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Significance of signet ring cells in high-grade mucinous adenocarcinoma of the peritoneum from appendiceal origin☆,☆☆

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Summary

Significance of signet ring cells in mucinous adenocarcinoma of the peritoneum from appendiceal origin has never been specifically studied. We retrospectively reviewed cases of mucinous adenocarcinoma of the peritoneum from appendiceal origin (n = 55) and collected clinical follow-up data. Signet ring cells were identified in 29 of 55 cases. No low-grade mucinous adenocarcinoma case (n = 11) had signet ring cells, whereas 29 of 44 high-grade mucinous adenocarcinoma cases did. Cases of high-grade mucinous adenocarcinoma were subdivided into 3 groups: (1) high-grade mucinous adenocarcinoma without signet ring cells (n = 15), (2) high-grade mucinous adenocarcinoma with signet ring cells only within mucin pools (n = 20), and (3) high-grade mucinous adenocarcinoma with signet ring cells invading tissue (n = 9). Overall survival (OS) and progression-free survival were subsequently evaluated. Five-year OS for cases of high-grade mucinous adenocarcinoma without signet ring cells and high-grade mucinous adenocarcinoma with signet ring cells within mucin pools were similar at 31.8% (SE, 14.4%) and 35.8% (SE, 13.9%), respectively. A significant survival difference was seen for cases of high-grade mucinous adenocarcinoma with signet ring cells invading tissue with a median OS of 0.5 years versus 2.9 and 2.4 years (P = .04 and P = .03), respectively, for cases of high-grade mucinous adenocarcinoma without signet ring cells and high-grade mucinous adenocarcinoma with signet ring cells within mucin pools. Finding signet ring cells floating in extracellular mucin pools made no prognostic difference when compared with cases of high-grade mucinous adenocarcinoma without signet ring cells. In contrast, high-grade mucinous adenocarcinoma with

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signet ring cells invading tissue was significant for worse survival, and thus, we propose reporting signet ring cell tissue invasion particularly when extensive.

Keywords

Signet ring cells; Signet ring carcinoma; Mucinous adenocarcinoma; Pseudomyxoma peritonei; Peritoneal mucinous carcinomatosis; Appendix

1. Introduction

Pseudomyxoma peritonei is characterized by disseminated collections of mucinous implants on the peritoneal surface in the abdomen and pelvis. Ronnett et al [1] initially proposed a 3-tiered grading system that separated pseudomyxoma peritonei into 3 prognostic groups: (1) peritoneal mucinous carcinomatosis (PMCA), (2) peritoneal mucinous carcinomatosis with intermediate features (PMCA-I), and (3) disseminated peritoneal adenomucinosis (DPAM). In a later series by Bradley et al [2], survival was examined in patients with pseudomyxoma peritonei treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy from 1 institution. The term *pseudomyxoma peritonei* was abandoned in favor of the term *mucinous carcinoma peritonei*, to emphasize the disease as a malignant rather than a benign process [2]. Through stratification by grade, a similar survival was found in patients with pseudomyxoma peritonei with histologic features qualifying for DPAM and PMCA-I. Based on that outcome, a simplified 2-tiered (high versus low) grading system was advocated. In Ronnett's scheme, DPAM was considered benign. However, as shown by Bradley et al, all forms of pseudomyxoma peritonei are malignant in the traditional sense. Furthermore, cases of DPAM were shown to metastasize to the thorax, an attribute that demonstrates the true malignant nature of this process [3].

The high-grade tier by Bradley et al was analogous to PMCA by Ronnett et al. The low-grade tier generally combined tumors with the histologic elements of DPAM and PMCA-I [2]. This 2-tiered grading scheme was further validated through results from a multi-institutional study of 2298 patients by Chua et al [4], which demonstrated similar prognoses between DPAM and PMCA-I. Regardless of the terminology, as proposed by Ronnett et al or Bradley et al, the term *mucinous adenocarcinoma* has been used in the *seventh edition of AJCC Cancer Staging Manual* [5] without the peritoneal moniker. Throughout the remainder of this article, the term *mucinous adenocarcinoma* is used in reference to these peritoneal tumors.

