

Clinicopathological features and survival outcomes of mucinous versus non-mucinous colon adenocarcinoma: a retrospective cohort study from a tertiary cancer centre in South India

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Abstract

Background: Mucinous adenocarcinoma (MAC) is a distinct histological subtype of colorectal cancer whose prognostic significance remains debated, and data from Indian patients are scarce. We compared the clinicopathological profile and overall survival (OS) of mucinous and non-mucinous adenocarcinoma (NMAC) of the colon treated at a tertiary cancer centre in South India. **Material and Methods:** This retrospective cohort study included consecutive patients with histologically confirmed colon adenocarcinoma diagnosed between December 2015 and February 2021 and treated at the Department of Medical Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore. Baseline characteristics were compared with Fisher's exact and Mann–Whitney tests. OS was estimated by the Kaplan–Meier method, compared with the log-rank test, and analysed with Cox proportional hazards regression. **Results:** Of 45 patients (median age 50 years; 55.6% stage IV), 10 (22.2%) had MAC. Stage distribution was similar between groups (stage IV 50.0% vs 57.1%; $p = 1.000$). MAC showed non-significant trends towards female sex (62.5% vs 25.0% of patients with recorded sex; $p = 0.086$), right-sided location (77.8% vs 57.1%) and younger age (median 48 vs 52 years). At a median follow-up of 41.1 months, 17 patients had died. Median OS was 11.7 months for MAC and not reached for NMAC (log-rank $p = 0.073$); 3-year OS was 45.7% vs 64.5%. After adjustment for stage, MAC was independently associated with inferior OS (hazard ratio [HR] 3.46 (1.25–9.61); $p = 0.017$), a finding unchanged in a stage-stratified model (HR 3.55 (1.28–9.90)). The difference was most marked in stage IV disease (median OS 6.6 vs 33.5 months; $p = 0.018$). **Conclusion:** MAC accounted for more than one in five colon cancers in this South Indian cohort and was associated with poorer stage-adjusted survival, particularly in metastatic disease. Given the small sample, these findings are hypothesis-generating and support larger multicentre Indian studies incorporating mismatch-repair and RAS/BRAF profiling.

Keywords: Colon Cancer, Mucinous Adenocarcinoma, Histological Subtype, Overall Survival, Prognosis; India.

Received: 05 September 2026

Revised: 26 September 2026

Accepted: 19 October 2026

Published: 26 October 2026

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide.^[1] Although its age-standardised incidence in India remains lower than in Western countries, the absolute burden is substantial and rising, and Indian hospital-based series consistently describe a younger patient population and a high proportion of advanced disease at presentation.^[2,3]

Mucinous adenocarcinoma (MAC) is defined by the World Health Organization as an adenocarcinoma in which more than 50% of the tumour volume consists of extracellular mucin.^[4] It represents approximately 10–15% of colorectal cancers and differs from conventional, non-mucinous adenocarcinoma (NMAC) in several respects: it occurs more frequently in the proximal colon, in younger patients and in women; it is enriched for microsatellite instability (MSI), BRAF and KRAS mutations; and it tends to present at a more advanced stage.^[5–7] The prognostic significance of mucinous histology has nevertheless been contentious. A meta-analysis of 44 studies by Verhulst and colleagues

found that mucinous subtype conferred a modest (2–8%) increase in the hazard of death that was not consistently independent of stage.^[8] whereas a recent meta-analysis of more than 340,000 patients reported a pooled hazard ratio (HR) of 1.44, with the strongest effect in stage IV disease.^[9]

In the metastatic setting, MAC is characterised by a propensity for peritoneal dissemination,^[10] and by reduced responsiveness to fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, with lower response rates and shorter survival in several retrospective series and in post hoc analyses of randomised trials.^[11–13] In resected stage III disease, the benefit

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DOI:
10.21276/amt.2026.v13.i3.1143

How to cite this article: Pooja D, Hafeez M, Saxena S, Angadi V, Nandennavar MI, Karpurmath S. Clinicopathological features and survival outcomes of mucinous versus non-mucinous colon adenocarcinoma: a retrospective cohort study from a tertiary cancer centre in South India. *Acta Med Int.* 2026;13(3):762-767.

of adjuvant chemotherapy for MAC appears to be preserved, although outcomes may be modified by MSI status.^[14,15]

Almost all of this evidence derives from Western and East Asian populations. Indian data on the frequency, clinical profile and prognostic impact of mucinous histology in colon cancer are limited, despite differences in age structure, stage at presentation and access to molecular testing and biological agents. We therefore compared the clinicopathological features and overall survival (OS) of patients with mucinous and non-mucinous colon adenocarcinoma treated at a tertiary cancer centre in South India.

