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Associations Among Histologic Characteristics and Patient Outcomes in Colorectal Carcinoma with a Mucinous Component

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Abstract

Aims: Colorectal carcinoma (CRC) often has a mucinous component, with more than 50% mucin by volume defining the mucinous subtype of CRC. The prognostic impact of the mucinous phenotype remains unclear.

Methods and results: We evaluated 224 CRC with at least 5% mucinous component (herein “mCRC”) for patient sex, age, race, and outcome; tumour size, location, stage, and microsatellite instability (MSI) status; percentage of glands producing mucin; percentage of tumour volume composed of mucin; whether tumoural epithelium floated in mucin pools; tumour budding; signet ring cells (SRCs); and peritumoural inflammation (PI). We related these features to disease-specific survival and compared outcomes to 499 stage-matched, conventional colorectal adenocarcinomas. Factors predicting worse prognosis in mCRC on univariable analysis included non-MSI-high status ($P=0.0008$), SRC ($P=0.0017$), and lack of PI ($P=0.0034$). No parameters were independently associated with outcome after adjusting for tumour stage in multivariate analysis. Percent of glands producing mucin and percent tumour volume composed of mucin did not affect prognosis, including at the recommended 50% cutoff for subtyping mCRC. Disease-specific survival for mCRC and adenocarcinomas were similar after accounting for stage.

Conclusions: Stage-matched mCRCs and adenocarcinomas have similar outcomes, with no prognostic significance to morphological subtyping. Histologic characteristics of mCRC, including percentage of tumor volume comprised of mucin, were not predictive of outcome.

Keywords

colon cancer; mucinous adenocarcinoma; microsatellite instability; tumour budding

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Conflicts of interest

None to declare.

Ethics statement

A waiver of consent was obtained for this project. The study was performed according to the Declaration of Helsinki. The Institutional Research Board at Vanderbilt University approved the study (IRB #130726, originally approved 13/05/2013).

Introduction

Mucinous colorectal carcinoma (mCRC) is one of the most common subtypes of colorectal carcinoma (CRC), accounting for roughly 10–15% percent of cases.¹ The malignant epithelium of mCRC either lines or floats within large pools of extracellular mucin. According to World Health Organization (WHO) criteria, CRC is classified as mucinous if “>50% of the lesion is composed of pools of extracellular mucin that contain malignant epithelium.”² This cutoff, while traditional, is arbitrary and has not been rigorously evaluated.

In some organs, the presence of mucinous features within a carcinoma is associated with differential outcomes; for instance, mucinous mammary carcinoma (also known as “colloid carcinoma”) has an improved prognosis compared to conventional ductal carcinoma.³ In the colon, the impact of a mucinous component is not as clear, as various studies have determined that mucinous phenotype does^{4–7} or does not^{8–14} independently predict outcome in stage-matched multivariable analysis. Still, some aspects of mCRC are known to affect prognosis. For instance, a mucinous component within a CRC, especially in the right colon, may indicate that the lesion harbors microsatellite instability (MSI),¹⁵ which is associated with a better prognosis.^{16–18} In contrast, the presence of signet ring cells (SRC), either within mucin pools or invading mural tissue, confers a worse prognosis,¹⁸ even though these may be seen in microsatellite-unstable CRC as well.^{18,20}

Since relatively few studies have analysed the clinicopathologic characteristics of mCRC (including percentage of mucinous component) in relation to patient outcome, we evaluated whether any clinical parameters or histologic findings affect prognosis of CRC with a mucinous component.

Materials and methods

With appropriate Institutional Research Board approval, slides from 1,638 CRC resections in the institution-restricted research files of one of the authors (KW) were reviewed for a mucinous component (either malignant glands closely associated with and thereby likely producing mucin, or sizable mucin pools forming part of the tumour volume) constituting at least 5% of the tumour area examined. Cases with predominantly tissue-invasive SRC morphology were excluded, as were cases treated with neoadjuvant therapy, as treatment effect can impart a mucinous appearance to CRC that may not have been mucinous prior to therapy.²¹ Cases of adenoma-like adenocarcinoma were also excluded; while they often contain a significant mucinous component, they appear to represent a special subset of CRC with a better prognosis than other well-differentiated CRC, meaning their inclusion in this analysis could skew outcome comparisons.²²