Several studies have evaluated the effect of signet ring cells in colorectal adenocarcinoma [6-9], and fewer studies have evaluated signet ring cells in appendiceal tumors [10,11]. As these studies focused on primaries and not specifically on mucinous adenocarcinoma and signet ring cells, questions are raised translating these findings to peritoneal mucinous adenocarcinoma and the impact of signet ring cells. One of our current initial questions is whether low-grade mucinous adenocarcinoma can possess signet ring cells. Under the Bradley grading scheme, the presence of signet ring cells is classified as high-grade mucinous adenocarcinoma [2]. In the series by Ronnett el al [1], signet ring cells were present in some cases of PMCA-I, which translates into low-grade mucinous

adenocarcinoma. A second question is, when signet ring cells are found, if other high-grade features are also present in the glandular epithelium through careful thorough examination on the tumor. A third question is whether the behaviors are similar for mucinous adenocarcinoma with signet ring cells and high-grade mucinous adenocarcinoma without signet ring cells. A fourth question is based on signet ring cells being localized to extracellular mucin pools and/or invading tissue and whether either leads to a difference in prognosis. Through addressing these questions, our study delves further than prior studies in qualifying the distribution and the extent of signet ring cells, specifically in mucinous adenocarcinoma.

2. Materials and methods

Our hypotheses include the following: (1) signet ring cells occur only in high-grade mucinous adenocarcinoma and (2) signet ring cells invading tissue convey a worse prognosis versus signet ring cells localized to extracellular mucin pools. We retrospectively examined cases of appendiceal mucinous adenocarcinoma (n = 55) from our institution from 1998 to 2012. The evaluation of these specimens was approved by the Wake Forest School of Medicine Institutional Review Board. All cases would be considered pT4 [5] disease [2]. Specimens were obtained from patients without extra-abdominal disease who underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for resectable or resected primary and debulkable peritoneal disease. The hyperthermic intraperitoneal chemotherapy as per protocol was always administered after surgical debulking. Occasional patients underwent more than 1 cytoreductive surgery. The resection specimens reviewed were composed mainly of tumor deposited on peritoneal sites and omentum. Deposits on visceral organs such as small and large bowel along with portions of urinary bladder, uterus, ovary, and spleen were also often present. All slides from the cytoreductive specimens were reviewed in their entirety for all 55 cases. In most of the cases, the primary appendiceal tumor was not available because most of the appendiceal resections were performed at referring hospitals for which all slides were returned. However, an exhaustive effort was attempted to reobtain the appendiceal primary slides for correlation with the peritoneal resection specimens performed at our institution.

The architectural and cytologic criteria of Bradley et al [2], excluding the criteria that signet ring cells constituted high-grade disease, were used to stratify all 55 cases into high-grade or low-grade tiers. Regardless of whether signet ring cells were encountered, the glandular epithelium was evaluated for either high-grade or low-grade features. For example, criteria for high-grade mucinous adenocarcinoma included high cellularity, frequent mitoses, and epithelium resembling moderately or poorly differentiated adenocarcinoma with high-grade cytology and prominent nucleoli and/or coarse chromatin. If signet ring cells were encountered, the presence, extent, and distribution of the signet ring cells were documented. The extensive presence of signet ring cells was acknowledged when signet ring cells were obvious, meaning signet ring cells were present in multiple specimens in the same patient and/or multiple consecutive high-power objective fields on the same specimen. The focal presence of signet ring cells constituted definitively less than 5% of the tumor burden but nearly always composed of a sparse scattering of cells, occupying less than 1 high-power objective field.