MATERIALS AND METHODS

Study design and setting: This was a single-centre, retrospective cohort study conducted in the Department of Medical Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, a tertiary care teaching hospital with a dedicated oncology service. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.^[17] The protocol was approved by the Institutional Ethics Committee of Vydehi Institute of Medical Sciences and Research Centre, which waived the requirement for individual informed consent in view of the retrospective design and use of de-identified data.

Participants: Medical oncology case records of consecutive patients with histologically confirmed adenocarcinoma of the colon (caecum to sigmoid colon) diagnosed between December 2015 and February 2021 were reviewed. Patients with rectal primaries or non-adenocarcinoma histology were not eligible. Patients were included irrespective of stage or treatment received.

Variables and definitions: Demographic, clinical, pathological, treatment and follow-up data were extracted from case records into a structured data sheet. Histological subtype was taken from the institutional pathology report; tumours reported as mucinous adenocarcinoma (>50% extracellular mucin, as per WHO criteria.^[4]) were classified as MAC and all other adenocarcinomas as NMAC, including five patients whose data sheet recorded adenocarcinoma without further histological description. NMAC tumours were further described by differentiation grade where reported. Tumour location was classified as right-sided (caecum, ascending colon, hepatic flexure, or right hemicolectomy without a more specific site) or left-sided (splenic flexure, descending and sigmoid colon, or left hemicolectomy/anterior resection/sigmoidectomy); when the stated tumour site and the operation recorded disagreed, the stated site was used. Stage was recorded according to the American Joint Committee on Cancer (AJCC) 8th edition.^[18] and grouped as stage II, III or IV. Treatment variables comprised resection of the primary tumour and the systemic regimen received (oxaliplatin-based [CAPEOX/FOLFOX], irinotecan-based, other, or best supportive care), as well as receipt of bevacizumab.

Outcome: The primary outcome was OS, defined as the time from the date of diagnosis to the date of death from any cause. Patients alive at last contact, or lost to follow-up, were censored at the date of last documented follow-up. Progression-free survival could not be assessed reliably from the available records.

Statistical analysis: Categorical variables are presented as numbers and percentages and continuous variables as medians with interquartile ranges (IQR). Groups were compared with Fisher's exact test for 2×2 tables, the Fisher–Freeman–Halton exact test (Monte Carlo, 20,000 permutations) for larger tables, and the Mann–Whitney U test for age; patients with missing values were excluded from the corresponding test only. Median follow-up was calculated with the reverse Kaplan–Meier method. OS was estimated with the Kaplan–Meier method, with 1-, 2- and 3-year survival probabilities and medians with 95% confidence intervals (CI), and compared with the log-rank test overall and within prespecified stage subgroups (stage II–III and stage IV).

Univariable Cox proportional hazards regression was used to estimate HRs with 95% CI for histological subtype, stage, age (≥ 50 vs < 50 years), sex and tumour side. Because of the limited number of deaths, the multivariable model was restricted to two covariates — histological subtype and stage (IV vs II–III) — to keep the ratio of events per variable close to recommended limits.^[19] The proportional hazards assumption was assessed using Schoenfeld residuals. As this assumption was violated for stage, a sensitivity analysis stratified by stage was performed; further sensitivity analyses added age group to the model among patients with recorded age, and excluded the five patients without a recorded histological description. All tests were two-sided, with $p < 0.05$ considered statistically significant; no adjustment was made for multiple comparisons, and secondary analyses are regarded as exploratory. Analyses were performed in Python 3.13 (pandas, SciPy and statsmodels).

RESULTS

Study population: A total of 45 patients with colon adenocarcinoma were included [Table 1]. The median age was 50 years (IQR 46–61; recorded in 36 patients), 17 of 36 patients (47.2%) were younger than 50 years and 8 (22.2%) were younger than 40 years. Of the 36 patients with recorded sex, 24 (66.7%) were men. The tumour was right-sided in 23 of 37 patients (62.2%) with known location. Twenty-five patients (55.6%) had stage IV disease, 3 (6.7%) stage III and 17 (37.8%) stage II. Abdominal pain was the most frequently documented presenting symptom (25 patients, 55.6%). The primary tumour had been resected in 36 patients (80.0%), and 32 (71.1%) received oxaliplatin-based chemotherapy.

