown	5 (1.6%)	2 (0.8%)	3 (5.9%)	
TNM Stage				
I			2 (3.9%)	N/A
II			5 (9.8%)	
III			13 (25.5%)	
IV			31 (60.8%)	

[a] Wilcoxon rank sum test.
[b] Pearson Chi-square test.

Table 3
Diagnostic laboratory workup.

	Total (N = 311)	Benign (N = 260)	Malignant (N = 51)	p value
Nadir Glucose (mg/dl)				
N	294	257	37	0.11[b]
Mean (SD)	41.2 (8.8)	41.5 (8.6)	39.2 (9.7)	
Median	42.0	42.0	37.0	
Q1, Q3	35.0, 48.0	36.0, 47.0	32.0, 48.0	
Range	(19.0–62.0)	(19.0–62.0)	(22.0–60.0)	
Insulin (mclU/ml)				
N	284	249	35	<0.01[b]
Mean (SD)	22.9 (43.4)	19.7 (27.8)	45.9 (97.2)	
Median	13.0	12.3	21.0	
Q1, Q3	7.0, 23.9	6.6, 23.0	12.0, 39.0	
Range	(2.1–576.0)	(2.1–316.0)	(2.1–576.0)	
Proinsulin (pmol/L)				
N	245	216	29	0.04[b]
Mean (SD)	171.1 (224.3)	149.1 (176.3)	334.9 (410.3)	
Median	85.0	83.5	190.0	
Q1, Q3	30.0, 200.0	29.5, 190.0	37.0, 480.0	
Range	(2.0–1400.0)	(2.0–880.0)	(13.0–1400.0)	
C-peptide (ng/ml)				
N	283	250	33	<0.01[b]
Mean (SD)	4.5 (9.9)	3.7 (2.7)	10.8 (27.5)	
Median	3.1	3.0	4.1	
Q1, Q3	2.1, 4.6	2.1, 4.2	2.7, 6.9	
Range	(0.6–154.0)	(0.6–23.6)	(0.9–154.0)	
BHOB[a] (mmol/L)				
N	220	196	24	0.54[b]
Mean (SD)	0.3 (0.5)	0.3 (0.5)	0.3 (0.5)	
Median	0.2	0.2	0.2	
Q1, Q3	0.1, 0.3	0.1, 0.3	0.1, 0.4	
Range	(0.0–4.5)	(0.0–4.5)	(0.1–2.7)	

[a] BHOB: β-hydroxybutyrate.
[b] Kruskal Wallis.

the data. This study was approved by Mayo Clinic's Institutional Review Board (IRB), and patients without Minnesota research authorization were excluded.

Patients' charts, pathology and operative reports were reviewed to collect data about demographics, neoplasm characteristics, surgical treatment and survival. Tumor size was reported based on the greatest dimension reported in the pathology reports for those who underwent resection or based on the greatest dimension reported in the diagnostic images for patients who did not undergo surgery.

Stage was reported based on the 8th edition of the TNM staging system. Malignancy was defined based on the presence of lymphovascular invasion or invasion into peripancreatic tissue for TNM I and TNM II stages, presence of positive regional lymph nodes or T4 lesions for TNM III or presence of distant metastases for TNM IV.[5] Tumor grade was classified according to the WHO classification criteria. Ki-67 proliferation index % was categorized into three groups based on WHO criteria (<3%, 3–20%, and >20%)

Chi-square, Fisher's Exact and Wilcoxon Rank Sum tests were used to analyze the data. Survival was analyzed using Kaplan-Meier analysis using date of diagnosis as the starting point and date of death as the end point, censoring at last patient contact. Logistic regression was used to generate receiver operating characteristic curve (ROC) to determine the best cutoff value for variables. The cutoff was determined by finding the value that maximized the absolute value of sensitivity-specificity for each model. Statistical analysis was performed using SAS version 9.4 statistical software (SAS Institute, Inc. Cary, NC).

Results

Baseline characteristics

A total of 311 patients were identified over the study period; 51 patients (16.4%) had malignant insulinoma and 260 (83.6%) had benign tumors. There was no difference in patient age (average ± SD) between those who had benign (52.5 ± 16.0 years) and malignant insulinoma (53.1 ± 18.2 years), p = 0.80, nor in patient sex as females represent 62% of those who had benign insulinoma compared to 49% of those with malignant neoplasms, p = 0.12. Baseline characteristics are summarized in Table 1. Among our cohort, 22 (7%) patients had MEN1 syndrome. MEN1 syndrome was present in 7% of patients with benign insulinoma compared to 8% of those with malignant insulinoma, p = 0.76. Among patients in our cohort with MEN1, 18 patients (82%) had benign and 4 patients (18%) had malignant insulinoma. Insulin staining was performed at metastatic sites for one MEN1 patient who had both insulinoma and gastrinoma. The other 3 patients who had MEN1 and metastatic insulinoma were found to have confirmed insulinoma in the pancreas with metastatic pancreatic neuroendocrine tumor to regional lymph nodes. Insulin staining was not performed on the regional lymph nodes. However, as these 3 patients did not have evidence of other types of pancreatic neuroendocrine tumor to explain the metastatic disease, they were considered to have

