Article published online: 2024-03-11

Appendiceal Goblet Cell Carcinoma: Comparison of Classification and Staging Systems with Evaluation of the Prognostic Role of Immunohistochemistry Stains

Rachel Masia[1] Vincent Marcucci[1] Colton Moore[2] Xiu Sun[3] Arthur Topilow[3] Timothy Gelatt[3] Glenn Parker[1,2]

[1] Department of Surgery, Jersey Shore University Medical Center, Neptune, NJ, United States
[2] Department of Surgery, Division of Colon and Rectal Surgery, School of Medicine, St. George's University, St. George's Grenada, West Indies, Grenada
[3] Department of Pathology, Jersey Shore University Medical Center, Neptune, NJ, United States

Address for correspondence Vincent Marcucci, MD, Department of Surgery, Jersey Shore University Medical Center, 1945 Route 33, Neptune, NJ, 07756, United States (e-mail: Marcucv1@gmail.com).

J Coloproctol 2024;44(1):e41–e46.

Abstract

Background Goblet cell carcinoma (GCC) of the appendix is a unique lesion that exhibits features of both adenocarcinoma and neuroendocrine tumors. Due to the rarity of this cancer, multiple grading (e.g., Tang, Yozu, and Lee) and staging systems (e.g., tumor, lymph nodes, and metastasis [TNM]) have been developed for classification. This study aimed to compare commonly used classification systems and evaluate the prognostic effectiveness immunohistochemical staining may or may not have for appendiceal GCC.

Methods An electronic medical records review of patients who were diagnosed with GCC of the appendix in our hospital system from 2010 to 2020. The data were collected regarding the age at diagnosis, gender, initial diagnosis at presentation, operation(s) performed, final pathology results, current survival status, and year of recurrent disease or death year.

Results Ten patients were evaluated. Seventy percent of the patients were above the age of 50 years at diagnosis. Postdischarge survival ranged from 1 month to 109 months postdiagnosis. Two patients expired from GCC at 13- and 54-months following diagnosis. When comparing the classification systems, Lee categorized more patients as high risk than Tang and Yozu. Immunohistochemical staining was analyzed using four staining methods: Ki67, E-cadherin, Beta-catenin, and p53. Tumor, lymph nodes, and metastasis staging has supportive evidence for worsening prognosis and overall survival secondary to the depth of invasion of the tumor.

Conclusion Tumor, lymph nodes, and metastasis staging may be superior to the other classification systems in predicting overall mortality. Our study demonstrated that immunohistochemistry staining does not appear to have a significant impact in determining the prognosis for GCC of the appendix.

Keywords
- general surgery
- colorectal
- appendiceal cancer
- goblet cell cancer
- surgical oncology

received
December 7, 2023
accepted after revision
January 10, 2024

DOI https://doi.org/10.1055/s-0044-1779601.
ISSN 2237-9363.

© 2024. The Author(s).
This is an open access article published by Thieme under the terms of the Creative Commons Attribution 4.0 International License, permitting copying and reproduction so long as the original work is given appropriate credit (https://creativecommons.org/licenses/by/4.0/).

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Table 1 Tumor, lymph node, and metastasis (TNM) classification

TNM	Stage	Description
T - tumor invasion	T1	Invades the submucosa
	T2	Invades the muscularis propria
	T3	Invades into the subserosa or mesoappendix
	T4	Invades through visceral peritoneum and adjacent organs/structures
N - lymph nodes (LN)	N0	No lymph node involvement
	N1	Less than 4 positive lymph nodes
	N2	4 or more positive lymph nodes
M - metastatic disease	M1	Evidence of distant metastatic disease

