A comparison of the WHO 2004 and 2010 classification systems in pancreatic neuroendocrine tumors (Pancreatic NET)

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ABSTRACT

Pancreatic NETs are rare tumors with multiple classification systems. Previous classification systems included tumor size, histologic grade, mitoses, Ki67, and metastases. The current WHO 2010 system utilizes mitotic rate and Ki67% to assign a grade. We compared the WHO 2004 and 2010 classification systems in predicting mortality and metastasis.

Pathologic parameters were used to classify 50 cases of Pancreatic NET according to the WHO 2004 and WHO 2010 systems. The relationship between the WHO 2004 and WHO 2010 grading was investigated using an exact Chi squared test. WHO grade categorization was next explored by vital status, by the exact method, in order to determine if there was a difference in survivorship and metastasis by grading system. Associations between death and categorical variables were tested using exact methods and between death and continuous variables by the Wilcoxon test. Survival was explored using Cox Proportional Hazards regression (Cox).

The WHO grades were significantly associated with one another (p <0.001). Both grading systems were strongly associated with predicting mortality; all cases of mortality were in the higher grades. The 2010 grades do slightly better than 2004 grades in predicting metastasis as metastases occur only in high grades (G2 and G3). Comorbidities, tumor characteristics, margins, and site were not significantly different by mortality; patients with lymphovascular or perineural invasion had significantly higher mortality. Mitotic Index was significantly different with a median of 0 in live patients versus 15 in deceased, p <0.001. This was similarly borne out in the survival analysis using Cox, where for every one unit increase in Mitotic Index, there was about a one third increase in the hazard of death (p = 0.001). There was no significant difference in survival by tumor size, comorbidities, or margins. Our data show that the WHO 2010 grading system is strongly associated with predicting mortality and performs better in predicting liver metastasis than the 2004 grading system.

INTRODUCTION

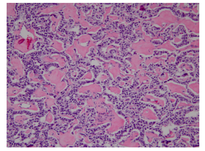
Pancreatic neuroendocrine tumors are rare tumors of the pancreas that are believed to develop from pluripotent ductal cells with the ability to differentiate along neuroendocrine lines. Approximately 80% of these tumor occur as part of inherited disorders including Multiple Endocrine Neoplasia type 1 (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis 1 (NF-1) (von Recklinghausen disease), and tuberous sclerosis complex (TSC) with the remaining 20% occurring sporadically. Pancreatic NETs comprise approximately 5% of pancreatic neoplasms and are typically associated with poor prognosis with a 10 year overall survival of 45%. Histologic features of Pancreatic NETs include small polygonal cells with moderate amount of eosinophilic cytoplasm, salt and pepper nuclei, and positive staining with neuroendocrine markers such as synaptophysin and chromogranin. High grade features include increased nuclear/cytoplasmic ration, increased mitoses, and nuclear atypia. High grade tumors often have necrosis as well as perineural and lymphovascular invasion.

Currently, these tumors are classified according to the World Health Organization 2010 grading system although there have been several revisions of this system in recent years. The 2010 classification system uses only Ki67 percentage and mitoses in grading Pancreatic NETs. Grade 1 tumors have mitotic count of <2 mitoses per 10 high-power fields (hpf) and <3% Ki67 index; Grade 2 tumors have mitotic count of 2 to 20 mitoses per10 hpf or 3% to 20% Ki67 index; and Grade 3 tumors have mitotic count of >20 mitoses per10 hpf or >20% Ki67 index.

Previous classifications included multiple pathologic and clinical parameters such as tumor size, histologic grade, mitoses, Ki67%, perineural/vascular invasion, and presence of metastasis. Accurate grading of Pancreatic NETs is critical to determine prognosis as well as determining follow-up monitoring and treatment. Our study looked at 50 resected Pancreatic NETs at Thomas Jefferson University to determine if the WHO 2010 system accurately classified tumors with respect to metastasis and survival. Future studies will investigate molecular markers that correlate with tumor grade and mortality.