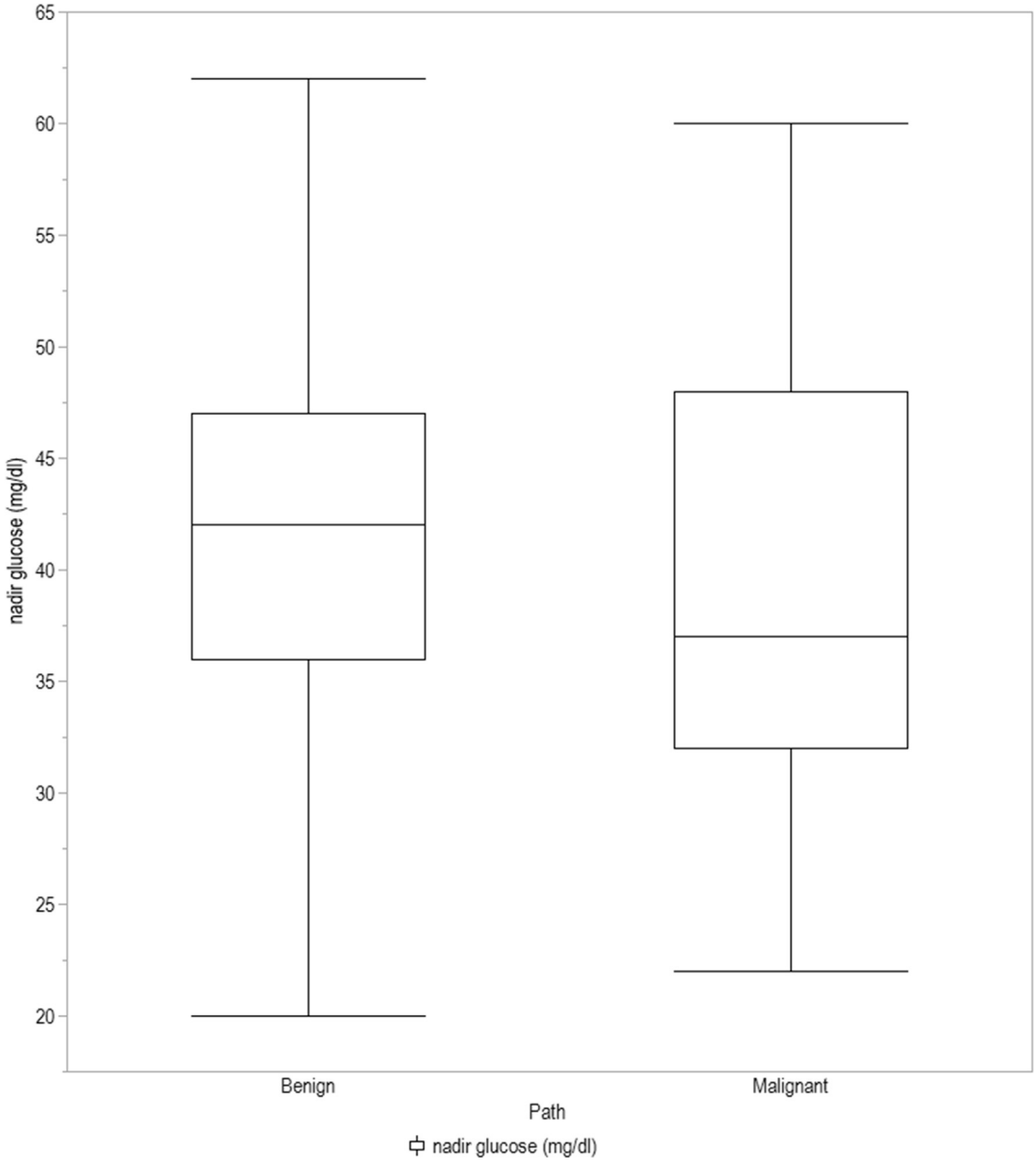

Fig. 2. Preoperative nadir glucose levels.

metastatic insulinoma. Of note, we excluded two patients who had insulinoma, gastrinoma and metastatic pancreatic neuroendocrine tumor to the liver from our cohort as the metastatic disease could not be proven to be insulinoma or other type of pancreatic neuroendocrine tumor.

Neoplasm characteristics

Tumor size was available for 292 (94%) cases: 36 malignant and 256 benign; malignant lesions were larger (4.2 ± 3.2 vs 1.8 ± 0.8 cm, $p < 0.01$) as shown in Fig. 1. Neoplasm grade was reported for 121 (39%) cases as shown in Table 2. Malignant insulinoma were grade I in 50%, II in 28% and III in 22% while benign insulinoma were grade I in 65%, grade II in 35% and III in 0%, $p < 0.01$. Ki-67% was reported for 60 cases (49 benign and 11 malignant); Ki-67% > 20% was associated with malignancy as shown in Table 2. The median tumor size for each Ki-76% category was: 1.5, 1.7 and 5.15 cm for Ki-67% < 3, 3–20, and >20% respectively. Of note all patients with Ki-67% > 20 presented with stage IV.

Malignant lesions were in the head/neck of the pancreas in 22%, body/tail in 71%, in both locations in 2% (this patient had MEN1), and location was not available for 6%. Benign lesions were in the head/neck in 45%, body/tail in 52%, both location for 2% (2 of 6 patients had MEN1) while the location was unknown for 0.8%, $P < 0.01$ as shown in Table 2. At presentation, 2 (4%) cases of malignant insulinoma were stage I and both were determined malignant based on peripancreatic adipose tissue invasion. On the other hand, 5 (10%) cases were stage II: 3 had peripancreatic adipose tissue invasion and 2 had lymphovascular invasion, 13 (25%) of malignant lesions were stage III and 31 (61%) were stage IV. All

