Ki-67 Proliferative Index Predicts Progression Free Survival in Ileal Carcinoids

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Introduction

- Despite similarities in the morphology of small intestinal carcinoids, there is a wide variation in their potential for metastasis as well as in the growth rate of metastases, thereby limiting the ability of clinicians to rationally define management strategies.
- The conventional indicators of prognosis such as tumor size, depth of tumor invasion, histologic features and mitotic index are currently used for assessing the metastatic potential of gastrointestinal neuroendocrine tumors (GI-NET's). Ki-67 proliferative index (Ki-67 index) has also been suggested to be useful in predicting the metastatic potential of GI-NETs and survival of patients with GI-NETs.
- The current study was undertaken to test the hypothesis that Ki-67 index predicts progression-free survival in ileal carcinoids.

Design

- Ki-67 immunohistochemical stain was performed on tissue sections that represented the histologically most aggressive areas of both primary and metastatic ileal carcinoid tumors from 57 patients.
- Ki-67 stained sections were initially screened microscopically. The areas with the highest numbers of Ki-67 labeled nuclei ("hot spots") were encircled and the Ki-67 index was calculated by the Ariol™ Imaging System (Applied Imaging, Santa Clara, CA) for computer assisted analysis.
- The tumors were graded based on mitotic index and Ki-67 index as per recent CAP guidelines.
- Clinical and pathologic variables affecting the progression free survival were analyzed.

Results

- Patients with a higher initial stage were more likely to experience disease progression, with 9 of 12 progressing patients being stage IV at initial diagnosis. Higher histologic grade was also associated with a greater likelihood of disease progression. Among the patients with stage IV disease at the time of initial diagnosis, the mean Ki-67 was significantly greater in both the primary and metastatic tumors in patients who subsequently experienced disease progression (10.5% and 14.8% respectively) than in patients with no progression during the follow-up period (1% and 1.5%, respectively).
- Patients with Ki-67 index > 2% (in either the primary tumor or at metastatic sites at the time of initial presentation) had a significantly greater risk of progression than patients with Ki-67 index ≤ 2%, with 2-year progression-free survival rates of 51% (95% CI: 30%, 87%) and 98% (95% CI: 95%, 100%), respectively (p<0.001).
- The only predictor found to be significant in an adjusted analysis of progression-free survival was having a Ki-67 index of > 2% at either primary or metastatic site.

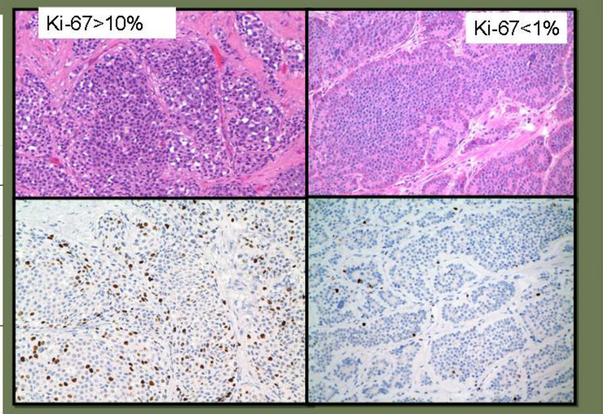
Patient and tumor characteristics (n=57); no. and %

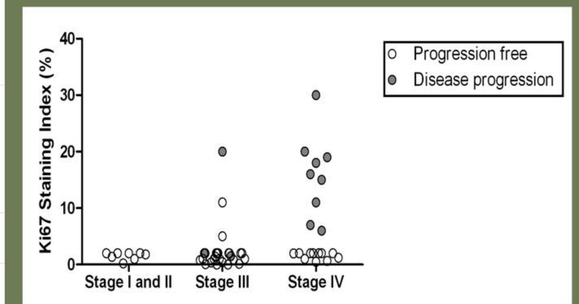
Age, y (mean±SD)	58.5	±	12.1
Time of follow up, mo (mean±SD)	31	±	32.1
Disease progression	12		21%
Initial stage			
I	4		7%
IIA	2		4%
IIB	2		4%
IIIB	29		51%
IV	20		35%
Multicentricity	19		33%
Tumor size, cm (mean±SD)	1.82	±	0.91
Tumor necrosis	5		9%
Morphologic atypia	10		18%
Overall Grade			
G1	45		79%
G2	11		19%
G3	1		2%

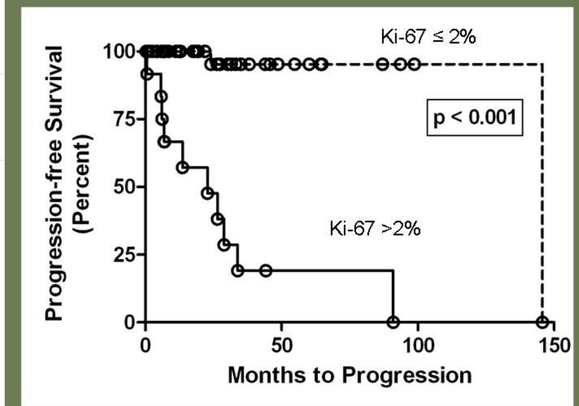
Significance of variables on progression-free survival

	Unadjusted Analysis		
	p-value	HR*	(95% CI)
Age, y (mean±SD)	0.453	1.02	(0.97, 1.06)
Initial stage IV	0.005	9.15	(1.96, 42.69)
Multicentricity	0.626	1.37	(0.39, 4.83)
Necrosis	0.893	0.87	(0.11, 6.90)
Atypia	0.002	6.96	(2.03, 23.86)
Overall Grade ≥G2	0.001	36.68	(4.69, 286.99)
Mitotic Index ≥2 per 10 hpf	0.149	2.69	(0.70, 10.28)
Ki67 staining index > 2% at either primary or metastatic	0.001	36.68	(4.69, 286.99)

* Hazard ratio







Conclusion

- Ki-67 index predicts progression-free survival in patients with ileal carcinoids.