Ten patients (22.2%) had MAC and 35 (77.8%) had NMAC. Among NMAC, 24 tumours were moderately differentiated, 4 well differentiated, and 7 were adenocarcinoma without a reported grade or with no grade recorded.

Table 1: Baseline clinicopathological and treatment characteristics of patients with mucinous and non-mucinous colon adenocarcinoma

Characteristic	All (n = 45)	Mucinous (n = 10)	Non-mucinous (n = 35)	p value
Age, years, median (IQR)†	50 (46–61)	48 (34–56)	52 (47–62)	0.435
Age group*				0.434
<50 years	17 (37.8)	5 (50.0)	12 (34.3)	
≥50 years	19 (42.2)	3 (30.0)	16 (45.7)	
Not recorded	9 (20.0)	2 (20.0)	7 (20.0)	
Sex*				0.086
Male	24 (53.3)	3 (30.0)	21 (60.0)	
Female	12 (26.7)	5 (50.0)	7 (20.0)	
Not recorded	9 (20.0)	2 (20.0)	7 (20.0)	
Primary tumour location*				0.434
Right	23 (51.1)	7 (70.0)	16 (45.7)	
Left	14 (31.1)	2 (20.0)	12 (34.3)	
Not recorded	8 (17.8)	1 (10.0)	7 (20.0)	
Presenting symptom				
Abdominal pain	25 (55.6)	5 (50.0)	20 (57.1)	
Abdominal distension	3 (6.7)	1 (10.0)	2 (5.7)	
Bleeding per rectum	1 (2.2)	0 (0.0)	1 (2.9)	
Not recorded	16 (35.6)	4 (40.0)	12 (34.3)	
AJCC stage group				1.000
II	17 (37.8)	4 (40.0)	13 (37.1)	
III	3 (6.7)	1 (10.0)	2 (5.7)	
IV	25 (55.6)	5 (50.0)	20 (57.1)	
Primary tumour resection				
Resection	36 (80.0)	9 (90.0)	27 (77.1)	
No resection	1 (2.2)	0 (0.0)	1 (2.9)	
Not recorded	8 (17.8)	1 (10.0)	7 (20.0)	
Systemic therapy				
Oxaliplatin-based	32 (71.1)	7 (70.0)	25 (71.4)	
Irinotecan-based	2 (4.4)	1 (10.0)	1 (2.9)	
Gemcitabine-based	2 (4.4)	1 (10.0)	1 (2.9)	
Chemotherapy, regimen NOS	2 (4.4)	0 (0.0)	2 (5.7)	
Best supportive care	1 (2.2)	0 (0.0)	1 (2.9)	
Not recorded	6 (13.3)	1 (10.0)	5 (14.3)	
Bevacizumab received				
Yes	2 (4.4)	0 (0.0)	2 (5.7)	
Vital status at last contact				
Alive on follow-up	25 (55.6)	4 (40.0)	21 (60.0)	
Died	17 (37.8)	6 (60.0)	11 (31.4)	
Lost to follow-up	3 (6.7)	0 (0.0)	3 (8.6)	

Values are n (%) of all patients in each column unless stated otherwise; percentages may not sum to 100 because of rounding. p values from Fisher's exact test (2 × 2) or Fisher–Freeman–Halton exact test (stage), excluding missing values; treatment and outcome variables are descriptive and were not tested. *Comparisons based on patients with recorded data. †Age recorded in 36 patients (mucinous 8, non-mucinous 28); Mann–Whitney U test. AJCC, American Joint Committee on Cancer (8th edition).

Clinicopathological comparison: The stage distribution was nearly identical in the two groups (stage IV: 5/10 [50.0%] MAC vs 20/35 [57.1%] NMAC; p = 1.000). Patients with MAC tended to be younger (median 48 [IQR 34–56] vs 52 [47–62] years; p = 0.435), and among those with recorded data were more often women (5/8 [62.5%] vs 7/28 [25.0%]; p = 0.086) and more often had right-sided

tumours (7/9 [77.8%] vs 16/28 [57.1%]; p = 0.434). None of these differences reached statistical significance. Rates of primary tumour resection (90.0% vs 77.1%) and of oxaliplatin-based chemotherapy (70.0% vs 71.4%) were similar. Two patients, both with NMAC, received bevacizumab [Table 1].