Clinical follow-up data were acquired including last date of contact (if alive), date of progression, and date of death, where applicable. If a patient died without a known date of progression, the patient's length of progression-free time was calculated as being half of their survival time; this midpoint approach avoids being potentially too conservative (placing progression at date of surgery) or too liberal (placing progression date at time of death). The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) times. This choice of progression-free time is routine when the date of progression is unknown. This is because if the date of death were chosen, an overestimate of PFS would likely occur. Patients who did not achieve a complete resection did not have PFS calculated, as these patients were not considered to be disease free. To assess differences in the study groups, the log-rank approximation of the χ^2 test was used, and $P < .05$ was deemed to be significant. Other clinical data were collected including age, sex, Eastern Cooperative Oncology Group (ECOG) status, and presence of neoadjuvant and/or adjuvant chemotherapy including regimen.

Information on completeness of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy was collected, evaluated, and categorized using a modification of clinical criteria as outlined by Wittekind et al [12]. This classification scheme has been in place in the long term, and it should also be indicated that it is based on the clinical (surgical) impression as opposed to pathologic evaluation. In this classification scheme, R0 represents no residual tumor, R1 represents residual microscopic tumor, and R2 represents residual macroscopic tumor. Given the setting of cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy, R0 and R1 resections are considered complete resections with no evidence of disease after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. The reasoning for R1 being considered a complete resection is due to hyperthermic intraperitoneal chemotherapy being capable of penetrating 3 to 5 mm into tissue and, thus, treating any residual tumor cells (free floating, positive margins, or otherwise). In addition, distinguishing R0 from R1, based on clinical impression, is essentially impossible. Hence, R0 and R1 are grouped together in our study. The R2 group is subdivided into R2a, meaning a residual nodule(s) less than 5 mm; R2b, meaning residual nodule(s) 5 mm to 2 cm; and R2c, meaning nodule(s) greater than 2 cm. R2 group (R2a/R2b/R2c) resections are incomplete and never considered disease free.

3. Results

Supplementary Table 1 provides a comprehensive overview of collected clinical and pathologic data, case by case and stratified by groups. Clinical data elements include age, sex, ECOG status, neoadjuvant chemotherapy, and adjuvant chemotherapy. Pathologic data elements include nodal submission and status, signet ring cell qualification in the peritoneal mucinous adenocarcinoma, abdominal resected sites, and correlation with the appendiceal primary (if obtained). Of the 55 cases, we classified 44 cases as high-grade mucinous adenocarcinoma and 11 cases as low-grade mucinous adenocarcinoma. Cases of high-grade mucinous adenocarcinoma were associated with more cellular "dirty" mucin with scattered epithelial cells and neutrophils than cases of low-grade mucinous adenocarcinoma. The presence of signet ring cells was not seen in any of the 11 cases of low-grade mucinous adenocarcinoma (Fig. 1A). By contrast, signet ring cells were found in two-thirds (29/44) of

the high-grade mucinous adenocarcinoma cases. The 44 cases of high-grade mucinous adenocarcinoma fell into 3 groups: (1) high-grade mucinous adenocarcinoma without signet ring cells (n = 15; Fig. 1B), (2) high-grade mucinous adenocarcinoma with signet ring cells only in mucin pools (n = 20; Fig. 2), and (3) high-grade mucinous adenocarcinoma with signet ring cells in tissues (n = 9; Fig. 3).

In the cases with signet ring cells, the glandular epithelial component subtracting the signet ring cells met the Bradley criteria for high-grade mucinous adenocarcinoma. In the cases of high-grade mucinous adenocarcinoma with signet ring cells in mucin pools, 16 (80%) of 20 cases showed focal versus extensive signet ring cells in mucin pools (Supplementary Table 1). In cases of high-grade mucinous adenocarcinoma with signet ring cells invading tissue, 8 (89%) of 9 cases showed extensive signet ring cell tissue invasion (Supplementary Table 1). In addition, within cases of high-grade mucinous adenocarcinoma with signet ring cells invading tissue, 7 (78%) of 9 showed dissecting mucin with signet ring cells. Interestingly, in 4 of these 7 cases, signet ring cells in the mucin were extensive (Supplementary Table 1).

