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Original contribution

A study of appendiceal crypt cell adenocarcinoma (so-called goblet cell carcinoid and its related adenocarcinoma) ☆

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Summary Goblet cell carcinoids (GCCs) of the appendix are rare tumors, characterized by a carcinoid-like organoid growth pattern. Despite the term *carcinoid*, neuroendocrine features are inconspicuous, and its behavior is distinct from carcinoid. Its high-grade counterpart is designated as adenocarcinoma ex GCC. We conducted a retrospective study of 105 tumors to find prognostic values of a variety of clinicopathologic features. The tumors were subclassified as low grade, equivalent to classic type, and high grade, defined as loss of organoid pattern, and a proportion (%) of low and high grades were documented in each tumor. Correlations between survival and various clinicopathologic parameters were investigated. One-third were pure low grade, while the remainder contained variable high-grade component ranging from 5% to 95%. Neuroendocrine cell component ranged from 0% to 90% (median, 5), while mucus cell component ranged from 5% to 100% (median, 70). By univariate analysis, size, stage, high-grade component, nuclear grade, surgery, and chemotherapy correlated with cancer-related survival (CSS), and by multivariate analysis, stage (P = .001), high-grade component (P = .008), and tumor size (P = .005) correlated with CSS. There was significant difference in CSS when the cases were grouped by high-grade component: <40%, 40% to 90%, and ≤90% (P < .001). Our results indicate that staging and proportion of high-grade histology may provide important prognostic information. Neuroendocrine component was insignificant in both low- and high-grade areas. In light of our findings, this tumor type is best regarded as a variant of adenocarcinoma, and the term *crypt cell adenocarcinoma* more appropriately reflects the nature and origin of this tumor group.

☆ Disclosures: None.

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1. Introduction

Goblet cell carcinoid (GCC) and adenocarcinoma ex GCC represent the low-grade and high-grade spectrum of a group of rare appendiceal tumors with distinct clinical and pathologic characteristics. A few studies have demonstrated correlation between high-grade transformation (so-called adenocarcinomatous transformation) and clinical outcome [1-4]. In this study, we performed a comprehensive analysis of 105 tumors to describe various clinical and pathologic features and investigate potential prognostic factors, with an aim to identify an informative and objective grading system. Issues regarding whether GCC is a variant of adenocarcinoma or carcinoid tumor will also be discussed.

2. Materials and methods

GCC of appendix and its related adenocarcinoma (adenocarcinoma ex GCC) were retrieved from the histopathology archives of The Christie NHS Foundation Trust during the period from 1993 to 2016. Inclusion criteria for the study were a primary appendiceal tumor treated by resection, availability of histologic slides, and follow-up information. Tumors arising in association with mucosal dysplastic lesion such as tubular adenoma were not included in the study. A total of 105 tumors (46 goblet cell carcinoids and 59 adenocarcinomas ex goblet cell carcinoid) were investigated.

Hematoxylin and eosin (H&E)–stained sections from only primary appendiceal tumor were evaluated for a variety of morphological features described below. When the tumor directly extended to neighboring organs, the whole tumor involving the appendix as well as invading the other organs was evaluated for histologic features. The number of slides examined for the primary tumor per case ranged from 2 to 51 (median, 16).

Tumors were assessed for low-grade and high-grade components, and proportions (%) of both components in 5% increments were documented. Low-grade tumor component was defined as organoid nests of cells constituting an admixture of 4 cell types: mucus cells, eosinophilic cuboidal to columnar cells, neuroendocrine cells, and Paneth cells. The nests were generally rounded with smooth contour, but could display compressed linear configuration when they were seen in the muscularis propria [1,5]. Some nests also contained lumens, which were mostly small, but could have dilatation due to accumulated intraluminal mucus secretion or necroinflammatory debris [5]. Low-grade component encompassed, on one end of the spectrum, classic GCC, where the tumor was composed of nests of predominantly goblet cells, and on the other end of the spectrum, tubular adenocarcinoid by Warkel or microglandular adenocarcinoma by Wolff, where the tumor was composed of small discrete acini or tubules lined by a single layer of cuboidal or columnar cells with eosiniphilic cytoplasm [1,6,7]. Of note, the latter type (tubular adenocarcinoid) is different from so-called tubular carcinoid, a variant of classic carcinoid tumor, which comprises exclusively neuroendocrine cells.

High-grade component was defined by any signs of loss of organoid pattern and acquired irregularity and complexity in nests, including complex branching cords, enlarged or confluent nests or irregular nests with jagged contours, and fused or cribriform glands. Furthermore, patterns generally indicating poorly differentiated tumor, such as large lobules and solid sheets, and individual discohesive (poorly cohesive) single cells or single files were also included in the high-grade category.

Nuclear grade was divided into low and high grade. Low grade was defined by small size, round and smooth nuclear contour, uniform chromatin pattern, and small pinpoint-sized nucleoli. Prominent nucleoli were often seen in eosinophilic cuboidal to columnar cells [6]. If other nuclear features were

Table 1 Clinical and pathologic characteristics

Characteristics	N (median)	%
Age	25–79 (54)	
Gender		
Male	54	51.4
Female	51	48.6
Stage		
Localized		
I	5	4.8
II	52	49.5
III	13	12.4
Metastatic		
IV	35	33.3
Primary tumor size (mm)	5–150 (32)	
Perineural invasion		
Yes	92	87.6
No	13	12.4
Vascular invasion		
Yes	10	9.5
No	95	90.5
Lymphovascular invasion		
Yes	50	52.4
No	55	47.6
High-grade component (%)	0–95 (40)	
Nuclear grade		
Low	74	70.5
High	31	29.5
Mucus cell component (%)	5–100 (70)	
Neuroendocrine cell component (%)	0–90 (5)	
Extravasated mucin component (%)	0–95 (5)	
Surgery		
Appendectomy	19	18.0
Extensive surgery	86	82.0
Resection margins		
Positive	21	20.0
Negative	84	80.0
Chemotherapy		
Yes	50	47.6
No	50	47.6
NA	5	4.8
Total	105	100