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Diagnosing colorectal medullary carcinoma: interobserver variability and clinicopathological implications

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Abstract

Colorectal medullary carcinoma, recognized by the World-Health-Organization as a distinct histologic subtype, is commonly regarded as a specific entity with an improved prognosis and unique molecular pathogenesis. A fundamental but as-yet unaddressed question, however, is whether it can be diagnosed reproducibly. In this study, by analyzing 80 colorectal adenocarcinomas whose dominant growth pattern was solid (thus encompassing medullary carcinoma and its mimics), we provided a detailed description of the morphological spectrum from “classic medullary histology” to non-medullary poorly-differentiated histologies and demonstrated significant overlapping between categories. By assessing a selected subset (n=30) that represented the spectrum of histologies, we showed that the inter-observer agreement for diagnosing medullary carcinoma by using 2010 World-Health-Organization criteria was poor; the Kappa value among 5 gastrointestinal pathologists was only 0.157 (95% confidence-interval, 0.127–0.263; p=0.001). When we arbitrarily classified the entire cohort into “classic” and “indeterminate” medullary tumors (group 1, n=19; group 2, n=26, respectively) and non-medullary poorly-differentiated tumors (group 3, n=35), groups 1 and 2 were more likely to exhibit mismatch-repair-protein-

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deficiency than group 3 ($p<0.001$); however, improved survival could not be detected in neither group compared to group 3. Our findings suggest that the diagnosis of medullary carcinoma, as currently applied, may only serve as a morphological descriptor indicating an increased likelihood of mismatch-repair-deficiency. Additional evidence including more objective classification system is needed before medullary carcinoma can be regarded as a distinct entity with prognostic relevance. Until such evidence becomes available, caution should be exercised when making this diagnosis, and when comparing results across different studies.

Keywords

Colorectal carcinoma; tumor histology; tumor classification; microsatellite instability; diagnostic reproducibility

Introduction

Colorectal carcinoma (CRC) represents the third most common cancer and the third leading cause of cancer-related death in men and women in the United States. In recent years, there has been significant progress in our understanding of CRC and its management. Estimates from 2001 to 2010 show that both the incidence of, and death rates from, CRC have decreased faster than in previous years (approximately 3% per year for both) [1].

Of the various emerging pathological and molecular characteristics of CRC that may bear clinical significance [2], medullary histology has received particular attention [3–7]. In both clinical and research settings, medullary carcinoma (MC) is commonly perceived as a distinct clinico-pathological entity with specific prognostic relevance and molecular pathogenesis. A number of studies have suggested that tumors with medullary histology tend to have a favorable clinical outcome and are strongly associated with DNA mismatch repair (MMR) deficiency despite their “poorly differentiated” histologic appearance [3, 4, 6, 8–10]. As such, the most recent World Health Organization (WHO) classification [11] as well as the American Joint Committee on Cancer (AJCC) [12] have incorporated MC as a distinct histologic subtype.

However, the specific diagnostic criteria for MC are not clearly defined. While some authors accept any amount of medullary morphology to classify a tumor as MC [13], others require 90% [4, 14], 95% [15], or 100% [16] of the tumor to show medullary differentiation. The number of specific features required for the diagnosis is also widely inconsistent across different studies [3, 6, 8, 9]. MMR deficiency is a stringent diagnostic requirement in some studies [4, 14], but not in others [9, 10]. At present, the only standard diagnostic guideline is that delineated in the 2010 WHO *Classification of Tumours of the Digestive System* [11], which states concisely that MC is composed of “sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and prominent infiltration by intraepithelial lymphocytes”. This guideline, unfortunately, does not address many of the above issues; and the interpretation of the features listed in the guideline is prone to subjectivity.

We performed this study to systematically analyze the diagnostic value and reproducibility of the WHO guidelines and other diagnostic criteria. We analyzed the pathologic features of a series of poorly differentiated CRCs, including MC. Our goals were two-fold: 1) to evaluate interobserver agreement with respect to the morphologic diagnosis of MC; and 2) to analyze the morphologic patterns that could potentially confound classification of tumors into medullary versus non-medullary types. Our findings were also correlated with other clinicopathological characteristics including MMR deficiency and clinical outcome.