Across the 4 groups, there were no differences in sex ($P = .87$), ECOG status ($P = .17$), neoadjuvant chemotherapy ($P = .65$), and adjuvant chemotherapy ($P = .91$), although age differences were seen among the 4 groups overall ($P = .041$). Basically, the high-grade mucinous adenocarcinoma with signet ring cells group was the youngest. The low-grade mucinous adenocarcinoma group was 57.1 years (±12.1 years). The high-grade mucinous adenocarcinoma without signet ring cells group was 52.5 years (±12.9 years), the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group was 46.8 years (±10.2 years), and the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group was 56.1 years (±9.5 years).

Table 1 provides comprehensive information of residual tumor status by study group. Complete cytoreduction (R0 or R1) was more common in the high-grade mucinous adenocarcinoma without signet ring cells group and the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group (53% and 50%, respectively) compared with the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group (22%). Incomplete resections (R2) formed the largest proportion for the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group with R2a being 44%. Despite these clinically significant differences between the R0/1, R2a, R2b, and R2c groups, however, the results did not reach statistical significance ($P = .12$).

Kaplan-Meier analysis showed significantly shorter OS for the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group versus the high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group (Fig. 4). The overall test of the 3 groups for survival differences was significant ($P = .0015$). There was close overlap between the high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group ($P = .58$). Table 2 details the specific OS and PFS statistics for the 3 groups. For the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group, median OS was 0.5 years versus the high-grade mucinous adenocarcinoma without signet ring cells group and high-

grade mucinous adenocarcinoma with signet ring cells in mucin pools group with median survival of 2.9 and 2.4 years, respectively; the survival is significantly higher in both of the latter groups (P = .004 and P = .003).

In Fig. 4A, Kaplan-Meier analysis showed a trend toward an initial shorter median PFS for the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group; however, this did not reach statistical significance (P = .32). Although early on (<1 year), there appeared to be a difference, at 2 years, the curves overlapped demonstrating no significant difference of PFS among the 3 groups. For the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group, median PFS was 0.2 years versus the high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group with 1.0 and 1.1 years, respectively.

Despite the exhaustive effort to recall the appendiceal primaries for evaluation, a considerable number remained at large. The retrieved cases, however, provided some correlation between the appendiceal primary and peritoneal disease (Supplementary Table 1). With the low-grade mucinous adenocarcinoma group, 5 of the 11 cases originated from appendiceal well-differentiated mucinous adenocarcinoma. Two of those cases had the appearance of either mucinous adenoma or low-grade mucinous neoplasm, but given the extra-appendiceal spread, these mucinous lesions qualified for appendiceal mucinous adenocarcinoma [13]. With the high-grade mucinous adenocarcinoma without signet ring cells group, 11 of the 15 cases were retrieved showing appendiceal mucinous adenocarcinoma ranging from well to poorly differentiated and none showing signet ring cells. With the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group, 13 of the 20 cases were retrieved with the appendiceal primary showing similar grading to the appendiceal primary of the high-grade mucinous adenocarcinoma without signet ring cells group. Four of those cases, however, showed some signet ring cell differentiation with 1 being potentially a signet ring cell ex–goblet cell carcinoid. Finally, with the signet ring cells invading tissue group, 6 of the 9 cases were retrieved and showed signet ring cell differentiation with 3 cases being potentially a signet ring cell ex–goblet cell carcinoid.

4. Discussion

Appendiceal mucinous tumors have long been enigmatic with arguably unpredictable biologic potential for extra-appendiceal spread to develop mucinous adenocarcinoma [14]. There are a few published series integrating laboratory and immunohistochemical information in inferring prognosis for mucinous adenocarcinoma [15,16]. This is further confounded because extra-appendiceal spread has been plagued by inconsistent and controversial histologic and reporting criteria to deduce biologic potential [14].

Although seemingly intuitive that signet ring cells should qualify as high-grade mucinous adenocarcinoma, it should be reiterated that, in the older series by Ronnett el al [1], signet ring cells were present in some cases of what is considered low-grade mucinous adenocarcinoma. In that series, those cases with signet ring cells should have been

categorized as PMCA or high-grade mucinous adenocarcinoma. However, by including signet ring cells in PMCA-I, this falsely widened the difference between DPAM and PMCA-I.