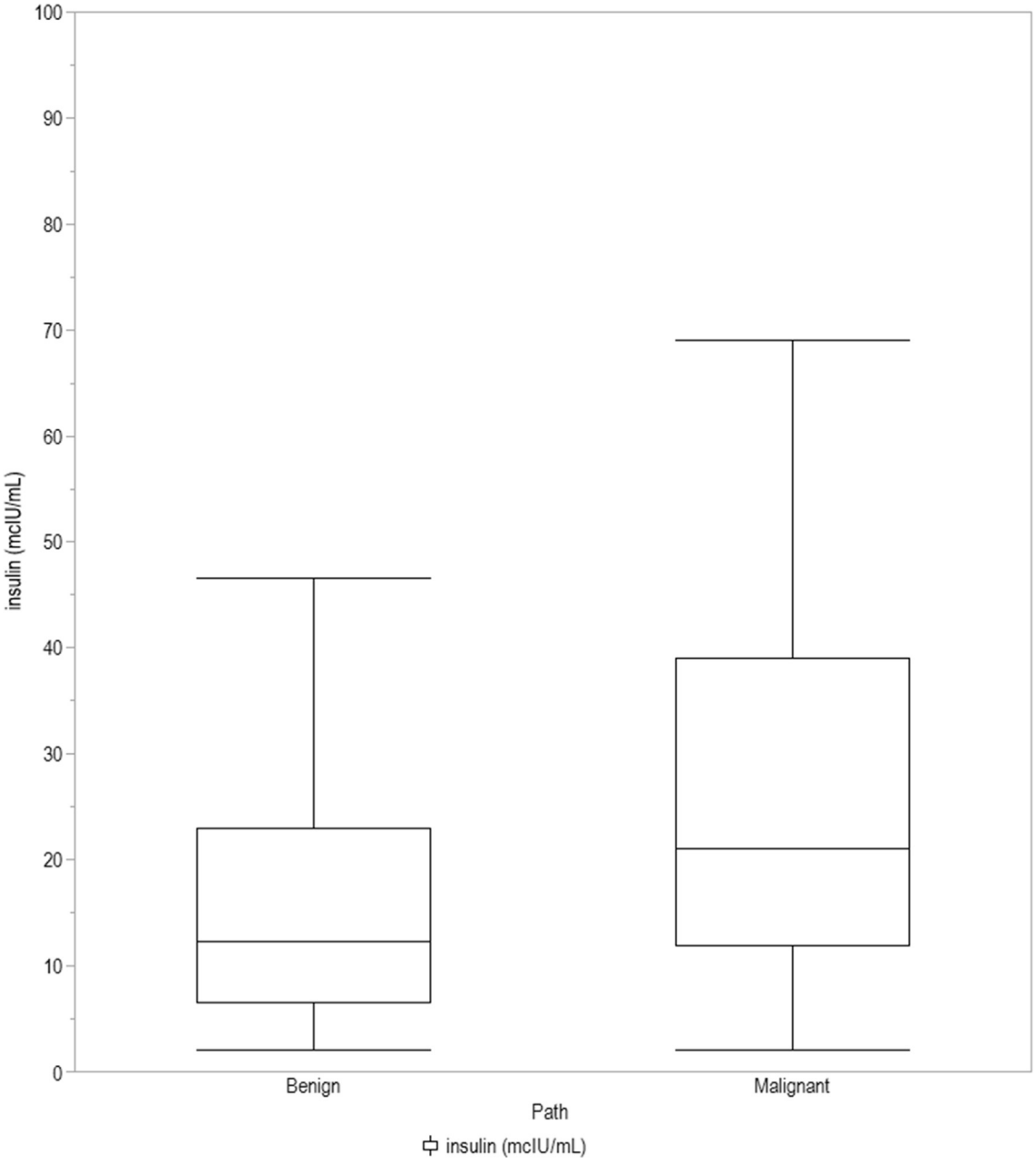

Fig. 3. Preoperative insulin levels.

patients with stage IV disease had metastases to liver with or without metastases to other organs. Patients with TNM stage I and II did not have pre-operative images or intra-operative finding that suggested malignant disease and therefore, they were found to have malignant insulinoma on the final pathology reports after surgery. On the other hand, 3 patients with stage III were diagnosed with malignant disease on pre-operative images, 1 patient based on intra-operative finding that suggested malignancy, and the rest of patients with stage III ($n = 9$) were diagnosed with malignancy on the final pathology report. For stage IV patients, 3 patients were found to have malignant disease intra-operatively and the rest ($n = 27$) were found to have malignant disease on preoperative images.

Nine patients developed malignant insulinoma after undergoing R0 resection of benign insulinoma; eight developed metastasis to regional lymph nodes or liver after R0 resection of benign insulinoma while one patient had pancreatic recurrence with invasion into peripancreatic tissue. Only one of these patients had MEN1 syndrome. The median (IQR) time from the resection of previous benign insulinoma till the development of malignant insulinoma was 5.3 (4.5, 12.2) years. The median (IQR) neoplasm size of the benign tumor in these nine patients was 2.2 (1.7, 4) cm, range (1.1, 5.2) cm. In terms of grades, benign insulinoma was grade I in one case, II in one case, and grade was not reported for the rest ($n = 7$ cases). Of note, it was reported that the benign tumor was associated with micro-calcification in one case which was associated with a size of 5.2 cm.