METHODS

We conducted a retrospective review of 50 patients with Pancreatic NET diagnosed and treated at Thomas Jefferson University Hospital between the years of 2000 and 2010. Pathologic parameters were reviewed including tumor size, histologic grade, Ki67%, mitoses, perineural and lymphovascular invasion, lymph node and distant metastasis. These parameters were used to grade each case according to the WHO 2004 and WHO 2010 grading system. The relationship between the WHO 2004 and WHO 2010 grading was investigated using an exact Chi squared test. WHO grade categorization was next explored by vital status, by the exact method, in order to determine if there was a difference in survivorship and metastasis by grading system. Associations between death and categorical variables were tested using exact methods and between death and continuous variables by the Wilcoxon test. Survival was explored using Cox Proportional Hazards regression (Cox).



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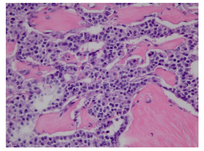

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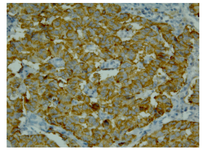

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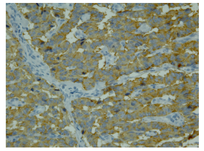

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RESULTS

Table 1 presents the summary of patient and disease characteristics. Patients were mostly female(62%) and had an average age of 60; over half had a cardiovascular comorbidity. Figure 1 presents the relationship between WHO grades 2004 and 2010. The WHO grades are significantly associated with one another (p <0.001). In Table 2, both grading systems were strongly associated with predicting mortality; all cases of mortality were in the higher grades: PDEC for 2004 and G2, and G3 for 2010. Table 3 presents similar results with regard to metastases. Again there are significant associations; however the 2010 grades does slightly better in that metastases occur only in high grades (G2 and G3). This is not the case for 2004 grading, where there is a metastasis in a lower-graded patient. Table 4 presents categorical factors and their association with mortality. Comorbidities and tumor characteristics margins and site were not significantly different by mortality; patients with lymphovascular or perineural invasion had significantly higher mortality.

Tumor size did not differ by mortality with a median [minimum, maximum] in live patients of 2.4 [0.08, 12] versus 3.45 [2.7, 7.6], p = 0.116, however mitotic Index was significantly different with a median [minimum, maximum] of 0 [0, 10] in live patients versus 15 [2, 30] in deceased, p <0.001. This was similarly borne out in the survival analysis using Cox Proportional Hazards regression (see Table 5), where for every one unit increase in Mitotic Index, there was about a one third increase in the hazard of death (p = 0.001). There was no significant difference in survival by tumor size, comorbidities, or margins.

Figure 1. WHO grade relationships

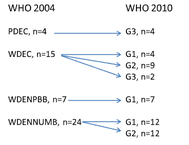

Table 2. Vital Status and WHO grades

	Vital Status		
	Alive/ Censored (n=43)	Deceased (n=7)	p-value
WHO 2004 grade			<0.001
PDEC	0	4	
WDEC	12	3	
WDENPBB	7	0	
WDENNUMB	24	0	
WHO 2010 grade			<0.001
G1	23	0	
G2	20	1	
G3	0	6	