Materials and Methods

Study cases

The study group consisted of 80 surgically resected CRCs retrieved from our pathology and clinical databases. The inclusion criteria were: 1) 50% of the tumor lacking overt gland formation with tumor cells growing in sheets, nests, cords, or individually; and 2) material available for haematoxylin and eosin evaluation and immunohistochemical evaluation for MMR proteins (MLH1, PMS2, MSH2, and MSH6); all available haematoxylin and eosin tumor slides of each case were included for review. Excluded from the study were 1) tumors that showed mucinous or signet ring cell morphology in 50% of the volume, as they would not be likely to cause diagnostic confusion with MC; 2) neuroendocrine carcinoma or mixed adeno-neuroendocrine carcinoma; and 3) tumors treated with prior chemotherapy or radiation therapy. Clinical information was obtained from the electronic medical records. All 80 cases were utilized for clinico-pathological analyses. Selected cases were utilized for inter-observer agreement analyses. The study was approved by the Institutional Research Board.

Histological evaluation and clinico-pathological correlative analyses

Histological features of all 80 cases were evaluated descriptively, without knowledge of tumor MMR status or other clinico-pathological features. Primary assessment of all cases was carried out by one pathologist with experience in gastrointestinal pathology. Specific features evaluated included: tumor growth pattern, tumor cell uniformity, WHO morphologic criteria (“vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm”), tumor infiltrating lymphocytes per 400× field (TILs/HPF), stromal lymphocytic infiltration, and stromal quality (i.e. cellularity and presence or absence of fibrosis or desmoplasia).

Based on current practice, we defined “classic medullary histology” as: 1) a solid or nested growth pattern, 2) a circumscribed tumor border, 3) a cellular (non-desmoplastic) stroma rich in lymphocytes or other inflammatory cells, 4) uniform and “syncytial” tumor cells frequently exhibiting vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and 5) abundant TILs. Depending on the extent to which the tumors exhibited these “classic” features, we separated the tumors into classic MC (termed “MC” for this study) when tumors fulfilled all 5 medullary features described above, CRC with MC features (termed “indeterminate carcinoma” or IC) when tumors had some but not all of these 5 medullary features, and poorly differentiated CRC (termed “PDC”) when tumors did not have apparent medullary features.

Immunohistochemical stains for MLH1, MSH2, MSH6, and PMS2 on all cases were performed on whole tumor sections using previously described methods [17]. Clinico-pathological characteristics, including MMR status, demographics, tumor site, size, and survival, were compared amongst the three tumor groups.

Assessment of interobserver agreement on diagnosing MC using morphological criteria

A collection of 30 tumor slides deemed to be representative of the morphological spectrum from classic MC to poorly differentiated carcinomas lacking medullary features was identified through the morphological assessment described above. These slides were utilized for interobserver agreement analysis. The observers consisted of 5 pathologists with interest in gastrointestinal pathology. Two rounds of testing were designed. For the first round, the observers were asked to follow the WHO description (i.e., sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and prominent infiltration by intraepithelial lymphocytes [11]) for diagnosing MC. For tumors that were deemed non-medullary, the observers were asked to further classify them into medullary-like or simply poorly differentiated carcinoma, using the criteria they employ in routine practice. For the second round, the observers were asked to follow a new set of definitions developed from the morphological assessment described above.

Statistics

Descriptive and comparative statistics were performed using Statistical Software for the Social Sciences (SPSS) version 22 software. Continuous variables were compared using the Student t test, Mann-Whitney test or ANOVA, as appropriate by the type of distribution. Categorical variables were compared using χ^2 or the Fisher exact test depending on the number of observations. Survival distributions were estimated using the Kaplan-Meier method. Time to event was calculated from date of diagnosis to date of event. An event for recurrence-free survival was defined as recurrence or death. Patients without the event of interest at last follow-up were censored. Log-rank test was used to compare the association between dichotomous and categorical prognostic factors and OS. Interobserver variabilities were assessed using κ statistics. A Cohen's κ statistic of less than 0.2 indicated poor agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 good agreement and 0.81–1 excellent agreement. For all statistical tests, a result was regarded significant when p-value is <0.05 .

Results

Morphological characterization

H&E slides of all 80 study cases were analyzed. The median number of tumor slides reviewed per case was 5 (range, 2 to 16). All 80 tumors showed lack of overt gland formation in 50% of the tumor, thereby meeting conventional criteria for poorly differentiated carcinoma. Thorough morphological assessment, emphasizing features commonly perceived as “medullary” as described in the Methods section, divided the tumors into 3 morphological groups as follows.