Introduction

Cancer of the appendix is rare, with the incidence being 0.12 cases per 1 million people per year.[1] Goblet cell carcinoma (GCC) is an appendiceal neoplasm that exhibits unique features of both glandular (adenocarcinoma) and neuroendocrine (carcinoid) components.[2] There is refutable literature as to whether GCC is a variant of adenocarcinoma, carcinoid family, or a separate entity.[3] This cancer is diagnosed more commonly in individuals over 50 years of age; with more than 50% of appendiceal GCC presenting as acute appendicitis.[1,4] However, GCC is diagnosed in less than 1% of patients who have undergone an appendectomy; usually as an incidental finding after pathological analysis from intraoperative specimens.[4] Patients commonly present with abdominal pain, and, in advanced stages, a palpable mass may be appreciated on physical exam.[3–5] Interestingly, up to 50% of cases have metastatic disease at presentation.[5] The most common site of metastasis is local invasion into the ileum, cecum, and ascending colon.[5,6] Goblet cell carcinoma has been found to metastasize to the lymphatic system, with implantation on the peritoneum, omentum, and ovaries.[6]

There is no standardization or consensus among institutions or scientific literature regarding the classification of appendiceal GCC; thus, multiple grading and staging systems are used inconsistently. Similarly to the staging of adenocarcinoma, TNM staging has been used as a predictor for outcomes of GCC.[4,6] Tang, Yozu, and Lee grading systems have been proposed to be more accurate in determining GCC outcomes when considering histological features.[5,6] The common classification systems we investigated are outlined in ►**Tables 1–4**.[5,7–9] In addition to non-standardized classification, there are variations in the investigative immunohistochemical stains performed. Inconsistent utilization of classification and staging systems make integrating and literature comparisons challenging, hindering the analysis of available data used to draw robust conclusions.

This study aims to evaluate a single institution patient population with GCC of the appendix. By comparing the four current classification systems, we hope to determine and further stratify which classification system should be utilized as the gold standard. In addition, we want to evaluate whether there is a role for immunohistochemistry stains in determining the prognosis and outcomes of this tumor burden.

Methods

An electronic medical records review of patients who were diagnosed with GCC of the appendix in the Hackensack Meridian hospital system from 2010 to 2020 was completed.

Table 2 Tang classification

	Description	Characteristics
Group A	Typical GCC	• Well defined goblet cells arranged in clusters or cohesive linear pattern • Minimal cytologic atypia • Minimal or no desmoplasia • Minimal architectural distortion of appendiceal wall • Degenerative change with extracellular mucin is acceptable
Group B	Adenocarcinoma ex GCC, signet ring cell type	• Goblet cells or signet cells in irregular, large clusters, but no confluent sheets of cells • Dyscohesive single cell infiltrating pattern • Significant cytologic atypia • Desmoplasia and destruction of appendiceal wall
Group C	Adenocarcinoma ex GCC, poorly differentiated carcinoma	• At least focal evidence of goblet cell morphology • A component of poorly differentiated adenocarcinoma, which appears as gland forming, confluent sheets of signet ring cells, or undifferentiated carcinoma

Abbreviation: GCC, goblet cell carcinoma.

Table 3 Yozu classification

Grade	Features	Diagnostic criteria
Low	• Tubular growth with round or oval discrete tumor clusters comprising goblets cells, cuboidal cells, and Paneth-like cells, with or without lumens. • Simple trabecular growth consistent with tubules sectioned longitudinally. • Limited tubule fusion or crowding. • Mucin pools with discrete tubules or clusters. • Tubular non-mucinous glands.	• $\geq$ 75% low grade features • $<$ 25% high grade features
Intermediate		• $\geq$ 50% low grade features
High	• Single cells mixed with abortive tubules. • Single file growth or sheets of tumor cells mixed with abortive tubules. • Fusion of goblet cell clusters to form anastomosing complex growth of goblet cell clusters or tubules. • Large aggregates of goblet cells or goblet cells in extracellular mucin. • Mucin-poor tumor cells in clusters or nests with high nuclear-to-cytoplasmic ratio. • Glands lined by cuboidal or columnar cells with high cytologic grade that resemble adenocarcinoma. • Glands floating in mucin lined by columnar cells with high cytologic grade.	• $<$ 50% low grade features