In total, 224 malignancies (14% of cases) meeting these criteria were identified; they are hereafter identified as mCRC for study purposes. For each case, patient medical records and gross descriptions were reviewed for patient sex, age, race, and outcome; and tumour size, location, number of sections reviewed, and American Joint Committee on Cancer (AJCC) combined tumour stage. Original haematoxylin and eosin (H&E)-stained slides were

reviewed to determine tumour edge (pushing vs. infiltrative), presence of SRC or non-SRC single cells floating within mucin, presence of lymphovascular or perineural invasion, presence and type of precursor adenoma, presence of tumour deposits, and number of positive lymph nodes. (As the WHO states that grading does not apply to CRC subtypes, histologic grade was not included in analysis.²) For large mucin pools, the associated epithelium was recorded as either floating within mucin or attached to the adjacent stromal wall, and epithelium associated with these pools was subcategorized as forming thin strips (architecturally), large glandular aggregates (easily observed at low magnification), or small clusters (10 or fewer cells, not always visible at low magnification). Tumour budding was quantified according to International Tumor Budding Consensus Conference criteria and scored as low, intermediate, or high.²³ Peritumoural inflammation immediately adjacent to the tumour was marked as absent, acute, or chronic. Cases where peritumoural inflammation manifested as large lymphoid aggregates in the general periphery, rather than scattered inflammatory cells immediately adjacent, were denoted as having a peripheral Crohn's-like reaction.

Two additional variables recorded for each mCRC were percentage of malignant glands producing mucin (Figure 1A) and percent of tumour volume composed of mucin (Figure 1B). Both were determined by eyeball estimation of the two parameters on each section of tumor; the percentages of each were then summed and divided by the number of tissue sections per case. Roughly one tissue section was submitted for microscopy per gross cm of tumor among the mCRC cases (mean number of sections per cm of tumor, 1.08; median, 1; range: 0.81–3.33).

Microsatellite instability (determined either by immunohistochemical methods and/or a sendout PCR-based assay test tumor DNA for hypermethylation of the *MLH1* promoter, performed at the Mayo Clinic [Rochester, MN]²⁴) had been assessed as part of patient care for 129 cases; this information was recorded as well, with cases dichotomized as MSI-negative (microsatellite stable or low instability by PCR) or MSI-high (high instability by PCR or mismatch repair protein-deficient by immunohistochemistry). *KRAS* and *BRAF* mutational analysis had been assessed by PCR as part of patient care for 54 cases (24%); given the relatively small subset of cases with this information, *KRAS* and *BRAF* status were excluded from subsequent analysis.

Of the remaining non-mucinous adenocarcinomas from the set of 1,638 CRC, there were 499 conventional colorectal adenocarcinomas with previously compiled outcome data and clinicopathologic findings, aside from those related to mucinous component (e.g., whether tumor cells floated in mucin) or SRC component. These 499 cases formed a comparison group. MSI status was available for 125 of these cases (25%).

Associations between clinicopathologic factors and disease-specific survival in mCRC cases were initially assessed by univariable Cox proportional hazard regression. Potential confounding variables (sex, race, age, AJCC stage, tumour size, anatomic site, and presence of Crohn's-like reaction, tumour budding, mesenteric tumor deposits, lymphovascular invasion, or perineural invasion) were evaluated by multivariate Cox proportional hazard regression. Variables were dropped from the multivariate model in order of increasing

absolute value of *z*-score until all variables were statistically significant. As only AJCC stage remained significant after this process, subsequent analysis of variables of interest was performed using Cox proportional hazard regression adjusted for AJCC stage. Similar methods, as well as Fisher's exact test and the unpaired *t* test, were used to compare clinicopathologic variables and stage-matched mCRC outcomes to the comparison group. Finally, a second multivariable analysis looking at both cohorts combined was performed. Statistical analysis was performed using Stata v13 (Stata Corp, College Station, TX). All hypothesis tests were two-sided, with $\alpha=0.05$.

Results

The cohort of patients with mCRC (n=224) and colonic adenocarcinoma (n=499) were similar overall. Mean age was 64 years both ($P=0.50$), males made up 51% of the former group and 53% of the latter group ($P=0.57$), and 88% of the former group and 85% of the latter group were Caucasian ($P=0.42$). While mean tumor size was larger (5.1 cm) for mCRC than for adenocarcinoma (4.0 cm; $P<0.0001$), a similar proportion of mCRC and adenocarcinoma cases were AJCC stage IV (16% vs. 20%, $P=0.25$), and, a similar proportion of mCRC and adenocarcinoma patients died from disease based on available follow-up data (25% vs. 31%, $P=0.11$).