Our findings support the presence of signet ring cells as high-grade mucinous adenocarcinoma and exclude their presence in low-grade mucinous adenocarcinoma. (1) Of all cases with signet ring cells, other high-grade features were present in the glandular epithelium such as high-grade cytology with coarse chromatin and/or prominent nucleoli. (2) The prognostic OS and PFS curves for high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group overlapped. (3) The 5-year OS for the high-grade mucinous adenocarcinoma without signet ring cells group (31.8% [SE, 14.4%]) and the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group (35.8% [SE, 13.9%]) corresponded similarly to historical 5-year OS of high-grade mucinous adenocarcinoma/ PMCA cases by Bradley et al (37.7% [SE, 11.2%]) [2]. (4) No cases of low-grade mucinous adenocarcinoma showed signet ring cells, although this reflected a limited number of cases.

There should be some acknowledgement that the presence of signet ring cells in extracellular mucin pools is arguably subjective due to the occasional bland appearance of signet ring cells. We also often found the presence of signet ring cells in extracellular mucin pools focal, and thus, both factors may have accounted for why cases with signet ring cells were included in the category of PMCA-I in the older series by Ronnett et al [1]. It was interesting, although not surprising, that the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group behaved similarly to the high-grade mucinous adenocarcinoma without signet ring cells group.

The most significant finding of our study was the observation that the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group drastically worsened prognosis (median OS, 0.5 years) when compared with the high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group (median OS, 2.9 and 2.4 years, respectively). Moreover, signet ring cell invasion of tissue was not subtle in our series, with most (90%) cases having extensive and readily identifiable tissue invasion. This striking drop in survival with the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group was far beyond what would be expected from just a designation of high-grade mucinous adenocarcinoma. For the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group in our series, 1-year OS was 33.3% (SE, 15.7%), whereas for the high-grade mucinous adenocarcinoma in the series by Bradley et al [2], 1-year OS was 70.0% (SE, 10.4%).

This is the first study to focus solely on the impact of signet ring cells in extra-appendiceal spread of appendiceal mucinous tumors. In their series, Pai et al [17] evaluated their specimens from the opposite perspective by stratifying appendiceal primaries into tiers. Their series, however, did not focus specifically on the effect of signet ring cells, and there was no stratification of the peritoneal deposits of mucinous adenocarcinoma [17]. Two other studies investigated the presence of signet ring cells in the appendiceal tumor in the setting

of mucinous adenocarcinoma and showed worse prognoses in primary tumors with signet ring cells [10,11]. With colorectal adenocarcinoma, the presence of signet ring cells was more established as a worse prognostic attribute [6-9]. Not only was our study the first study to focus specifically on signet ring cells in extra-appendiceal spread of appendiceal mucinous tumors, but we also went further than prior studies in examining the extent and localization of signet ring cells in extracellular mucin pools or in tissue, plus correlated clinical survival data and clinical resection status. Based on the relatively dismal prognosis in patients with signet ring cell tissue invasion, we propose that such characterization should be included in the pathology report as additional prognostic information.