Table 4 Lee classification. A low-grade classification score is 0 to 1/3, and a high-grade classification score is 2 to 3/3

Feature	Description	Score
Cytologic atypia	High nuclear-to-cytoplasmic ratio with reduction or loss of intracytoplasmic mucin. Nuclei are enlarged with irregular shape.	1. absent 2. present
Stromal desmoplasia	Dense fibrous connective tissue surrounding tumor cell clusters or cells. Replaces smooth muscle of muscularis propria. Distorts the normal architecture of appendix.	1. absent 2. present
Solid growth pattern	Loss of distinct cell cluster architecture. Cells tightly packed together with minimal or no stroma.	1. absent 2. present

Data were collected regarding the age at diagnosis, gender, initial diagnosis at presentation, operation(s) performed, final pathology results (staging and stains performed), current survival status, and year of recurrent disease or year of death (if applicable). The pathology department at Jersey Shore University Medical Center (JSUMC) was able to stage and grade each patient using the TNM, Tang, Yozu, and Lee classification systems. In addition, staining was performed on the specimens using Ki67, p53, E-cadherin, and β-catenin to evaluate the association of these stains with prognosis. Data were analyzed using a Microsoft Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet.

Results

Ten patients were diagnosed with GCC of the appendix at our institution. Nine patients presented with acute appendicitis, while one patient presented with a small bowel obstruction, as demonstrated in ►**Table 5**. Demographics of the patient population included 8 males and 2 females, with 7 patients above the age of 50 at diagnosis. The overall ages ranged from 37 to 84 years old. Ninety percent of this patient population underwent laparoscopic appendectomies at presentation. The patient who had presented with a small bowel obstruction underwent a laparoscopic right hemicolectomy to resect the obstructing mass. One patient underwent reoperation secondary to positive margins on permanent pathology requiring another a right hemicolectomy. Postdischarge follow-up revealed that 8 patients are alive, with survival ranging from 1 month to 109 months postdiagnosis. Two patients (patients 4 and 9) expired from GCC at 13 and 54 months following diagnosis, respectively. Patient 4 died from metastatic disease after surgical resection and adjuvant chemotherapy. Patient 9 died from complications of coronavirus disease 2019 (COVID-19); his cancer status was unknown at the time of his death.

A summary of the results from TMN staging, treatment, and survival outcomes is displayed in ►**Table 5**. Patient 8 was staged as T1 disease, with the remainder of the patients staged as T2 (20%), T3 (50%), and T4 (20%) disease. All patients with T4 disease expired. Patient 4 presented with invasive disease and a staging consistent with T4N2M1 disease. Compared with patient 4, who expired at 13 months, patient 9 passed away after 54 months, secondary to complications of COVID-19. Using the Tang grading system, patients were classified as A (30%), B (60%), and C (10%). The Yozu system classified patients as low (60%), intermediate (30%), and high (10%) grade. The Lee grading system classified patients as low (60%) and high (30%) grade. When comparing the classification systems, Lee categorized more

Table 5 Summary of patient epidemiology, classification systems, treatments, and overall survival outcomes

Patient	Initial presentation	Age at diagnosis	Gender	TNM	Tang	Yozu	Lee	Treatment	Status	Months alive since diagnosis
1	Appendicitis	78	M	T3	A	Low	Low	Appendectomy	Alive	56
2	Appendicitis	37	M	T2	B	Intermediate	Low	Appendectomy	Alive	42
3	Appendicitis	84	F	T3	B	Intermediate	High	Appendectomy	Alive	45
4	Bowel obstruction	74	M	T4 N2 M1	C	High	High	Right hemicolectomy	Dead	13*
5	Appendicitis	53	F	T3	B	Intermediate	High	Appendectomy	Alive	77
6	Appendicitis	43	M	T2	B	Low	High	Appendectomy	Alive	109
7	Appendicitis	49	M	T3	B	Low	Low	Appendectomy, Right hemicolectomy for positive margins	Alive	63
8	Appendicitis	72	M	T1	B	Low	Low	Appendectomy	Alive	1
9	Appendicitis	81	M	T4	A	Low	Low	Appendectomy	Dead	54*
10	Appendicitis	71	M	T3	A	Low	Low	Appendectomy	Alive	90