MC—These tumors exhibited a solid or nested growth pattern with a circumscribed tumor border and a cuff of inflammatory stroma at the invasive front, a distinctly cellular stroma rich in mononuclear cells and sometimes abundant neutrophils without overt fibrosis or desmoplasia, and uniform tumor cells with a “syncytial” appearance and poorly defined cell borders that merged imperceptibly with the stroma. Notably, these tumors contained abundant tumor infiltrating lymphocytes (TILs/HPF: mean, 55, median, 40, range, 30–140) (Fig. 1). A total of 19 tumors exhibited these features in 50% or more of the tumor volume.

IC—In these “indeterminate” carcinomas, the dominant tumor component had an overall appearance resembling classic MC, and displayed one or more of the classic features described above. However, they did not have all the features, often as a minor component of the tumor. They frequently showed other features of conventional poorly differentiated carcinoma: 1) non-syncytial growth (such as prominent cord like growth resembling breast lobular carcinoma or diffuse type gastric carcinoma, nodules of cribriform glands, mixed well-formed glands and solid areas, or an infiltrative tumor border); 2) fibrotic or desmoplastic stroma; and 3) atypical cytologic features, such as conspicuous signet ring cell cytology that did not fulfill criteria for signet ring cell carcinoma, neuroendocrine-like nuclei, or squamoid differentiation. These tumors contained variably increased TILs (TILs/HPF: mean, 22; median, 20; range, 2–60) (Fig. 2). We detected 26 tumors belonging to this group.

PDC—These tumors lacked any features commonly perceived as “medullary”. They displayed a solid or irregular growth pattern, high-grade cytology, desmoplastic stroma, and inconspicuous lymphocytic infiltration (TILs/HPF: mean, 3; median, 2; range, 0–23) (Fig.3). We detected 35 such “non-medullary” PDCs.

The characteristic features for these 3 groups are summarized in Table 1.

Clinicopathological correlations

As shown in Table 2, the MC and IC cases had significantly overlapping clinical and pathologic features: both MC and IC groups occurred more frequently in the proximal colons of older patients and were more likely to be large despite an absence of regional lymph node or distant metastases. They also showed higher TIL counts (> 10 TILs/HPF) and higher rates of MMR deficiency, and presented at lower stage. All these features, except tumor size, differed significantly from the PDC group, although it was notable that a minor subset of PDCs exhibited high TILs, MMR deficiency and low TNM stage as well.

Clinical follow up was available in 78 patients. The median follow-up was 25 months (range: 1–101 months) and the median follow-up for survivors was 32 months (range: 1–101 months). While a significantly better overall survival (OS) was observed in patients with low stage disease ($p=0.02$) (Fig. 4), a statistically significant survival difference could not be detected when tumors were stratified by histologic subtypes (MC vs IC vs PDC) and other clinico-pathologic features including age, gender, tumor location, size, TIL counts, MMR status. Of note, MC/IC/PDC subtyping (Fig. 5), as well as TIL counts and MMR status showed a tendency towards better survival when compared to PDC.

Interobserver agreement on diagnosing MC

Thirty representative tumor slides encompassing the morphological spectrum from classic MC to indeterminate carcinoma to non-medullary PDCs were assessed by 5 gastrointestinal pathologists (see Methods). When using the WHO criteria, there was poor overall interobserver agreement ($\kappa = 0.157$, 95% Confidence Interval, 0.127 to 0.263, $p=0.001$). Total agreement by all 5 observers on a diagnosis of MC was achieved in only 3 cases, all 3 cases had a TIL count of $>50/\text{HPF}$. The interobserver agreement was highest for PDC as compared to MC and IC ($\kappa = 0.256$, $p<0.001$), and it was lowest for IC as compared to MC and PDC ($\kappa = 0.046$, $p=0.222$). When MC was defined as having all the features we observed for our group 1 tumors (Table 1), the overall interobserver agreement improved to moderate ($\kappa = 0.41$, 95% Confidence Interval, 0.274 to 0.497, $p<0.001$). Using this definition, the interobserver agreement was highest for PDCs as compared to MC and IC ($\kappa = 0.576$, $p<0.001$), and it was lowest for IC as compared to MC and PDC ($\kappa = 0.126$, $p=0.015$). The interobserver agreement for MC as compared to IC and PDC was moderate ($\kappa = 0.4652$, $p<0.001$).