Table 1. Patient and Disease Characteristics

WHO 2010 grade, n(%)	
G1	23 (46)
G2	21 (42)
G3	6 (12)
WHO 2004 grade, n(%)	
PDEC	4 (8)
WDEC	33 (66)
WDENPBB	7 (14)
WDENNUMB	24 (48)
Gender, n(%)	
Female	31 (62)
Male	19 (38)
Age, mean(sd); median [min, max]	60.20 (13.14); 62 [19, 82]
Vital Status, n(%)	
Alive	38 (76)
Deceased	7 (14)
Censored	5 (10)
Comorbities, n(%)	
Cardiovascular	31 (62)
History of other malignancy	12 (24)
GI-related	12 (24)
Number of Comorbities, n(%)	
0	17 (34)
1	13 (26)
2	18 (36)
3	2 (4)
Presenting Symptoms, n(%)	
Incidental	17 (34)
Abdominal pain	12 (24)
Change in bowels habits	7 (14)
Weight Loss	4 (8)
Other	13 (26)
Number of Presenting Symptoms, n(%)	
0	6 (12)
1	36 (72)
2	7 (14)
3	1 (2)
Site, n(%) (n=49)	
Body	6 (12.2)
Head	18 (36.7)
Multifocal	7 (14.3)
Tail	18 (36.7)
Mitoses, mean(sd); median [min, max]	3.48 (6.74); 1 [1, 30]
Tumor Size, mean(sd); median [min, max] (n=46)	3.67 (2.99); 2.85 [0.8, 12]
Ki-67, mean(sd); median [min, max]	7.92 (17.11); 1.80 [0.2, 75]
Confined, n(%) (n=38)	
No	9 (23.7)
Yes	29 (76.3)
Lymphovascular Invasion, n(%) (n=40)	
No	22 (55)
Yes	18 (45)
Perineural Invasion, n(%) (n=34)	
No	20 (58.8)
Yes	14 (41.2)
Margins, n(%)	
Negative	43 (86)
Positive	7 (14)
Metastases, n(%) (n=21)	
Liver	7 (33.3)
None	14 (66.7)

Table 3. Liver Metastasis and WHO grades (n=19)

	Liver Metastasis (n=21)		p-value
	No (n=14)	Yes (n=7)	
WHO 2004 grade			0.0149
PDEC	0	1	
WDEC	2	5	
WDENPBB	2	0	
WDENNUMB	10	1	
WHO 2010 grade			0.0127
G1	8	0	
G2	6	5	
G3	0	2	

Table 4. Associations with Mortality

	Alive (n=43)	Deceased (n=7)	
	n		p-value
*Comorbidity			
Cardiology			
No	26 (83.87)	5 (16.13)	0.695
Yes	17 (85.47)	2 (10.53)	
History of Other Malignancy			
Yes	10 (83.33)	2 (16.67)	1.000
No	33 (86.84)	5 (13.16)	
GI-related			
Yes	10 (83.33)	2 (16.67)	1.000
No	33 (86.84)	5 (13.16)	
Margins			0.250
Negative	38 (88.837)	5 (11.63)	
Positive	5 (71.43)	2 (28.57)	
Site			0.557
Body	5 (83.33)	1 (16.67)	
Head	14 (77.78)	4 (22.22)	
Multifocal	6 (85.71)	1 (14.29)	
Tail	17 (94.44)	1 (5.56)	
LVI Invasion (n=40)			0.0335
Yes	14 (77.78)	4 (22.22)	
No	22 (100.00)	0 (0.00)	
PN Invasion (n=34)			0.0216
Yes	10 (71.43)	4 (28.57)	
No	20 (100.00)	0 (0.00)	

Table 5. Univariate Survival Analysis using Cox Proportional Hazards Regression

	Hazard Ratio	95% CI	p-value
Mitotic Index	1.33	(1.13, 1.57)	0.001
Tumor Size	1.06	(0.83, 1.35)	0.629
Comorbidity			
Cardiology	1.32	(0.24, 7.22)	0.749
History of Other Malignancy	1.12	(0.21, 6.01)	0.896
GI-Related	1.06	(0.20, 5.67)	0.945
Mangins, Pos vs. Neg	3.38	(0.62, 18.50)	0.160

CONCLUSION

The WHO 2010 grading system is strongly associated with predicting mortality and performs better in predicting liver metastasis than the 2004 grading system. Future studies include determining which tumors responded best to chemotherapy following surgery as well as finding molecular markers that correlate with tumor grade and prognosis.

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