* Represents the patients who expired.

patients as high risk than Tang and Yozu. Although patient 9 was stage T4, he was considered low grade when using the Tang, Lee, and Yozu grading systems. Patient 4 was high grade according to all classification systems showing consistency for this specific patient.

Immunohistochemical staining was analyzed using 4 prognostic staining methods: Ki67, E-cadherin, Beta-catenin, and p53, which can be seen in ►**Table 6**. The range of Ki67 was between 7 and 80% and was not significantly elevated in the patients who died from their disease. Excluding patient 4's adenocarcinoma component, all patients were positive for E-cadherin and Beta-catenin. Our patient population was focally weak for p53, except for patient 6 and patient 4's adenocarcinoma component. Patient 6 stained diffusely strong for p53 but did not have a poorer prognosis (currently alive for 109 months since diagnosis). Patient 4's adenocarcinoma component stained focally strong, and his overall survival was low compared with the other patients in the study.

Discussion

Goblet cell carcinoma can commonly spread lymphatically and to other peritoneal structures; for this reason, TNM staging for adenocarcinoma can be used.[10] Tumor, lymph nodes, and metastasis staging system uses tumor depth of invasion, nodal status, and presence of metastatic disease to further classify tumors.[10] Continued confusion regarding these released guidelines was demonstrated by Wen et al., who showed that incorrectly diagnosing GCC as a neuroendocrine tumor led pathologists to misuse the staging classification for GCC.[11] In 2008, Tang et al. presented a grading system for GCC of the appendix based on histology. This

Table 6 Immunohistochemistry staining used to evaluate role in prognosis

Patient	Ki67	E-cadherin	Beta catenin	p53
1	7%	+	+	Focal weak
2	40%	+	+	Focal weak
3	40%	+	+	Focal weak
4	NEC 7% Adenocarcinoma 40%	NEC (+) Adenocarcinoma (-)	NEC (+) Adenocarcinoma (-)	NEC (focal weak) Adenocarcinoma (focal strong)
5	20%	+	+	Focal weak
6	50%	+	+	Strong diffuse
7	80%	+	+	Focal weak
8	60%	+	+	Focal weak
9	15%	+	+	Focal weak
10	40%	+	+	Focal weak

 © 2024. The Author(s).

system outlined three groups: A) typical GCC, B) adenocarcinoma ex GCC, signet ring cell, and C) adenocarcinoma ex GCC, poorly differentiated.[5] Based on our literature review, Tang's system has been the most used in conjunction with the TNM system; however, there is still no universally accepted model. In our institution, the Tang classification was not originally included in pathology reports. This may be due to the limitations of Tang's classification system. Wang et al. highlighted that the lack of immunomarkers to objectively separate group A (goblet cells) from group B (signet cells) leads to subtle histologic interpretations and variations among pathologists.[12] Similarly, Yozu et al. demonstrated the inability of Tang's system to quantitatively distinguish one group from another.[10] Recently, in 2018, Yozu et al. proposed a new classification system that categorized GCC into 3 grades: $>75\%$ tubular or clustered growth for low grade (grade 1), 50 to 75% for intermediate grade (grade 2), and $<50\%$ for high grade (grade 3)[10]. The 2019 World Health Organization (WHO) classification of tumors (5th edition) adopts Yozu's system and recommends that pathologists use it for tumor grading.[8] Our institution utilizes the WHO recommendation in practice. Lastly, Lee et al., in 2015, created a scoring system incorporating cytologic atypia, stromal desmoplasia, and solid growth pattern to differentiate low-grade from high-grade tumors.[13] Our goal was to determine which present-day classification system is consistently valid in staging and prognosis of GCC of the appendix. We also wanted to evaluate whether there were any stains that have prognostic value.