Discussion

In 1977, Gibbs [8] described 8 “undifferentiated carcinomas” of the large intestine. It was clear from this early report that, among colorectal adenocarcinomas with a solid growth pattern, there existed a subset that tended to grow to a large size but nonetheless had a good prognosis. Jessurun et al. [6] and Ruschoff et al. [3] further solidified the existence of such tumors with additional case series (albeit small, $n=11$, and $n=13$ respectively), and proposed that the term “medullary carcinoma” be used to distinguish them from other solid CRCs. These descriptions coincided with the discovery of microsatellite instability (MSI) in CRC [18, 19]. An association between MC and MSI was soon recognized [20–22], and several subsequent studies have indeed suggested that both medullary histology and MSI are favorable prognostic indicators in CRC.

What appears to have been under-recognized, however, is that the morphological diagnosis of MC can be problematic and the clinical outcome of these tumors can be variable [7]. For the issue of diagnosis, our study shows that a wide spectrum of “medullary” morphology exists in CRCs, and there are frequent intermediate forms between classic MC and conventional poorly differentiated carcinoma. The existing WHO definition merely states: “sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, and prominent infiltration by intraepithelial lymphocytes [11]”. Such a definition does not allow satisfactory distinction between the various patterns, and thus results in poor interobserver agreement. A set of more detailed morphological criteria developed from our analysis improve the interobserver agreement, but only to a limited extent.

Our analysis represents the first to systematically evaluate the reliability of morphological criteria for diagnosing MC. As highlighted by our results, morphological parameters that can potentially detect “classic” MC from non-medullary poorly differentiated carcinomas include: growth pattern, tumor border, tumor stroma, cellular morphology, and lymphocytic infiltration. Contrast to the defining features for most other histologic subtypes (such as

mucin production for mucinous type, and signet ring cells for signet ring cell carcinoma), these parameters are prone of subjectivity, and all can have significant variation both across different tumors and within the same tumor. This is well reflected in the varied descriptions in the literature. In Gibbs' initial report [8], the tumor cell size was described as "similar to other cases of carcinoma of the colon" and "not small", whereas others regarded them as small to medium [3] and with high N/C ratios [10], the WHO mentions "abundant eosinophilic cytoplasm", and still others simply characterized them as having "lack of marked nuclear pleomorphism" [9]. Stroma quality was described as "delicate fibrovascular" by some [6] but was not particularly specified by others. Our demonstration of atypical forms that show mixed medullary features and features of non-medullary poorly differentiated carcinoma is further evidence of such morphological variabilities. TILs seem to be a more objective criterion that may potentially help the classification of MC. Indeed, in our first round of inter-observer analysis, a common feature of the 3 tumors that were diagnosed as MC unanimously by all 5 observers was a TIL/HPF count of >50. However, the TIL count is not consistently that high in MCs, and some non-MCs can have high TIL counts as well. Given the brief and descriptive nature of the WHO definition [11], it is not surprising that the interobserver agreement based on this definition was poor. Even with a detailed list of features developed from our analysis (including a defined TIL count), the interobserver agreement was still only barely moderate. Thus, our results call for attention to such limitations and inconsistencies, and indicate a need that these diagnostic caveats be addressed in both clinical and research scenarios.

An additional issue regarding the definition of MC relates to the extent of medullary component required for making the diagnosis. This is an important issue as it has been well demonstrated that colorectal MC are almost invariably associated with one or more non-medullary components [16, 21]. The initial descriptions [3, 6, 8] referred to tumors with either <5% [3] or <20% [6] showing gland formation. The existing WHO definition, however, failed to define a percentage cutoff [11]. Consequently, studies have employed inconsistent standards resulting in inconsistent conclusions. For example, Rosty et al. [16] required 100% medullary morphology for the diagnosis (irrespective of the MMR status), and identified only 1 MC among 738 CRCs (for a prevalence of 0.1%). Knox et al. [4] used 90% medullary morphology as the cutoff and required the presence of MMR deficiency, and found a 2.8% prevalence. Other studies that required either any amount or undefined amount of medullary morphology [13, 23, 24] or MMR deficiency [13, 16, 23, 25] have reported prevalences ranging from <0.1% [13] to 65.7% [24]. Following the AJCC and CAP recommendation requiring $\geq 50\%$ of the tumor to lack overt gland formation to diagnose poor differentiation, we regarded 50% as a reasonable cutoff in this study.

