Surgery vs surveillance for well-differentiated pancreatic neuroendocrine tumors (PanNETs): An Eleven-year analysis of the National Cancer Database (NCDB)

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BACKGROUND

- Pancreatic neuroendocrine tumors (PanNETs) are rare group of tumors that comprise 1-2% of pancreatic tumors with an incidence of 0.43 per 100 000. [1]
- Behavior of these tumors are affected by size as well as grade of the tumor. [2]
- Pancreatic surgery has significant morbidity and non-negligible mortality. In one series, 50 % of the patients had complications including post-surgical infection, pancreatic fistula, diabetes and severe hemorrhage. [3]
- There have been vigorous attempts to determine the factors that predict overall survival (OS) in PanNETs with inconsistent results. [3]
- Although resection is usually recommended, optimal management is still controversial.
- NCCN and ENETS suggest different size cutoffs for non-surgical options for small Pan NETs (NCCN < 1cm, ENETS < 2cm). [4,5]
- Our objective is to evaluate whether surgical resection is associated with improved OS in small well-differentiated (WD) PanNETs. In addition, we aim to identify prognostic factors for OS in PanNETs.

METHODS

- Using the National Cancer Database (NCDB), we identified 5057 patients diagnosed with PanNET between 2004 and 2015.
- After excluding patients with grade 3 tumors, metastatic disease, and patients with missing survival data, we analyzed 2004 patients with non-metastatic WD PanNETs.
- Patient's clinicopathologic characteristics and treatment modalities were analyzed using frequency statistics and chi-square method.
- Covariates included age, sex, race, Charlson-Deyo Score, tumor primary site, tumor size, stage, grade, regional LN surgery, chemotherapy, and radiation therapy.

METHODS (continued)

- Tumor sizes were divided into 3 categories: <1cm, 1-2cm, >2cm.
- Kaplan-Meier Survival analysis and plots were created for all covariates to determine unadjusted OS
- Variables that showed significance with OS on a univariate basis or were potential confounders were included in Cox proportional hazards model for multivariable analysis.
- Stratified analysis was done by tumor size group. Hazard ratios with corresponding confidence intervals and p-values. $p<0.05$ was considered to be significant.

RESULTS

Table 1 : Patient demographics

Characteristics	No Surgery n= 223	Surgery n=1781	P-value
Age			
Median	68	60	**<.0001**
Interquartile range	57-76	50-68	
Gender, n (%)			
Male	113 (50.7)	909 (51.0)	0.9179
Female	110 (49.3)	872 (49.0)	
Race, n (%)			
White	171 (77.4)	1456 (82.7)	0.0907
Black	39 (17.6)	226 (12.8)	
Other	11 (5.0)	79 (4.5)	
Charlson-Deyo Score, n (%)			
0	153 (68.6)	1275 (71.6)	0.1379
1	46 (20.6)	388 (21.8)	
2	20 (9.0)	93 (5.2)	
3	4 (1.8)	25 (1.4)	

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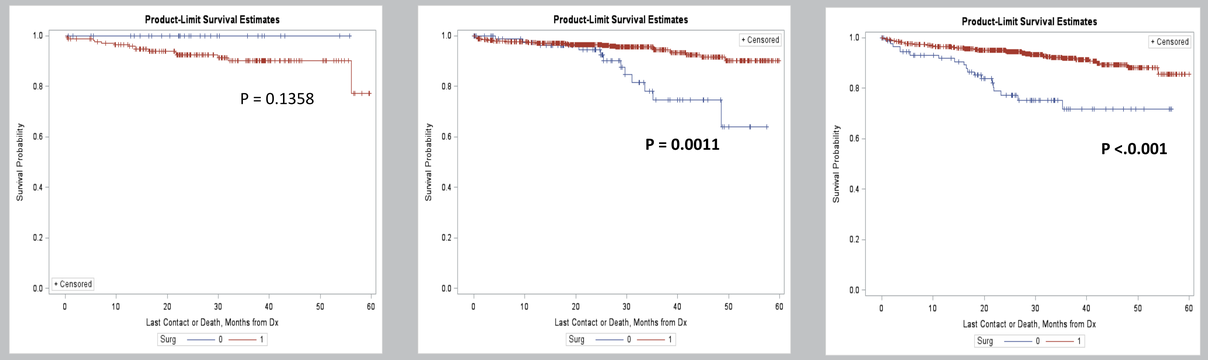
RESULTS (CONTINUED)