Based on our institution's data, it is difficult to conclude which classification system is the most consistent when determining the prognosis of appendiceal GCC. Initially, TNM staging appeared to be superior compared with the other grading systems. The supportive evidence for worsening prognosis and overall survival was secondary to the depth of invasion of the tumor. Patients 4 and 9 were the only ones to expire, and both were diagnosed with T4 disease. Complications of COVID-19 may have contributed to the death in patient 9. Using TNM staging, patient 4 had positive lymph node involvement and distant metastatic disease. This patient's overall survival was lower compared with that of other patients (13-month survival after diagnosis), confirming that the spread of cancer cells to distant organs leads to worse outcomes. In addition, patient 9 was categorized as low grade in Tang, Yozu, and Lee's classification systems, meaning that the prognosis should have been a favorable outcome. Yet, this patient's survival outcome was poor possibly due to the invasiveness of the tumor (T4); however, mortality from COVID-19 remains high. After reviewing the histologic classification systems, we were unable to determine which classification was better when focusing on prognosis. This is most likely due to our institution's small sample size. Based on our institution's data, it was unclear which classification system is superior when evaluating patient outcomes.

When looking at pathologic features of tumors, immunohistochemistry stains can be crucial in determining cancer diagnosis and prognosis. The Ki67 antigen is a nuclear protein associated with proliferative activity. It is used as a prognostic marker for cancers, such as breast, soft-tissue, lung, prostate, cervical, and central nervous system tumors.[9,14] Beta-catenin is another protein which advances transcription of genes that encourage tumor cell survival and proliferation.[14] Beta-catenin has been found to be an important cancer marker for colorectal, breast, and liver cancers, as well as melanoma and leukemias.[15] In addition, E-cadherin is a tumor suppressor protein that plays a role in the ability of a cancer cell to metastasize to a distant site of the body.[16] Adhesion between neighboring cells is influenced by E-cadherin, when lost, tumor cells can invade beyond the basement membrane.[17] Loss of another tumor suppressor protein, p53, fosters tumor aggressiveness and has been linked to osteosarcoma, soft-tissue sarcoma, acute leukemia, breast, adrenal, and kidney cancer.[18] Cancer research has demonstrated the utility of immunohistochemistry staining determination of prognosis, the extent of cancer invasion, response to therapy, and residual positive tumor tissue posttreatment for tumors such as those found in breast cancer.[19] We, however, were unable to demonstrate whether these prognostic stains can be used for GCC of the appendix. Staining is important when diagnosing this tumor because it has both neuroendocrine features (stains for chromogranin and synaptophysin) as well as features of adenocarcinoma. In our study, we evaluated four possible prognostic cancer stains: Ki67, E-cadherin, β-catenin, and p53. These stains have been shown in other cancers to be helpful in determining invasiveness and prognosis. However, in our study, it is unclear whether these stains play a role in the prognosis and survival outcomes for GCC of the appendix. One of the major limiting factors in determining their significance in our study may be attributed to a small sample size.

In summary, there is no standardized classification system for GCC of the appendix, making it challenging to compare and combine studies amongst different institutions. Our study could not determine the most reliable classification system for GCC of the appendix when evaluating survival outcomes. However, TNM staging may be superior to the other classification systems in predicting overall mortality. Our data may be limited by the patient with COVID-19 making it difficult to conclude whether TNM staging was a better classification system than the grading systems mentioned. The Tang, Yozu, and Lee grading systems failed to determine survival outcomes accurately. For this reason, it is unclear which classification system should be used routinely. Our study demonstrated that immunohistochemistry staining does not appear to have a significant impact in determining the prognosis for GCC of the appendix. However, the results may be more robust with a larger sample size. The most significant limitation of our study is the small sample size, with only 10 patients, likely due to the rarity of this tumor. In the future, it would be beneficial to have a multi-institutional study to further evaluate which classification system is most consistent when considering prognosis and survival for GCC of the appendix. We hope a broader study can determine more significant conclusions for this rare tumor.