Table 2: Kaplan–Meier estimates of overall survival by histological subtype and stage

Group	n	Deaths	Median OS, months (95% CI)	1-yr OS, %	2-yr OS, %	3-yr OS, %	Log-rank p
All patients	44	17	56.1 (30.7–NR)	72.9	67.2	60.8	
Mucinous	10	6	11.7 (0.4–NR)	45.7	45.7	45.7	
Non-mucinous	34	11	NR (30.7–NR)	80.7	73.2	64.5	0.073
Stage IV – mucinous	5	5	6.6 (0.4–37.3)	20.0	20.0	20.0	
Stage IV – non-mucinous	19	10	33.5 (11.0–NR)	71.7	58.6	45.6	0.018
Stage II–III – mucinous	5	1	NR (7.4–NR)	75.0	75.0	75.0	
Stage II–III – non-mucinous	15	1	NR	92.3	92.3	92.3	0.301

One patient was excluded from survival analysis because the recorded date of diagnosis followed the date of last follow-up. Log-rank p values compare mucinous with non-mucinous histology within each row pair. CI, confidence interval; NR, not reached / not estimable; OS, overall survival.

Table 3: Univariable and multivariable Cox proportional hazards analysis of overall survival

Variable	Patients / deaths	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Mucinous vs non-mucinous histology	44 / 17	2.42 (0.89–6.57)	0.083	3.46 (1.25–9.61)	0.017
Stage IV vs stage II–III	44 / 17	7.28 (1.66–31.93)	0.009	8.89 (2.00–39.54)	0.004
Age ≥ 50 vs <50 years	35 / 15	0.78 (0.28–2.19)	0.639	–	–
Male vs female	35 / 15	0.53 (0.19–1.51)	0.237	–	–
Right-sided vs left-sided primary	37 / 11	0.79 (0.23–2.74)	0.710	–	–

Multivariable model includes histological subtype and stage only (44 patients, 17 deaths). Sensitivity analyses: stratified by stage, HR for mucinous histology 3.55 (1.28–9.90), $p = 0.015$; additionally adjusted for age group (35 patients, 15 deaths), HR 3.40 (1.16–9.96), $p = 0.025$; excluding patients without recorded histological description (39 patients, 16 deaths), HR 3.41 (1.20–9.72), $p = 0.022$. Proportional hazards assumption (Schoenfeld residuals): histology $p = 0.40$; stage $p = 0.007$. CI, confidence interval; HR, hazard ratio.

Overall survival: One patient whose recorded date of diagnosis followed the date of last follow-up was excluded from survival analyses, leaving 44 patients (10 MAC, 34 NMAC). The median follow-up was 41.1 months (range 0.4–70). Seventeen patients died (6/10 [60.0%] MAC; 11/34 [32.4%] NMAC) and three were lost to follow-up. For the whole cohort, median OS was 56.1 (30.7–NR) months and 1-, 2- and 3-year OS were 72.9%, 67.2% and 60.8%, respectively (Table 2). Stage IV disease was associated with markedly worse OS than stage II–III disease (median 30.7 months vs not reached; 3-year OS 40.2% vs 88.5%; log-rank $p = 0.002$).

Median OS was 11.7 months (95% CI 0.4–NR) for MAC and was not reached for NMAC. The 1-year OS was 45.7% vs 80.7% and the 3-year OS 45.7% vs 64.5%. The unadjusted difference did not reach statistical significance (log-rank $p = 0.073$; Figure 1A).

Stage-specific survival

In stage IV disease, all five patients with MAC died, compared with 10 of 19 with NMAC. Median OS was 6.6 (0.4–37.3) months for MAC versus 33.5 months (95% CI 11.0–NR) for NMAC, with 1-year OS of 20.0% vs 71.7% (log-rank $p = 0.018$; Figure 1B). Four of the five patients with metastatic MAC died within 12 months of diagnosis despite first-line systemic therapy (oxaliplatin-based in two, irinotecan-based in one and gemcitabine-based in one). In stage II–III disease, only two deaths occurred (one in each group), and 3-year OS was 75.0% for MAC and 92.3% for NMAC (log-rank $p = 0.301$).

