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Impact of peritumoral and intratumoral budding in esophageal adenocarcinomas☆

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Summary Tumor budding has prognostic significance in many carcinomas and is defined as the presence of detached isolated single cells or small cell clusters up to 5 cells at the invasion front (peritumoral budding [PTB]) or within the tumor (intratumoral budding [ITB]). For esophageal adenocarcinomas (EACs), there are currently only few data about the impact of this morphological feature. We investigated tumor budding in a large collective of 200 primarily resected EACs. Pancytokeratin staining was demonstrated to be superior to hematoxylin and eosin staining for the detection of buds with substantial to excellent interobserver agreement and used for subsequent analysis. PTB and ITB were scored across 10 high-power fields (HPFs). The median count of tumor buds was 130/10 HPFs for PTB (range, 2-593) and 80/10 HPFs for ITB (range, 1-656). PTB and ITB correlated significantly with each other ($r = 0.9$; $P < .001$). High PTB and ITB rates were seen in more advanced tumor categories ($P < .001$ each); tumors with lymph node metastases ($P < .001$/$P = .002$); and lymphatic, vascular, and perineural invasion and higher tumor grading ($P < .001$ each). Survival analysis showed an association with worse survival for high-grade ITB ($P = .029$) but not PTB ($P = .385$). However, in multivariate analysis, lymph node and resection status, but not ITB, were independent prognostic parameters. In conclusion, PTB and ITB can be observed in EAC to various degrees. High-grade budding is associated with aggressive tumor phenotype. Assessment of tumor budding, especially ITB, may provide additional prognostic information about tumor behavior and may be useful in specific cases for risk stratification of EAC patients.

1. Introduction

The incidence of esophageal adenocarcinoma (EAC), mostly arising from preneoplastic Barrett metaplasia, has been on the rise over the last decades in Western countries, with a dramatic 7-fold increase reported in the United States

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since the 1970s [1,2]. Biologically, it is a highly aggressive tumor, and patients often present with already advanced disease. This results in a poor overall prognosis with 5-year survival of less than 30%, despite marked improvements in surgery, multimodal therapeutic concepts, and early detection programs [3,4].

Today, reliable risk stratification is essential for choosing the appropriate "tailored" treatment for cancer patients. Pretherapeutic staging and also the determination of tumor aggressiveness, which may be estimated by histopathologic tumor grading, provide crucial information [5]. However, tumor features, which have the ability to enhance the prognostic accuracy of the current staging systems, such as the Union for International Cancer Control/American Joint Committee on Cancer TNM classification or the World Health Organization (WHO) tumor classification, are still lacking for EACs.

Tumor budding is a morphological feature detectable in many solid cancers and is defined as single cells or cell clusters of up to 5 cells at the invasion front or within the tumor [6-9]. Tumor budding has been studied in a large number of different carcinomas and has shown to be associated with a more aggressive tumor phenotype. In a subset of cases, tumor budding may represent the process of epithelial-mesenchymal transition, which is associated with higher invasiveness of single carcinoma cells that have lost their cell-to-cell contacts, which subsequently leads to higher rates of metastatic spread [10]. In gastrointestinal cancers, most studies about tumor budding have been conducted in colorectal cancer, where it has been shown to be an additional independent prognostic factor in several studies and clinical settings. This has led to the general acceptance and the inclusion of tumor budding as an additional

Table 1 Peritumoral and intratumoral budding and pathologic features

	Total	Peritumoral budding			Intratumoral budding		
		Low	High	χ^2	Low	High	χ^2
Total		100	99		100	100	
pT category							
pT1	60	50	10	<0.001	49	11	<0.001
pT2	28	15	12		15	13	
pT3	109	35	74		36	73	
pT4	3	0	3		0	3	
Lymph node metastases							
Absent	93	58	34	0.001	56	37	0.007
Present	107	42	65		44	63	
Lymphatic vessel invasion							
Absent	93	63	29	<0.001	62	31	<0.001
Present	107	37	70		38	69	
Venous invasion							
Absent	169	92	76	0.003	92	77	0.006
Present	31	8	23		8	23	
Perineural invasion							
Absent	137	87	49	<0.001	89	48	<0.001
Present	63	13	50		11	52	
Distant metastases							
Absent	189	94	94	1.0	95	94	1.0
Present	11	6	5		5	6	
Grading							
G1-G2	105	68	36	<0.001	71	34	<0.001
G3-G4	95	32	63		29	66	
Lauren classification							
Intestinal	165	94	70	<0.001	95	70	<0.001
Mixed	17	3	14		3	14	
Diffuse	12	0	12		0	12	
Unclassified	6	3	3		2	4	
Resection status							
R0	178	96	81	0.01	95	83	0.012
R1	22	4	18		5	17	

NOTE. Cutoff for low grade versus high grade: median (median PTB, 130 buds/10 HPFs; median ITB, 80 buds/10 HPFs). Because of the small tumor size in 1 case, ITB was assessed in 200 carcinomas; and PTB, in 199 carcinomas.