There was no difference in median (IQR) neoplasm size between benign insulinoma compared to localized malignant insulinoma (malignant stage I/II): neoplasm size was 0.2 (0.1, 0.3) cm vs 0.2 (0.1,

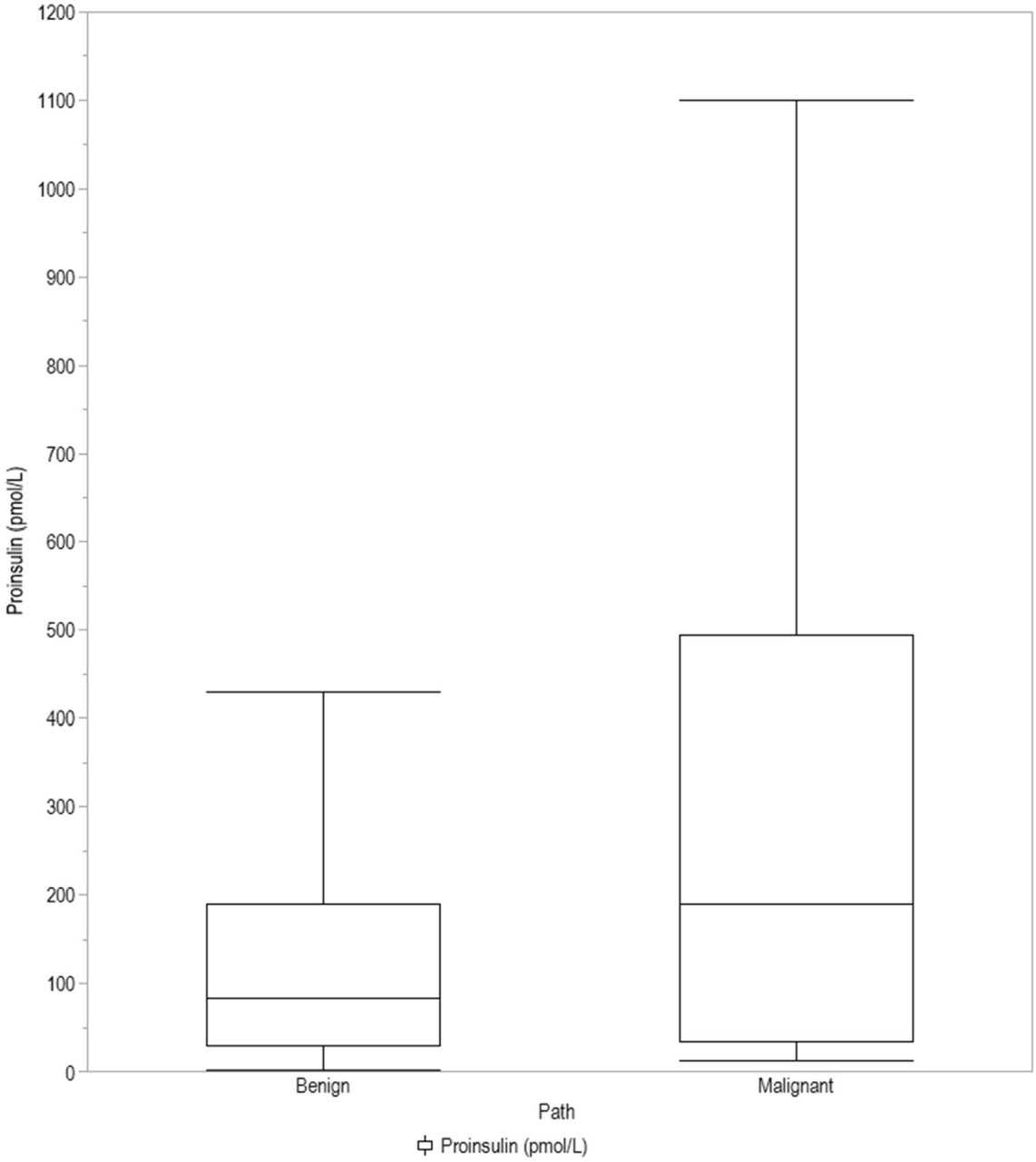

Fig. 4. Preoperative pro-insulin levels.

2.7), p < 0.52 for benign and localized malignant insulinoma respectively. The suggested tumor size cutoff to help differentiate benign vs malignant insulinoma is 2.1 cm as shown in Table 5.

Diagnostic work-up

Preoperative fasting test results were available for the majority of patients in our cohort as shown in Table 3. There was no difference in the median nadir glucose levels between groups: 37.0 (32.0, 48.0) vs 42.0 (36.0, 47.0) mg/dl for malignant and benign insulinoma respectively, p > 0.11 as shown in Table 3 and Fig. 2. Patients with malignant insulinoma tended to have higher median (IQR) levels of insulin: 21.0 (12.0, 39.0) vs 12.3 (6.6, 23.0) mcIU/ml, p < 0.01 and higher levels of proinsulin: 190.0 (37.0, 480.0) vs 83.5 (29.5, 190.0) pmol/L, p = 0.04 and higher levels of c-peptide: 4.1 (2.7, 6.9) vs 3.0 (2.1, 4.2) ng/ml, p < 0.01, Figs. 3–5.

There were no differences in nadir glucose levels, insulin, pro-insulin and c-peptide levels in patients with benign insulinoma compared to localized malignant insulinoma (stage I and II) as shown in Table 4.

On ROC analysis, the suggested cutoff levels to help differentiate benign vs malignant insulinoma are 17 mcIU/ml for insulin, 100 pmol/L for proinsulin, and 3.6 ng/ml for C-peptide as shown in Table 5 (seeFig. 7).