As mentioned, the prior appendiceal primaries were returned to the referring institution. The cases dated back to 1998, and relying on the older pathology reporting to subtype accurately the appendiceal primary tumor was ineffective due to the ever changing terminologies used to describe appendiceal tumors [14]. Although a large number of appendiceal tumors were at large, some correlations were able to be made from retrieved primaries for which there was correlation between the appendiceal primary and peritoneal mucinous adenocarcinoma. Of the low-grade mucinous adenocarcinoma group, no appendiceal primary was moderate to poorly differentiated, and none showed signet ring cell differentiation. Of both the high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group, the appendiceal primary showed varying degrees of differentiation from well to poorly differentiated. With the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group, there was signet ring cell differentiation in some of the appendiceal primaries, 3 cases having signet ring cells focally and 1 being potentially a signet ring cell ex–goblet cell carcinoid. As the high-grade mucinous adenocarcinoma without signet ring cells group and high-grade mucinous adenocarcinoma with signet ring cells in mucin pools groups behaved similarly, finding some signet ring cells in the appendiceal primary may counter some of the evidence as presented in prior studies of appendiceal primaries showing signet ring cells with worse survival [10,11]. Those studies, unlike ours, did not focus specifically on signet ring cell extent particularly when signet ring cell presence was focal and most likely included only cases where signet ring cell presence in the appendiceal primary was extensive. The most aggressive pathology in the appendiceal primary was seen in the signet ring cells invading tissue group where 6 cases showed signet ring cell differentiation with 3 cases potentially being signet ring cell ex–goblet cell carcinoid. It is acknowledged that the suspicion for signet ring cell ex–goblet cell carcinoid was made through morphology alone. As these appendiceal resection specimens were older and tissue blocks irretrievable, neuroendocrine marker immunohistochemistry was not performed for support.

Our hypotheses for the dismal prognosis of the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group are 2-fold. The first hypothesis is that the pathobiology of signet ring cells invading tissue is more aggressive. The signet ring cell subtype has already shown worsened prognosis in primary appendiceal tumors [10,11]; however, the molecular pathogenesis behind signet ring cells invading tissue may be different from signet ring cells situated in mucin. In the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group, not only were signet ring cells seen invading tissue, but signet ring cells were also present within mucin, suggesting that

invasion into tissue potentially reflects an additional step in the molecular pathogenesis. Furthermore, mucin within the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group showed a tendency for dissection to suggest that the signet ring cells in this group may either be changing the microenvironment or eliciting factors into the mucin or tissue to enable for both invasion and dissecting mucin. This obviously requires future investigation into the molecular pathogenesis.

The second hypothesis for the dismal prognosis is that those signet ring cells invading tissue make complete resection improbable and, hence, worsen outcome. Although not statistically significant, the high-grade mucinous adenocarcinoma without signet ring cells group and the high-grade mucinous adenocarcinoma with signet ring cells in mucin pools group had a higher proportion of complete resections versus the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group. The higher proportion of incomplete surgical resections reflected in the high-grade mucinous adenocarcinoma with signet ring cells invading tissue group raises the possibility of selection bias toward a worsened outcome. However, it is also justly argued that signet ring cells invading tissue, by their aggressive nature with widespread extension, make complete resections much more difficult and, therefore, pose a potential contraindication to cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy.

5. Conclusions

Signet ring cells occurred in mucinous adenocarcinoma where glandular epithelium showed high-grade features. Signet ring cells were absent for all of our cases of low-grade mucinous adenocarcinoma; however, the sample was limited for more definitive inference. Finding signet ring cells floating in extracellular mucin pools made no difference in prognosis compared with cases of high-grade mucinous adenocarcinoma without signet ring cells with the caveat that signet ring cells floating in extracellular mucin pools was often focal. By contrast, signet ring cell tissue invasion was often extensive and dramatically worsened survival. Thus, the qualification of signet ring cells invading into tissue particularly when it is extensive appears justified in the reporting of high-grade mucinous adenocarcinoma of appendiceal origin and especially if the appendiceal primary is not known.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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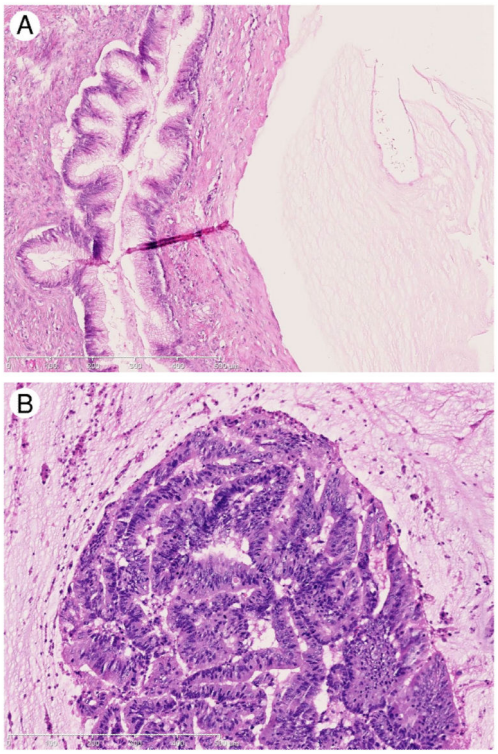

Fig. 1.