Clinicopathologic details of the 224 mCRC cases, along with the results of statistical analyses, are summarized in Tables 1 and 2. On univariable analysis, factors influencing prognosis included size (hazard ratio [HR] 1.12 for every 1.0 cm increase in size, 95% confidence interval [CI] 1.06–1.17, $P<0.001$) and number of positive lymph nodes (HR 1.11 for every incremental positive node, 95% CI 1.09–1.13, $P<0.001$). Additionally, by log-rank test, more adverse events occurred than would otherwise be expected for patients whose mCRC was MSI-negative ($P=0.0008$), formed small epithelial clusters (Figure 1C) rather than strips (Figure 1D) or large aggregates (Figure 1E) ($P=0.022$), lacked peripheral inflammation ($P=0.0034$) (Figure 1F), lacked a peripheral Crohn's-like reaction ($P=0.026$), had tumour deposits ($P<0.0001$), had SRC or single non-SRC cells floating in mucin ($P=0.0017$) (Figure 1G), showed lymphovascular invasion ($P<0.0001$), or was stage IV by AJCC criteria ($P<0.0001$). The other factors, including tumour budding (Figure 1H), did not significantly impact prognosis. Micropapillary features were only seen in nine mCRC and were therefore excluded from analysis.

None of the analyzed attributes, however, remained statistically significant on AJCC stage-matched multivariable analysis. Furthermore, survival within the mCRC group was not impacted by percent of mucin-producing glands or percent volume of tumour composed of mucin (HR 1.00 for both [10% intervals], 95% CI 0.99–1.01 for volume and 1.00–1.01 for glands, $P=0.60$ for volume and $P=0.27$ for glands). After stratifying the cases as having 50% or >50% tumour volume composed of mucin (i.e., the definitional criteria advocated by the WHO), there remained no prognostic difference ($P=0.23$). This was also the case for stratifying cases as having 50% or >50% mucin-producing glands ($P=0.38$).

A multivariable analysis including the cases from both cohorts (mCRC and adenocarcinoma) is shown in Table 3. Factors that had a significant negative effect on prognosis in this larger

analysis included increased age, increased tumor size, female sex, black race, mesenteric tumor deposits, large-vessel invasion, lack of Crohn's-like reaction, and AJCC stage III or IV disease.

Stage-matched disease-specific survival was similar for the two patient cohorts, namely mCRC (median follow-up, 35 months) and adenocarcinoma (median follow-up, 50 months) (Figure 2A; $P=0.95$). This finding held after paring down the mCRC comparison group to only include cases with >50% mucin by volume (Figure 2B; $P=0.15$).

Discussion

When evaluating a colorectal carcinoma specimen, pathologists must determine whether the carcinoma meets criteria for a particular subtype and whether certain histologic features or findings are relevant to patient treatment and prognosis. Historically, CRC has been termed mCRC when more than 50% of the tumour volume is composed of extracellular mucin. This has been adopted by the WHO,² and most studies comparing CRC to mCRC use this criterion (if any is mentioned). The prognostic impact of this criterion remains unclear. Our study suggests that, in concurrence with most other studies that account for tumour stage,^{8–14} the mucinous component of CRC has no significant impact on patient prognosis. The lack of prognostic significance was not only observed using a dichotomized 50% cutoff, but also when evaluating percent mucin as a continuous variable.

In addition to investigating the prognostic significance of tumour volume composed of extracellular mucin, we also evaluated the percentage of tumour glands producing mucin. These two percentages can be quite different, as a few markedly dilated glands producing copious mucin in an otherwise unremarkable CRC would lead to a high percentage of mucin comprising tumour volume, but a low percentage of malignant glands producing mucin. Regardless, this characteristic similarly had no prognostic significance.