Surgical resection and outcomes

Surgical resection was performed in 239 (92%) benign patients and 35 (69%) malignant insulinoma patients with complete R0 resection being successful in 231 (97%) of patients who underwent

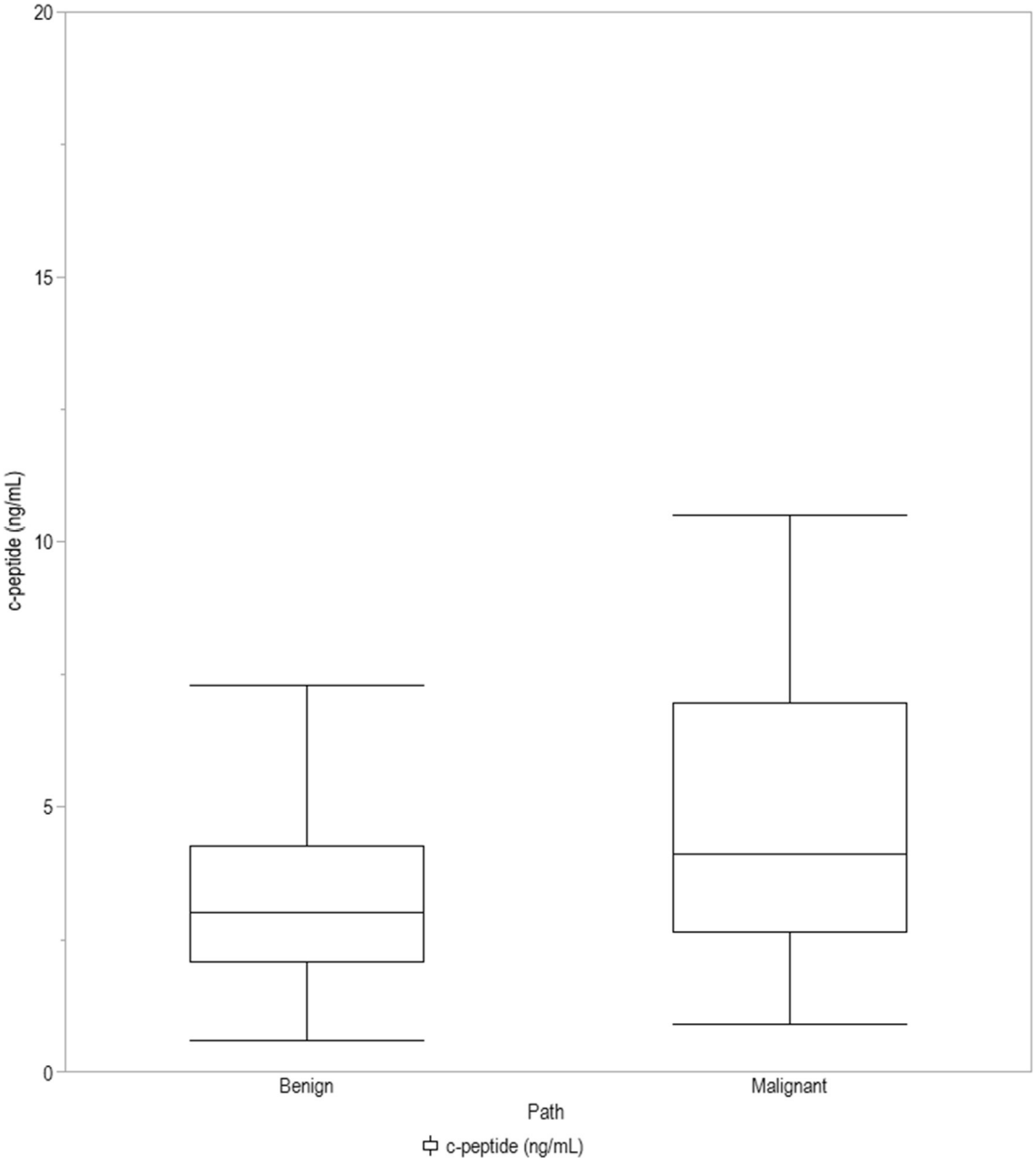

Fig. 5. Preoperative c-peptide levels.

surgery for benign disease compared to 27 (77%) patients who underwent surgery for malignant disease, $p < 0.01$. Among patients who underwent resection for benign insulinoma, R0 was performed in 97% and R1 in 3% of cases while among patients who underwent resection for malignant insulinoma, 77% had R0, 11.5% had R1 and 11.5% had R2 resection. The overall 5-year survival was 67% for malignant and 95% for benign insulinoma, $p < 0.01$. Among patients who underwent R0 resection, the overall 5-year survival was 87% and 96% for malignant and benign insulinoma respectively, $p = 0.12$. There was no difference in overall 5-year survival among benign insulinoma patients with and without MEN1 syndrome; 5-year survival for benign insulinoma with MEN1 syndrome was 93% compared to 96% in patients without MEN1 syndrome, $p = 0.56$. The overall 5-year survival for malignant insulinoma was 100% for stage I/II, 89% for stage III and 53% for stage IV, $p = 0.37$ as shown in Fig. 8.

Discussion

Given that insulinoma is rare, very little is known about malignant insulinoma. Moreover, the differences in clinical presentations and outcomes between benign and malignant insulinoma are not well understood and there is not an agreement on the diagnostic criteria for malignant insulinoma. To our knowledge, this is the first study that compares presenting clinical features between benign and malignant insulinoma. Interestingly, our results show that malignant and benign insulinoma differ in their clinical behavior as malignant neoplasms tend to be larger and are associated with