Cox regression analysis: On univariable analysis, stage IV disease (HR 7.28 (1.66–31.93); $p = 0.009$) was significantly associated with death, and mucinous histology showed a trend towards worse survival (HR 2.42 (0.89–6.57); $p = 0.083$). Age, sex and tumour side were not associated with OS (Table 3). In the multivariable model, mucinous histology was independently associated with inferior OS (HR 3.46 (1.25–9.61); $p = 0.017$), together with stage IV disease (HR 8.89 (2.00–39.54); $p = 0.004$). The effect of mucinous histology strengthened after adjustment because the two groups had a similar stage distribution, while within each stage stratum MAC fared worse. The proportional hazards assumption held for histology (Schoenfeld $p = 0.40$) but not for stage ($p = 0.007$); in a model stratified by stage, the HR for MAC was 3.55 (1.28–9.90) ($p = 0.015$). Adding age group (35 patients, 15 deaths) did not materially change the estimate (HR 3.40 (1.16–9.96); $p = 0.025$), nor did

excluding the five patients without a recorded histological description (39 patients, 16 deaths; HR 3.41 (1.20–9.72); $p = 0.022$).

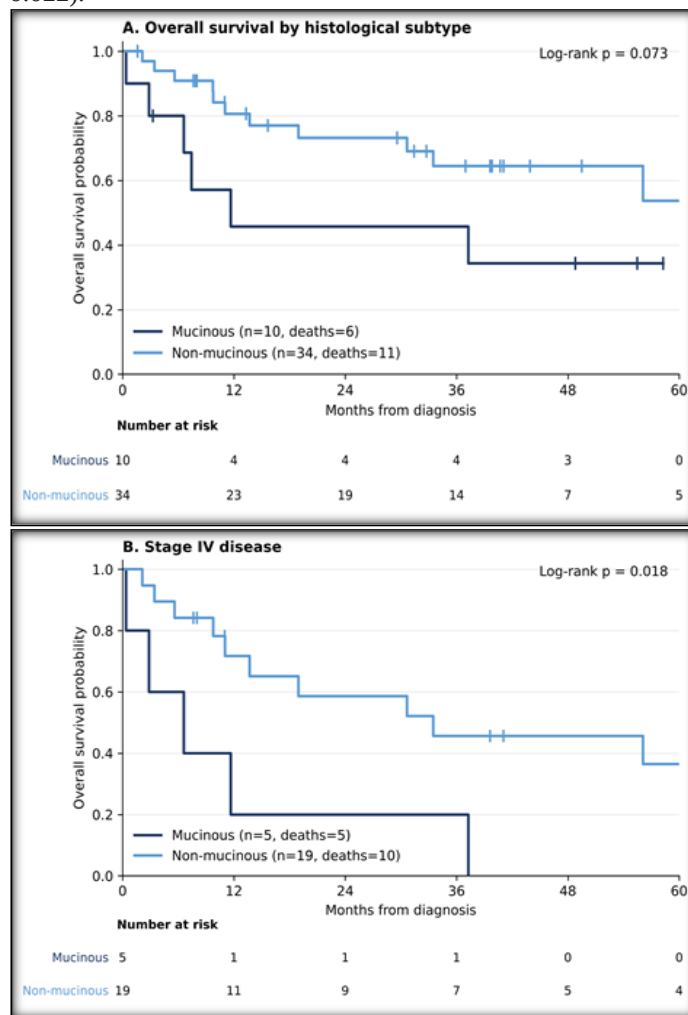


Figure 1: Kaplan–Meier curves of overall survival for mucinous versus non-mucinous colon adenocarcinoma (A) Whole cohort (n = 44). (B) Patients with stage IV disease (n = 24). Vertical ticks indicate censored observations; numbers at risk are shown beneath each panel.

DISCUSSION

In this retrospective cohort from a South Indian tertiary cancer centre, mucinous histology accounted for 22% of colon adenocarcinomas and was associated with a more than three-

fold higher hazard of death after adjustment for stage. The excess risk was concentrated in metastatic disease, where every patient with MAC died and median OS was approximately one-fifth of that observed with NMAC. In contrast, the two groups did not differ in stage at diagnosis and showed only non-significant trends towards female sex, right-sided location and younger age among patients with MAC.