Although properly identifying the mucinous subtype of CRC may not have prognostic significance, it may connote potentially important biologic and therapeutic information. Mucinous CRC have higher rates of MSI²⁵ and lower rates of *TP53* mutation than adenocarcinoma,²⁶ and they also demonstrate higher expression of *HATH1*²⁷ and *MUC2*.²⁸ *KRAS* mutation may²⁹ or may not²⁶ be related to mucinous differentiation in CRC. Some of these associations are important from a prognostic and therapeutic perspective, as MSI-high status confers improved survival in mCRC²⁵ and may qualify a patient for anti-PD-1 therapy,³⁰ and tumours with a *KRAS* mutation are not eligible for treatment with EGFR inhibitors.³¹ Mucinous CRC may also respond differently to chemotherapy than adenocarcinoma, as the mucin may act as a barrier to drug delivery.¹ To our knowledge, no specific targetable mutations have been identified in mCRC not also seen in adenocarcinomas, although loss of *HES1* (which is associated with worse prognosis) occurs more commonly in mCRC.³² As therapeutically relevant molecular properties can be tested on individual cases, there appears to be little intrinsic relevance to mucinous phenotype in CRC. While mucinous features should still be mentioned in a signout report (if for no other reason than to guide histologic interpretation of potential future metastatic lesions), utilizing criteria such as a 50% cutoff is not supported by currently available data.

While univariable analysis did identify a few clinicopathologic variables as potentially prognostic, none remained so on multivariate analysis. These included abundant SRC (which others have linked to poor prognosis²⁰) and chronic inflammation surrounding a tumour (which others have linked to improved outcome^{33,34}). Tumour budding, which has undergone much scrutiny recently in CRC,²³ did not emerge as a prognostic factor in our mCRC cohort. The majority of cases showed low or intermediate tumour budding, potentially in keeping with reports that tumour budding is uncommon in MSI-high CRC.^{35,36}

Our study admittedly has at least two notable limitations. The first is that percentage of malignant glands producing mucin and percent of tumour volume composed of mucin for mCRC were both estimated by eyeballing. Eyeballing is generally considered to be less accurate than more precise methods of quantification, such as software analysis. However, in our experience, eyeballing remains the most common method of quantification in daily practice and therefore the most translatable to routine pathologic evaluation. Additionally, determining the “true” percentages of the above parameters would be nearly impossible, even with specialized software, as most carcinomas in the study were not entirely submitted for microscopy, and mucin volume and mucin production sometimes varied widely from section to section within a tumor. For these reasons, we considered eyeballing an acceptable modality to utilize in this study, despite its disadvantages.

The second notable limitation is the relative lack of molecular data. MSI status was available for 58% of our mCRC cases, as the others predated routine evaluation of mismatch repair immunohistochemistry on colon carcinomas. Far fewer mCRC cases – only 24% – had undergone molecular analysis for *KRAS* and *BRAF* mutational status. Recent studies have reported intriguing results regarding molecular findings in mCRC; most notably, Liddell et al³⁷ suggested that mCRC can be split into four distinct subtypes depending on clinical and molecular factors. Our lack of molecular data in most cases precluded us from evaluating our cases in a similar, statistically sound manner.

In conclusion, colorectal carcinoma with a mucinous component, matched stage for stage, shows no prognostic difference compared to conventional colorectal carcinoma. This holds true when dichotomizing cases at any cutoff of mucinous volume, including the 50% value typically required for a diagnosis of mCRC.

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RSG co-conceived the study, reviewed cases, and wrote the manuscript. JMMC provided statistical analysis and expert advice. KW co-conceived the study, collected cases, and gathered clinical and molecular data.

* The work for this project was performed while Dr. Gonzalez was at the University of Rochester. Dr. Gonzalez is currently at Beth Israel Deaconess Medical Center.

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Figure 1.

A, In this mucinous colorectal carcinoma, most of the malignant glands produce visible mucin, but the mucin itself constitutes a low overall percentage of the tumour volume.

B, In contrast, while only 30% of the malignant glands in this carcinoma produce mucin, the mucin itself constitutes 60% of the tumor volume.

C, The epithelium in this carcinoma floats within mucin, forming small clusters of malignant cells.

D, The epithelium in this carcinoma forms strips lining the mucin-filled pools.

E, The epithelium in this carcinoma forms large complex aggregates rather than thin strips.

F, Peripheral chronic inflammation closely associated with mucinous colorectal carcinoma.

G, Abundant signet ring cells floating within mucin pools.

H, Tumour budding at the leading edge of a mucinous colorectal carcinoma, which was not significantly linked to outcome in these tumours.