A, Example of low-grade mucinous adenocarcinoma (hematoxylin and eosin [H&E], original magnification ×20). Mucin pools are paucicellular with complete absence of signet-ring cells and occasional “adenoma-like” epithelium that lacks architectural complexity. The nuclei are elongated with low-grade cytology and without prominent nucleoli or coarse chromatin. Mucin pools are situated with circumscribed borders that never dissect. B, Example of high-grade mucinous adenocarcinoma without signet-ring cells (H&E, ×20). Glandular epithelium shows complex architecture. Nuclei show high-grade cytology with prominent nucleoli or coarse chromatin. The epithelium is reminiscent of moderate to poorly differentiated adenocarcinoma. Mucin is cellular and dirty but without signet-ring cells.

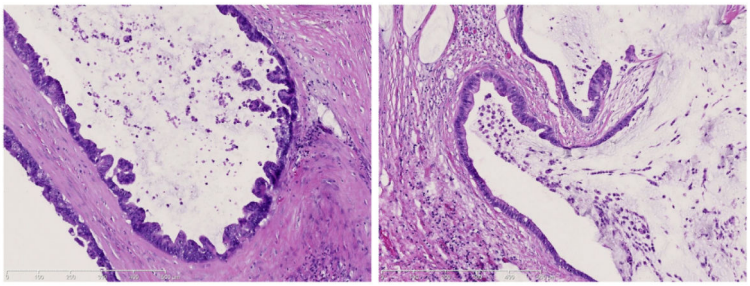

Fig. 2.

Examples of high-grade mucinous adenocarcinoma with signet-ring cells in mucin pools (H&E, ×20). Glandular epithelium shows often complex architecture. Nuclei show high-grade cytology with prominent nucleoli or coarse chromatin. Mucin is cellular and dirty, with occasional signet-ring cells. Tissue invasion by signet-ring cells is absent.

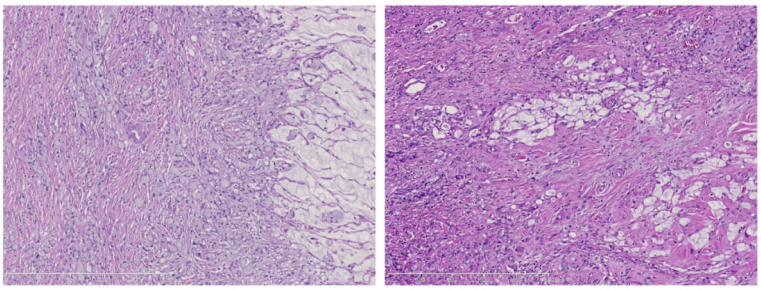

Fig. 3.

Examples of high-grade mucinous adenocarcinoma with signet-ring cells invading tissue (H&E, ×20). Signet-ring cells are widely invasive into tissue. Mucin is dissecting, and signet-ring cells within the mucin are occasionally extensive.