Table 2: Tumor characteristics and treatment modalities of patients with PanNETs

Characteristics	No Surgery n= 223	Surgery n=1781	P-value
Primary Site, n (%)			
Head of pancreas	83 (37.2)	435 (24.4)	**<.0001**
Body of pancreas	52 (23.3)	325 (18.2)	
Tail of pancreas	52 (23.3)	726 (40.8)	
Other	36 (16.1)	295 (16.6)	
Tumor Size, n (%)			
<1cm	31 (13.9)	189 (10.6)	0.1701
1-2cm	93 (41.7)	701 (39.4)	
>2cm	99 (44.4)	891 (50.0)	
Stage, n (%)			
1	177 (79.4)	1317 (73.9)	**<.0001**
2	30 (13.5)	457 (25.7)	
3	16 (7.2)	7 (0.4)	
Grade, n (%)			
1	195 (87.4)	1591 (89.3)	0.3933
2	28 (12.6)	190 (10.7)	
Regional Nodes Positivity, n (%)			
No positive LNs	5 (2.3)	1195 (67.2)	**<.0001**
Positive LNs	8 (3.6)	265 (14.9)	
LNs not examined	208 (94.1)	318 (17.9)	
Chemotherapy, n (%)	22 (9.9)	29 (1.6)	**<.0001**
Radiation therapy, n (%)	9 (4.0)	18 (1.0)	**0.0018**

RESULTS (CONTINUED)



(a) (b) (c)

Figure 1: Kaplan-Meier curves of OS by surgery, stratified by tumor size groups: (a) tumor <1cm, (b) tumor 1-2cm, (c) tumor >2cm

Table 3: Unadjusted 5–year OS by tumor size group

Tumor size	No Surgery n= 223	Surgery n=1781	P-value
<1cm	100%	91.7%	0.1358
1-2cm	86.5%	95.2%	**0.0011**
>2cm	80.2%	93.1%	**<.0001**

Table 4: Adjusted Hazard Ratios of death for surgery OS by tumor size group

Tumor size	<1cm	1-2cm	>2cm
HR (95%CI) Surgery	1.92 (0.17-21.53)	0.4 (0.18-0.95)	0.34 (0.16-0.72)
P-value	0.5986	**0.0364**	**0.0050**

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RESULTS (CONTINUED)

Table 5: Cox proportional Hazards Model – Multivariable analysis

Prognostic factor	Hazard Ratio of Death	95% confidence interval	P-value
Age >60	3.62	2.36 – 5.55	**<0.001**
Female sex	0.76	0.54 – 1.06	0.108
CD comorbidity score			
0	1.00		
1	1.60	1.08 – 2.36	**0.0195**
2	1.83	1.03 – 3.25	**0.0383**
3	3.62	1.57 – 8.36	**0.0026**
Tumor size			
<1cm	1.00		
1-2cm	0.68	0.38 – 1.21	0.1906
>2cm	0.95	0.55 – 1.66	0.8673
Positive regional LNs	1.61	0.99 – 2.61	0.0533
Grade 2 vs 1	0.71	0.44 - 1.14	0.1603
Surgery	0.41	0.24 – 0.70	**0.0011**

• A total of 2004 patients with non-metastatic WD PanNETs were analyzed. Among those patients, 1781 underwent surgical resection, while 223 patients did not.

• The non-surgical group was significantly older (median 68 vs 60, p<0.0001) and had a shorter median time of follow-up (25.1 vs 27.8 months, p<0.0001).

• After adjusting for age, sex, CD comorbidity score, and regional LN positivity, surgical resection was associated with improved OS in patients with tumor size 1-2cm (HR 0.41, 95% CI 0.18-0.95; p=0.0364) and >2cm (HR 0.34, 95% CI 0.16-0.72; p=0.0050), but not <1cm (HR 1.92, 95% CI 0.17-21.53; p=0.5986).

RESULTS (CONTINUED)

•Multivariable analysis shows that age, Charlson-Deyo (CD) comorbidity score, and surgery were independent prognostic factors. (Table 5)

CONCLUSIONS

• To our knowledge, this retrospective analysis is the largest on well-differentiated Pan NETs.

• Active surveillance is potentially a safe approach for Pan NETs < 1cm. Larger tumors likely need active intervention.

• Prospective randomized clinical trials are needed in order to conquer the current challenges of patients with Pan NETs.

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