Figure 2.

A, Kaplan–Meier plot comparing disease-specific survival for colorectal carcinoma with any mucinous component and conventional colorectal adenocarcinoma, stage by stage ($P=0.95$).

B, Kaplan–Meier plot comparing disease-specific survival for mucinous colorectal carcinoma meeting WHO criteria (>50% mucinous tumor volume) and colorectal adenocarcinoma, stage by stage ($P=0.15$).

Table 1 –

Cox Regression of Continuous Variables in Mucinous Colorectal Carcinoma

	Findings in mCRC (n=224)	Hazard Ratio	95% CI	P-value
Age	Median: 66 years Range: 10–93 years	1.0	0.99–1.01	0.98
Size	Median: 5.0 cm Range: 0.4–18.5 cm	1.12	1.06–1.17	<0.001
Percent mucin-producing glands	Median: 50% Range: 5–100%	1.00	0.99–1.01	0.60
Percent mucin by tumour volume	Median: 60% Range: 5–100%	1.00	1.00–1.01	0.27
Positive node count	Median: 0 Range: 0–41	1.11	1.09–1.13	<0.001

Table 2 –

Log-rank Test for Equality of Survivor Functions in Categorical Variables in Mucinous Colorectal Carcinoma

	Findings in mCRC (n=224)	Events Observed	Events Expected	P-value
Sex	Male: 114	25	28	0.49
	Female: 110	31	28	
Race	White: 196	47	48	0.38
	Black: 19	5	6	
	Other: 9	4	2	
AJCC Stage	1: 39/221	2	10	<0.0001
	2: 80/221	6	23	
	3: 67/221	17	16	
	4: 35/221	28	5	
MSI Status	Negative: 69/129	21	13	0.0008
	MSI-high: 60/129	3	11	
Epithelium lining mucin pools	Detached: 45	14	10	0.21
	Attached: 134	31	37	
	Mixed: 45	11	10	
Architectural pattern of epithelium	Strips: 130	29	35	0.022
	Aggregates: 63	15	16	
	Clusters: 31	12	6	
Grade	Low: 37	7	10	0.015
	Intermediate: 134	29	34	
	High: 53	20	11	
Signet ring cells	Absent: 177	39	47	0.0017
	Single non-SRC cells: 14	5	3	
	Focal: 14	3	3	
	Abundant: 19	9	3	
Peripheral inflammation	Absent: 155	47	34	0.0034
	Acute: 32	6	10	
	Chronic: 37	3	12	
Peripheral Crohn's-like reaction	Absent: 145	36	28	0.026
	Present: 62	20	28	
Tumour budding	Low: 82/222	15	17	0.79
	Intermediate: 92/222	27	25	
	High: 48/222	13	13	
Site	Cecum: 48/220	10	11	0.62

	Findings in mCRC (n=224)	Events Observed	Events Expected	P-value
	Ascending: 78/220	17	20	
	Transverse: 18/220	10	7	
	Descending: 19/220	4	3	
	Sigmoid: 34/220	9	8	
	Rectum: 23/220	4	6	
Edge	Pushing: 104/217	24	24	0.91
	Infiltrative: 113/217	30	30	
Precursor adenoma	No residual: 128/220	33	33	0.084
	Tubular adenoma: 19/220	5	3	
	Tubulovillous/villous adenoma: 63/220	15	17	
	Sessile serrated adenoma/polyp: 6/220	0	2	
	Traditional serrated adenoma: 4/220	3	1	
Tumour deposits	Absent: 172/219	27	47	<0.0001
	Present: 47/219	29	9	
Lymphovascular invasion	Absent: 141/223	22	38	<0.0001
	Present: 82/223	33	17	
Perineural invasion	Absent: 210	50	52	0.17
	Present: 14	6	4	
Molecular findings	<i>KRAS</i> mutant: 20/54	9	6	0.26
	<i>BRAF</i> mutant: 22/54	3	4	
	Neither: 12/54	3	5	

Table 3 –

Comparison of Clinicopathologic Features for Molecular Subtypes of Mucinous Colorectal Carcinoma