The proportion of MAC in our cohort is higher than the 10–15% usually reported.^[5,6] This may reflect referral patterns to a tertiary oncology centre, the restriction of our cohort to colon (rather than colorectal) primaries — mucinous tumours being more frequent in the proximal colon,^[5,7] and the young age structure of Indian colorectal cancer, since early-onset tumours are enriched for mucinous and signet-ring differentiation.^[3,16] Almost half of our patients were younger than 50 years, a striking contrast to Western series and consistent with previous Indian reports.^[3] The clinicopathological trends we observed — younger age, female predominance and right-sided location among MAC — are concordant in direction with the larger literature.^[5–7] although our sample was too small to confirm them statistically.

Our survival findings are consistent with the bulk of contemporary evidence in metastatic disease. In 255 patients treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy, Catalano and colleagues reported a response rate of 18% for MAC vs 49% for NMAC and median OS of 14.0 vs 23.4 months, with mucinous histology remaining independently prognostic.^[12] Similar results were reported by Negri et al. for fluorouracil-based therapy,^[11] and by Mekenkamp et al. in a pooled analysis of the CAIRO and CAIRO2 trials.^[13] The recent pooled HR of 1.89 for stage IV disease,^[9] is smaller than our estimate, which is unsurprising given the wide confidence interval around our figures and the likely higher prevalence of poor-prognosis features (such as peritoneal disease and BRAF mutation) in a small referral cohort.

Several biological mechanisms may explain the poorer outcome of metastatic MAC. Mucinous tumours have a strong propensity for peritoneal dissemination, which is associated with poor survival and limited chemotherapy penetration.^[10] The abundant extracellular mucin may act as a physical barrier to drug delivery, and mucinous tumours are enriched for BRAF V600E mutations and for the CpG island methylator phenotype, both linked to chemoresistance and adverse outcome in microsatellite-stable disease.^[5,6] In earlier-stage disease, by contrast, the frequent co-existence of MSI-high status may offset the adverse effect of mucinous histology, which may explain the attenuated or absent prognostic effect reported in stage II–III cohorts.^[7,14,15] and the small, non-significant difference seen in our stage II–III subgroup. Our observation that tumour side was not prognostic should be interpreted in light of the small number of left-sided tumours and the known interaction between sidedness, stage and molecular subtype.^[20]

These data have practical implications for Indian practice. Mucinous histology is routinely reported and costs nothing

to ascertain, yet it is often overlooked when counselling patients and planning treatment. Our findings suggest that patients with metastatic MAC represent a particularly high-risk group in whom early comprehensive molecular profiling (mismatch repair/MSI, RAS and BRAF), dedicated assessment for peritoneal disease, and consideration of intensified or alternative strategies — including anti-angiogenic therapy, immunotherapy for MSI-high tumours, and early referral for clinical trials — deserve evaluation. Prospective multicentre Indian registries capturing histological subtype alongside molecular data would help determine whether these patients benefit from tailored approaches.

Strengths and limitations: To our knowledge, this is one of the few reports from India to compare mucinous and non-mucinous colon adenocarcinoma with survival outcomes. Strengths include the restriction to colon primaries, follow-up exceeding three years, and analytical choices designed to avoid overfitting, including a parsimonious multivariable model and stage-stratified sensitivity analysis.

The limitations are important. First, the sample was small, with only 10 patients with MAC and 17 deaths; estimates are therefore imprecise, the confidence intervals are wide, and the multivariable model could adjust for stage only. The large stage-adjusted HR in particular should be regarded as an upper-range estimate requiring confirmation. Second, the retrospective design led to missing data for age, sex and tumour location in approximately one-fifth of patients, and performance status, carcinoembryonic antigen, sites and number of metastases (including peritoneal involvement), and lines of therapy were not consistently available. Third, MSI/mismatch-repair, RAS and BRAF status were not available, so we could not determine whether the effect of mucinous histology is independent of these molecular features. Fourth, histology was taken from routine pathology reports without central review, and signet-ring cell components were not recorded separately. Fifth, cause of death and progression-free survival could not be assessed. Finally, as a single-centre study from a referral institution, the findings may not be generalisable to all Indian patients with colon cancer.

CONCLUSION

Mucinous adenocarcinoma constituted more than one in five colon cancers in this South Indian tertiary-centre cohort. Although its stage distribution was similar to that of conventional adenocarcinoma, mucinous histology was associated with significantly poorer stage-adjusted overall survival, with the most pronounced effect in metastatic disease. Histological subtype should be considered in prognostic assessment, and larger multicentre Indian studies incorporating molecular profiling are warranted to confirm these findings and to define optimal treatment strategies for this subgroup.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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