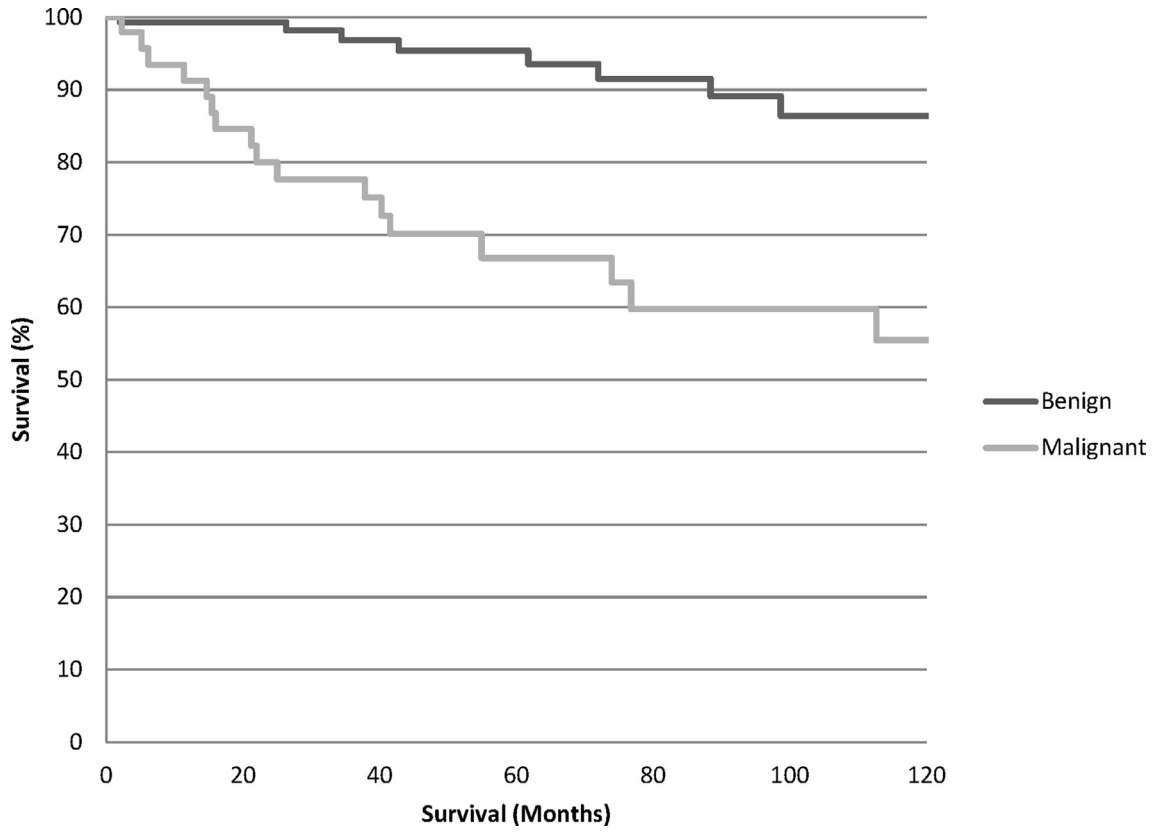

Fig. 6. Overall survival for all patients by pathology.

Table 4
Comparison of laboratory workup for benign vs localized malignant insulinoma.

	Total (N = 267)	Benign (N = 260)	Malignant stage I/II (N = 7)	p value
Nadir Glucose (mg/dl)				
N	263	257	6	0.39[2]
Mean (SD)	41.4 (8.7)	41.5 (8.6)	39.5 (11.7)	
Median	42.0	42.0	35.5	
Q1, Q3	36.0, 47.0	36.0, 47.0	32.0, 46.0	
Range	(19.0–62.0)	(19.0–62.0)	(28.0–60.0)	
Insulin (mcIU/ml)				
N	254	249	5	0.18[2]
Mean (SD)	19.9 (27.6)	19.7 (27.8)	28.5 (19.1)	
Median	12.5	12.3	26.3	
Q1, Q3	6.6, 23.0	6.6, 23.0	22.0, 39.0	
Range	(2.1–316.0)	(2.1–316.0)	(2.1–53.0)	
Proinsulin (pmol/L)				
N	219	216	3	0.52[2]
Mean (SD)	148.1 (175.4)	149.1 (176.3)	74.3 (74.8)	
Median	83.0	83.5	41.0	
Q1, Q3	29.0, 190.0	29.5, 190.0	22.0, 160.0	
Range	(2.0–880.0)	(2.0–880.0)	(22.0–160.0)	
C-peptide (ng/ml)				
N	255	250	5	0.80[2]
Mean (SD)	3.7 (2.7)	3.7 (2.7)	3.4 (1.8)	
Median	3.0	3.0	3.5	
Q1, Q3	2.1, 4.2	2.1, 4.2	2.7, 4.2	
Range	(0.6–23.6)	(0.6–23.6)	(0.9–5.9)	
BHOB[a] (mmol/L)				
N	199	196	3	0.52[2]
Mean (SD)	0.3 (0.5)	0.3 (0.5)	1.0 (1.5)	
Median	0.2	0.2	0.2	
Q1, Q3	0.1, 0.3	0.1, 0.3	0.1, 2.7	
Range	(0.0–4.5)	(0.0–4.5)	(0.1–2.7)	

[1]Kruskal Wallis.
[a] BHOB: β-hydroxybutyrate.

Table 5
The suggested cutoff points for neoplasm size and diagnostic labs to detect malignant insulinoma based on ROC curves.

	Cutoff	Sensitivity	Specificity
Neoplasm size (cm)	2.1	0.25	0.28
Insulin (mcIU/ml)	17	0.36	0.34
Proinsulin (pmol/L)	100	0.44	0.44
C-peptide (ng/mL)	3.6	0.39	0.36

increased serum β-cell polypeptide concentrations. These findings are important as they suggest that further work-up to rule out malignancy may be indicated for larger pancreatic lesions and for patients presenting with higher than expected levels of insulin and pro-insulin. Based on our results, the suggested cutoff points that favor malignancy are 2 cm for neoplasm size, 17 mcIU/ml, 100 pmol/L, and 3.6 ng/mL for insulin, proinsulin and c-peptide respectively.