Disclosures
None.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer 2002;94(12):3307–3312
2 Ramnani DM, Wistuba II, Behrens C, Gazdar AF, Sobin LH, Albores-Saavedra J. K-ras and p53 mutations in the pathogenesis of classical and goblet cell carcinoids of the appendix. Cancer 1999;86(01):14–21
3 Palmer K, Weerasuriya S, Chandrakumaran K, et al. Goblet Cell Adenocarcinoma of the Appendix: A Systematic Review and Incidence and Survival of 1,225 Cases From an English Cancer Registry. Front Oncol 2022;12:915028
4 Rossi RE, Luong TV, Caplin ME, et al. Goblet cell appendiceal tumors–management dilemmas and long-term outcomes. Surg Oncol 2015;24(01):47–53
5 Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol 2008;32(10):1429–1443
6 Pahlavan PS, Kanthan R. Goblet cell carcinoid of the appendix. World J Surg Oncol 2005;3:36. Doi: 10.1186/1477-7819-3-36
7 Burgart L, Chopp W, Jain D, et al. Protocol for the Examination of Specimens from Patients With Carcinoma of the Appendix. CAP 2021; (June):1–19
8 Yozu M, Johncilla ME, Srivastava A, et al. Histologic and Outcome Study Supports Reclassifying Appendiceal Goblet Cell Carcinoids as Goblet Cell Adenocarcinomas, and Grading and Staging Similarly to Colonic Adenocarcinomas. Am J Surg Pathol 2018;42(07):898–910
9 Lee LH, McConnell YJ, Tsang E, et al. Simplified 2-tier histologic grading system accurately predicts outcomes in goblet cell carcinoid of the appendix. Hum Pathol 2015;46(12):1881–1889
10 Edge SB. Appendix. In: AJCC cancer staging manual., editor. 7th ed. New York:: Springer;; 2010. pp. 133–138
11 Wen KW, Hale G, Shafizadeh N, Hosseini M, Huang A, Kakar S. Appendiceal goblet cell carcinoid: common errors in staging and clinical interpretation with a proposal for an improved terminology. Hum Pathol 2017;65:187–193
12 Wang HL, Dhall D. Goblet or signet ring cells: that is the question. Adv Anat Pathol 2009;16(04):247–254
13 Nagtegaal ID, Odze RD, Klimstra D, et al; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76(02):182–188. Doi: 10.1111/his.13975
14 Li LT, Jiang G, Chen Q, Zheng JN. Ki67 is a promising molecular target in the diagnosis of cancer (review). (Review)Mol Med Rep 2015;11(03):1566–1572
15 Shang S, Hua F, Hu ZW. The regulation of β-catenin activity and function in cancer: therapeutic opportunities. Oncotarget 2017;8(20):33972–33989
16 Petrova YI, Schecterson L, Gumbiner BM. Roles for E-cadherin cell surface regulation in cancer. Mol Biol Cell 2016;27(21):3233–3244
17 Martin TA, Ye L, Sanders AJ, et al. Cancer Invasion and Metastasis: Molecular and Cellular Perspective. Madame Curie Bioscience Database. 2000–2013.
18 Mantovani F, Collavin L, Del Sal G. Mutant p53 as a guardian of the cancer cell. Cell Death Differ 2019;26(02):199–212
19 Duraiyan J, Govindarajan R, Kaliyappan K, Palanisamy M. Applications of immunohistochemistry. J Pharm Bioallied Sci 2012;4(Suppl 2):S307–S309. Doi: 10.4103/0975-7406.100281