The inconsistent definitions employed in the different studies thus hamper valid comparisons of the reported results on the clinical impact of medullary histology in CRCs. In our analysis, with a set of detailed definitions as listed in Table 1, we found a high concordance rate with MMR deficiency in both classic and atypical medullary carcinomas (MCs and ICs). This suggests that both types should be regarded as predictive of MSI-H; the detection of either classic or atypical medullary features should prompt further MMR testing. Interestingly, while the association with MMR deficiency (as well as other low grade clinico-pathological features such as high TILs and low stage) would suggest that medullary

histology portends a better outcome than non-medullary poorly differentiated histologies, we were not able to detect statistically significant survival differences among the different histologic groups. Of note, in this cohort of patients, MMR status also did not stratify survival in a statistically significant manner.

The lack of a survival difference between CRCs stratified by MMR status may seem unexpected at first given the widely accepted notion that MSI CRCs have an improved prognosis. This general concept, however, is largely derived from studies that examined CRCs of all histologic types as a whole [26]. In such cohorts, poorly differentiated carcinomas including MC are significantly underrepresented. Our results reflected the effect of MMR deficiency specifically among poorly differentiated CRCs. In fact, two other studies [27, 28] that also focused on this group of tumors found essentially identical results: MSI-H poorly differentiated CRCs showed a tendency towards having a better survival but the difference did not reach statistical significance. Together, the findings suggest that the prognostic impact of MSI may differ in different tumor groups. To this effect, there are recently emerged data that indeed indicated a lack of survival benefit of MSI among patients with metastatic CRCs [29, 30].

With regard to the influence of medullary histology per se on clinical outcome, data from many studies suggest that medullary histology confers a favorable outcome [3, 4, 6, 8–10, 13]. Noteworthy again, however, are potentially confounding factors in these studies. Aside from the inconsistent diagnostic criteria discussed above, these studies were either descriptions of small series collected over long periods of time from different populations (presumably subject to selection bias) [3, 6, 8], or were confounded by a lack of control for MMR status [9, 10, 13]. A study by Knox et al [4] considered MMR status and included a large cohort of patients (102 medullary and 2875 non-medullary carcinomas, the latter included 17% poorly differentiated carcinomas and 13% MMR deficient tumors). However, the MMR status was used as an integral criterion for the diagnosis of MC in this study. Although the study demonstrated an improved survival in MC when compared to poorly differentiated CRCs, it is difficult to decipher whether it was the MMR deficiency (a defining feature of their MC) or the medullary histology per se that impacted the outcome.

In our analysis, by evaluating medullary histology independent of the MMR status, we only observed a slight tendency towards a better survival in patients whose tumors had medullary histology (comparing to those with poorly differentiated non-medullary histology); no statistically significant difference was detected. It is to be pointed out, however, that our analysis was limited by the retrospective nature of the study. Although ours represented one of the largest to systematically evaluate the outcome of medullary histology relative to other poorly differentiated histologies, the case numbers were still relatively small and the patient follow-up time was still limited.

Nonetheless, our study serves to highlight the insufficiencies of the current morphological criteria for diagnosing MC, and underscore the need for future research efforts to be guided by better defined and more reproducible classification system. Our results suggest that MC, as currently applied, cannot be regarded reliably as a distinct tumor type carrying the connotation of a better clinical outcome. We propose that, before an improved classification

system is accomplished, medullary histology – either in the form of “classic MC” or in the form of “carcinoma with medullary features” – be regarded only as a morphological descriptor and its significance be limited to the suggestion of MMR deficiency (therefore guiding further MMR testing). We also propose that we continue to catalogue colorectal adenocarcinomas with a solid growth into the 3 categories (MC, carcinoma with medullary features, and PDC) for the purpose of collecting data for future analysis; the diagnostic features we listed (Table 1) can serve as a guide for such categorization.

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Figure 1.
H&E appearances of typical colorectal medullary carcinomas. Note the circumscribed tumor border (A, 40× magnification), the appearance of sheets of cells at low power (B, 40× magnification) imparted by uniform and syncytial tumor cell nests merging with a cellular stroma (C, 100× magnification). Typically, these tumors have abundant tumor-infiltrating lymphocytes (D, 100× magnification).

Figure 2.

H&E appearances of high grade colorectal adenocarcinoma with medullary features.

Although the tumor cells may appear uniform and are associated with some tumor-infiltrating lymphocytes, they have a cord like growth pattern with a fibrotic stroma (A, 40× magnification), an infiltrative border (B, 40× magnification), or with regions showing solid growth mixed with small but well formed lumina (C, 100× magnification, and D, 200× magnification).

Figure 3.