According to the Endocrine Society Clinical Practice Guidelines, endogenous hyperinsulinism is diagnosed when hypoglycemic signs and/or symptoms are present in association with plasma glucose levels <55 mg/dl, insulin levels ≥3.0 mcIU/ml, c-peptide ≥0.6 ng/ml and pro-insulin ≥5.0 pmol/l.[6] In addition, β-hydroxybutyrate levels≤ 2.7 mmol/l and an increase in plasma glucose to IV glucagon of ≥25 mg/dl indicate mediation of the hypoglycemia by insulin (or by an IGF).[6,7] While the biochemical diagnostic criteria for insulinoma are well established and proven to be sensitive and specific, the differences between benign and malignant neoplasms in the diagnostic laboratory values were not studied before.[7] Our results showed increased levels of insulin, proinsulin and c-peptide in malignant lesions in comparison to benign insulinoma. These results may be due to higher tumor burden in malignant cases as these lesions tend to be larger, and a large proportion of them presented with distant metastatic disease.

In addition to the differences in presenting biochemistry, our results show a significant difference in pancreatic tumor sizes between benign and malignant insulinoma as the mean size was twice as large in malignant lesions. Another study including 17 patients with metastatic insulinoma reported an average tumor size of 6.2 cm which supports our finding that larger lesions are associated with higher malignancy risks.[8] On the other hand, benign insulinoma tend to present at much smaller sizes as it is estimated that over 80% of benign insulinoma cases are smaller than 2 cm.[9,10] Among the nine patients in our cohort who developed malignant insulinoma after a previously resected benign tumor, the median (IQR) neoplasm size of the benign insulinoma was 2.2 (1.7, 4) cm. These findings suggest that with relatively large insulinoma lesions, one should have low threshold to rule out malignancy especially for lesions larger than 2 cm as our results showed that about 75% of malignant insulinoma are larger than 2 cm.

It is well known that benign insulinoma is associated with better survival compared to malignant ones. Our previous study using the Surveillance, Epidemiology, and End Results (SEER) set of population-based cancer registries showed a 5-year survival rate of 58% for malignant insulinoma.[11] However, given SEER limitations, we were unable to compare malignant to benign insulinomas.[11] In the present study of our institutional experience, our results suggest that malignant insulinoma is associated with worse survival if it presents at advanced stages while early staged tumors have a survival rate similar to normal population. Our results showed that the 5-year survival rate was 100% for malignant insulinoma stage I and II, 89% for stage III and about 50% for stage IV. While one should be cautious in interpreting our survival results for stage I and II given

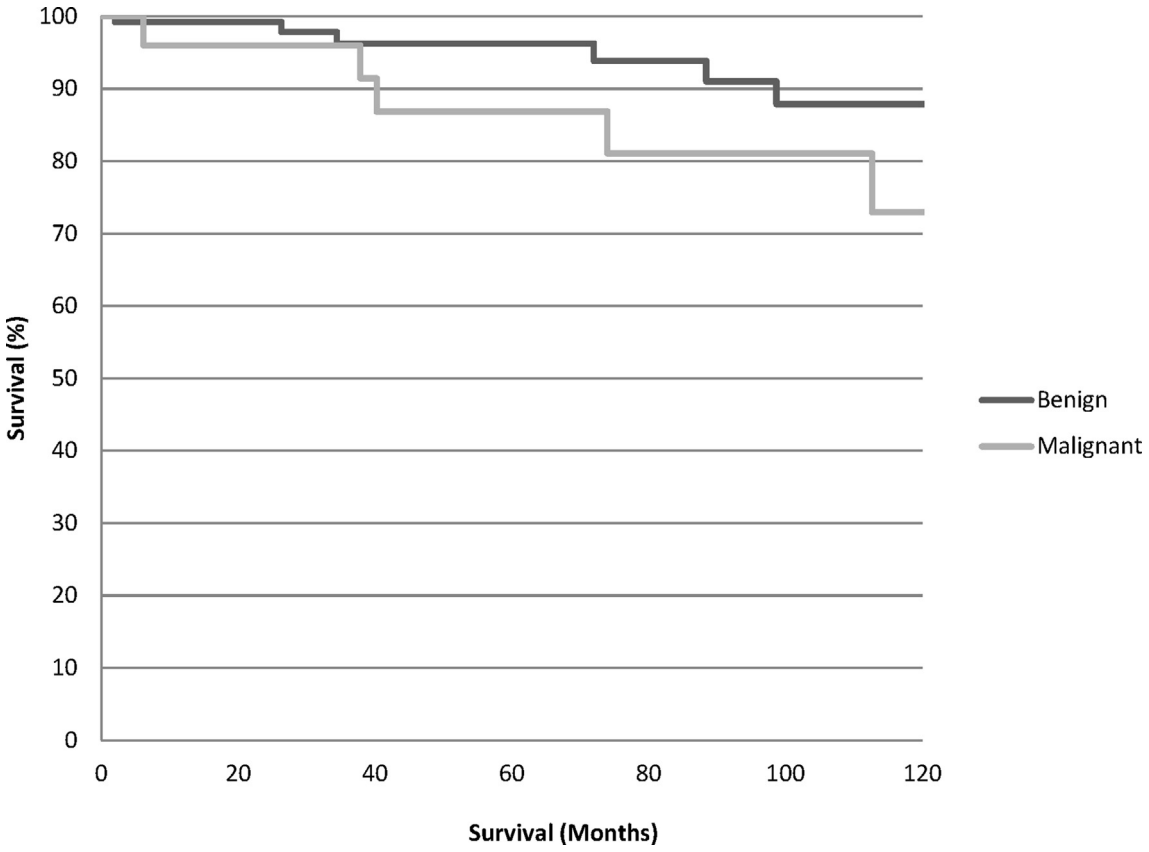

Fig. 7. Overall survival for patients who underwent R0 resection by pathology.