	KRAS (n=20)	BRAF (n=22)	Neither (n=12)	P-value
Age (years)				0.77
Mean	64	70	62	
Range	37–83	49–88	41–78	
Sex				0.24
Male	11 (55%)	9 (41%)	3 (25%)	
Female	9 (45%)	13 (59%)	9 (75%)	
Race				0.51
White	16 (80%)	21 (95%)	11 (92%)	
Black	2 (10%)	0	0	
Other	2 (10%)	1 (5%)	1 (8%)	
Size (cm)				0.015
Mean	5.98	6.74	5.16	
Range	2.5–10.0	1.9–14.2	2.0–8.0	
AJCC Stage				0.12
I	0	3 (14%)	0	
II	6 (30%)	10 (45%)	8 (67%)	
III	7 (35%)	7 (32%)	2 (17%)	
IV	7 (35%)	2 (9%)	2 (17%)	
MSI Status				0.004
Negative	12/16 (75%)	5/21 (24%)	8 (67%)	
MSI-high	4/16 (25%)	16/21 (76%)	4 (33%)	
Percent mucin-producing glands				0.93
Mean	56%	60%	46%	
Range	5–100%	5–100%	5–100%	
Percent mucin by tumour volume				0.64
Mean	56%	64%	50%	
Range	5–100%	5–100%	5–95%	
Epithelium lining mucin pools				0.26
Detached	2 (10%)	7 (32%)	1 (8%)	
Attached	15 (75%)	11 (50%)	10 (83%)	
Mixed	3 (15%)	4 (18%)	1 (8%)	
Architectural pattern of epithelium				0.64
Strips	14 (70%)	13 (59%)	10 (83%)	
Aggregates	4 (20%)	5 (23%)	2 (17%)	

	KRAS (n=20)	BRAF (n=22)	Neither (n=12)	P-value
Clusters	2 (10%)	4 (18%)	0	
Grade				0.33
Low	4 (20%)	3 (14%)	3 (25%)	
Intermediate	14 (70%)	11 (50%)	7 (58%)	
High	2 (10%)	8 (36%)	2 (17%)	
Signet ring cells				0.11
Absent	18 (90%)	13 (59%)	11 (92%)	
Single non-SRC cells	0	3 (14%)	1 (8%)	
Focal	0	1 (5%)	0	
Abundant	2 (10%)	5 (23%)	0	
Peripheral inflammation				0.65
Absent	16 (80%)	19 (86%)	8 (67%)	
Acute	3 (15%)	2 (9%)	2 (17%)	
Chronic	1 (5%)	1 (5%)	2 (17%)	
Crohn's-like reaction				0.49
Absent	14 (70%)	13 (59%)	6 (50%)	
Present	6 (30%)	9 (41%)	6 (50%)	
Tumour budding				0.043
Low	3 (15%)	11 (50%)	5 (42%)	
Intermediate	14 (70%)	8 (36%)	3 (25%)	
High	3 (15%)	3 (14%)	4 (33%)	
Site				0.38
Cecum	9 (45%)	10 (45%)	2 (17%)	
Ascending	5 (25%)	6 (27%)	7 (58%)	
Transverse	2 (10%)	4 (18%)	1 (8%)	
Descending	0	1 (5%)	0	
Sigmoid	3 (15%)	1 (5%)	1 (8%)	
Rectum	1 (5%)	0	1 (8%)	
Edge				0.68
Pushing	10 (50%)	12/21 (57%)	8 (67%)	
Infiltrative	10 (50%)	9/21 (43%)	4 (33%)	
Precursor adenoma				0.67
No residual	9 (45%)	13/21 (62%)	7 (58%)	
Tubular adenoma	3 (15%)	2/21 (10%)	0	
Tubulovillous/villous adenoma	6 (30%)	4/21 (19%)	5 (42%)	
Sessile serrated adenoma/polyp	0	1/21 (5%)	0	
Traditional serrated adenoma	2 (10%)	1/21 (5%)	0	

	KRAS (n=20)	BRAF (n=22)	Neither (n=12)	P-value
Tumour deposits				0.030
Absent	11 (55%)	19/21 (90%)	9/11 (82%)	
Present	9 (45%)	2/21 (10%)	2/11 (18%)	
Lymphovascular invasion				0.76
Absent	10/19 (53%)	13 (59%)	9 (75%)	
Present	9/19 (47%)	9 (41%)	3 (25%)	
Perineural invasion				0.32
Absent	18 (90%)	22 (100%)	11 (92%)	
Present	2 (10%)	0	1 (8%)	