H&E appearances of conventional poorly differentiated colorectal adenocarcinoma. These tumors typically show high grade cytology and a desmoplastic stroma (A–C, each 100× magnification). Tumors may grow in solid sheets; however, the cells show high grade cytological features such as increased nuclear-to-cytoplasmic ratio (D, 100× magnification). Note the lack of apparent tumor infiltrating lymphocytes in these tumors.

Figure 4.

Overall survival of high grade colorectal adenocarcinomas with stages II, III, and IV diseases.

Figure 5. Overall survival of high grade colorectal adenocarcinomas of medullary, indeterminate, and conventional poorly differentiated types.

Table 1

Morphological features of medullary carcinoma versus carcinoma with medullary features versus conventional poorly differentiated carcinoma.

Tumor Subtype	Morphological Features
Medullary Carcinoma (MC)	<p>50% of the tumor showing all of the following 5 features:</p> <ol style="list-style-type: none"> 1 Solid or nested growth pattern; 2 An overall circumscribed tumor border; 3 A cellular stroma rich in lymphocytes, may be accompanied by abundant neutrophils; 4 Uniform tumor cells with a syncytial appearance, the cytoplasm is characteristically eosinophilic or amphophilic, but can vary in both tinctorial quality and amount; 5 Conspicuous tumor-infiltrating lymphocytes (often >30 TILs/HPF). <p><i>A typical medullary carcinoma (with >=50% showing the above features) may be accompanied by any of the other conventional or non-conventional histological types of colorectal carcinomas (including foci with medullary features as described below).</i></p>
Carcinoma with medullary features (indeterminate carcinoma, IC)	<p>50% of the tumor showing features resembling medullary carcinoma but not fulfilling all the criteria listed above. Instead, they typically show:</p> <ol style="list-style-type: none"> 1 One or more of the following cyto-architectural features: <ol style="list-style-type: none"> a. Cord-like growth pattern (may resemble breast lobular carcinoma or diffuse type gastric carcinoma); b. Nodules of cribriform glands with well formed lumina; c. Well formed glands admixed with solid areas; d. Irregular tumor configuration at invasive front; e. Presence of easily discernible “signet ring” tumor cells among otherwise “medullary” looking tumor cells; f. Presence of relatively uniform cells with stippled chromatin reminiscent of neuroendocrine morphology; g. Squamoid cytology; 2 A more fibrotic or desmoplastic stroma separating the tumor cords or nests; 3 An increased lymphocytic infiltration, but TIL count often not exceeding 30/HPF.
Conventional poorly differentiated carcinoma (PDC)	<p>Lack typical medullary features, instead, 50% of the tumor show:</p> <ol style="list-style-type: none"> 1 Solid or irregular growth pattern; 2 Desmoplastic stroma; 3 High grade cytology with cellular/nuclear pleomorphism; 4 Often inconspicuous tumor-infiltrating lymphocytes.

Table 2

Patient and tumor characteristics stratified by histologic subtypes.

	MC (n=19)	IC (n=26)	p ¹ value	PDC (n=35)	p ² value
Age (yrs) Median (range)	73 (36–91)	71.5 (36–85)	0.6	49 (20–78)	<0.001
Gender Female	11 (58%)	19 (73%)	0.3	13 (35%)	0.01
Right site *	17 (90%)	21 (80%)	0.4	20 (54%)	0.009
Tumor size >5cm	11 (58%)	18 (69%)	0.4	14 (40%)	0.07
TILs/HPF Median (range)	40 (30–140)	20 (2–60)	0.01	2 (0–35)	<0.001
# cases with >10TILs/HPF	19 (100%)	19 (73%)	0.01	4 (11%)	<0.001
MMRd by IHC	19 (100%)	22 (85%)	0.1	5 (14%)	<0.001
TNM stage low (I or II)	11 (58%)	14 (54%)	0.8	7 (20%)	0.005
TNM Stage III	7 (37%)	8 (31%)		17 (49%)	
TNM Stage IV	1 (5%)	4 (15%)		11 (31%)	
	MC (n=19)	Indeterminate (n=26)		PDC (n=33)	
5-year overall survival rates (n=78)	88%	61%	0.4	55%	0.5

MC, medullary carcinoma; IC, indeterminate carcinoma; PDC, poorly differentiated carcinoma; TIL, tumor infiltrating lymphocytes; MMRd, DNA mismatch repair deficiency; IHC, immunohistochemistry. Continuous variables are expressed as median (range), categorical variables are expressed as n (%).

* Proximal to splenic flexure.

p¹-value refers to the comparison of the MC versus IC group.

p²-value refers to the comparison of the MC, IC versus PDC group.