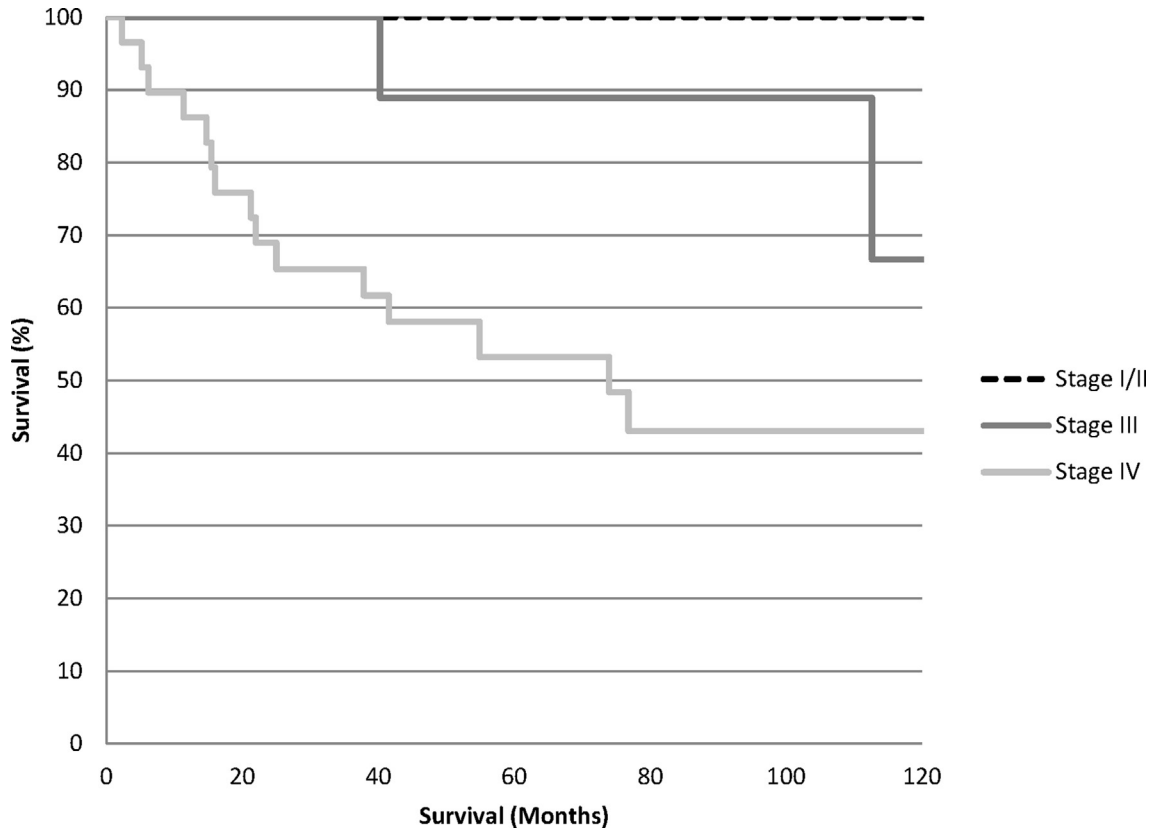

Fig. 8. Overall survival for malignant insulinoma by TNM stage.

the limited number of patients, survival rates for early stage malignant insulinoma are not well reported in the literature as the majority of studies included patients with metastatic disease only.[5,12] Another SEER based study has shown that the 5-year survival for malignant functional pancreatic neuroendocrine tumors was over 80% for stage I/II, over 60% for stage III and less than 40% for stage IV which is in line with our results.[13] It is important to note that the staging system utilized in that study is different than the TNM staging system that we have used. Similar to other studies, our results suggest that patients who developed benign insulinoma in the setting of MEN1 syndrome had overall worse survival compared to patients without MEN1 but the difference was not statistically significant.[1] The optimal approach when malignant insulinoma is suspected preoperatively is to proceed with oncological complete resection along with regional lymph nodes dissection.[11] We avoid enucleation when malignant insulinoma is suspected. However, in our practice if malignant insulinoma was diagnosed on the final pathology report after an enucleation or if lymph node dissection was not performed, we do not take the patient back to surgery but rather follow them with surveillance images.

Our study has some limitations related to its retrospective design. Despite that this is one of the largest institutional cohorts to have studied malignant insulinomas, our absolute malignant numbers remain small due to it being an extremely rare condition, which challenged further subgroup analysis. Further, given that this study looked at patients over a relatively long period of time, we encountered some missing information due to the transition from paper to electronic medical records. Moreover, the histological grading of tumors has evolved over time with routine use of Ki67 immunohistochemical staining within the last decade. Finally, we reported overall survival and not cancer-specific survival as we were unable to confirm cause of death for all patients.

Conclusion

Larger size of insulinoma and increased serum β-cell polypeptide concentrations at presentation are associated with malignancy. Malignant insulinoma had poorer survival compared to benign lesions when presenting at advanced stages. Further workup to rule out malignancy may be indicated for larger pancreatic lesions and for patients with higher pre-operative insulin and proinsulin levels.

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Disclosure/conflict of interest

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