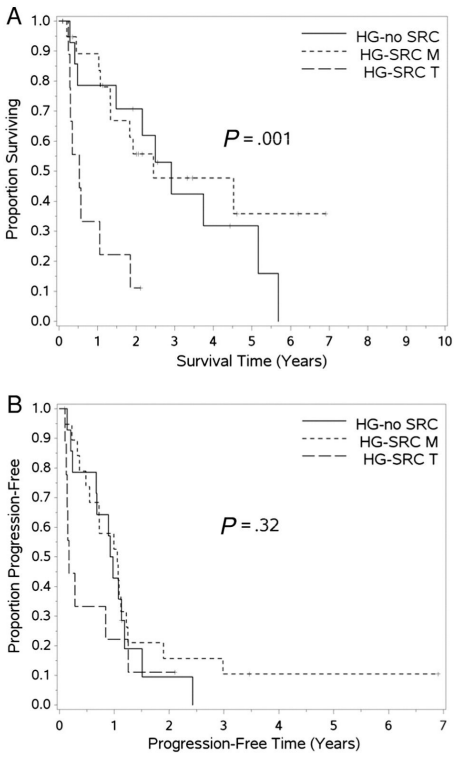

Fig. 4.

Kaplan-Meier analysis of overall (A) and progression free (B) survival for all 3 groups of high-grade mucinous adenocarcinoma. A, There is close overlap between groups HG–no SRC and HG-SRC M. Group HG-SRC T shows a statistically significant worsened prognosis (P = .0015 overall). B, Initially (<1 year), there appears to be a difference between HG-SRC T and the other 2 groups. At 2 years, the PFS curves nearly overlap. Differences in PFS among the 3 groups did not reach statistical significance (P = .32). HG–no SRC, high-grade mucinous adenocarcinoma without signet-ring cells; HG-SRC M, high-grade mucinous adenocarcinoma with signet-ring cells in mucin pools; HG-SRC T, high-grade mucinous adenocarcinoma with signet-ring cells invading tissue.

Table 1

Completeness of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion

Residual tumor status by study group					
Group	**Category**				
	R0/R1	**R2a**	**R2b**	**R2c**	**Total**
HG–no SRC	8/15 (53%)	2/15 (13%)	4/15 (27%)	1/15 (7%)	15
HG-SRC M	10/20 (50%)	3/20 (15%)	7/20 (35%)	0/20 (0%)	20
HG-SRC T	2/9 (22%)	4/9 (44%)	1/9 (11%)	2/9 (22%)	9
Total	20	9	12	3	44

Abbreviations: HG–no SRC, high-grade mucinous adenocarcinoma without signet-ring cells; HG-SRC M, high-grade mucinous adenocarcinoma with signet-ring cells in mucin pools; HG-SRC T, high-grade mucinous adenocarcinoma with signet-ring cells invading tissue.

Table 2

Specific OS and PFS statistics

	Median	1 y	2 y	3 y	4 y	5 y			
Group HG–no SRC							Group comparisons for significance for OS		
OS	2.9 y	78.6 (11.0)	70.7 (12.4)	42.4 (14.8)	31.8 (14.4)	31.8 (14.4)	HG–no SRC	HG-SRC M	$P = .58$
PFS	1.0 y	42.9 (13.2)	9.5 (8.8)	0	0	0	HG–no	SRC HG-SRC T	$P = .004$
Group HG-SRC M							HG-SRC M	HG-SRC T	$P = .003$
OS	2.4 y	89.2 (7.2)	55.7 (11.7)	47.8 (12.4)	47.8 (12.4)	35.8 (13.9)	Group comparisons for significance for PFS		
PFS	1.1 y	52.6 (11.5)	15.8 (8.4)	10.5 (7.0)	10.5 (7.0)	10.5 (7.0)	HG–no SRC	HG-SRC M	$P = .49$
Group HG-SRC							HG–no SRC	HG-SRC T	$P = .28$
OS	0.5 y	33.3 (15.7)	11.1 (10.5)	NA[a]	NA[a]	NA[a]	HG-SRC M	HG-SRC T	$P = .18$
PFS	0.2 y	22.2 (13.9)	11.1 (10.5)	NA[a]	NA[a]	NA[a]			

Abbreviations: OS, overall survival; PFS, progression-free survival; HG–no SRC, high-grade mucinous adenocarcinoma without signet ring cells; HG-SRC M, high-grade mucinous adenocarcinoma with signet ring cells in mucin pools; HG-SRC T, high-grade mucinous adenocarcinoma with signet-ring cells invading tissue; NA, not available.

[a]No one has this much follow-up.