

Mdm2 in Colon Carcinoma: an immunohistochemical and fluorescence in situ hybridization study



Monirath Hav¹, Louis Libbrecht¹, Piet Pattyn², Marc Peeters³, Marleen Praet¹, and Patrick Pauwels¹
Department of Pathology¹, Department of Abdominal Surgery², Department of Gastroenterology³,
Ghent University Hospital, Belgium



BACKGROUND

New pharmacological agents targeting mdm2-p53 axis are available. By blocking p53 degradation mediated by mdm2, wild-type p53 could restore its function and induce tumour cell apoptosis, especially when these cells express high p53 levels as a result of chemo and/or radiation therapy. These molecules could be effective in the subset of patients whose mdm2 protein levels are particularly high. Published studies on mdm2 status show rather conflicting results. In this colon carcinoma study, we checked mdm2 status by immunohistochemistry (IHC) and Fluorescence In Situ Hybridization (FISH). FISH is less susceptible to interobserver variation. We correlated mdm2 gene amplification status with mdm2 protein expression.

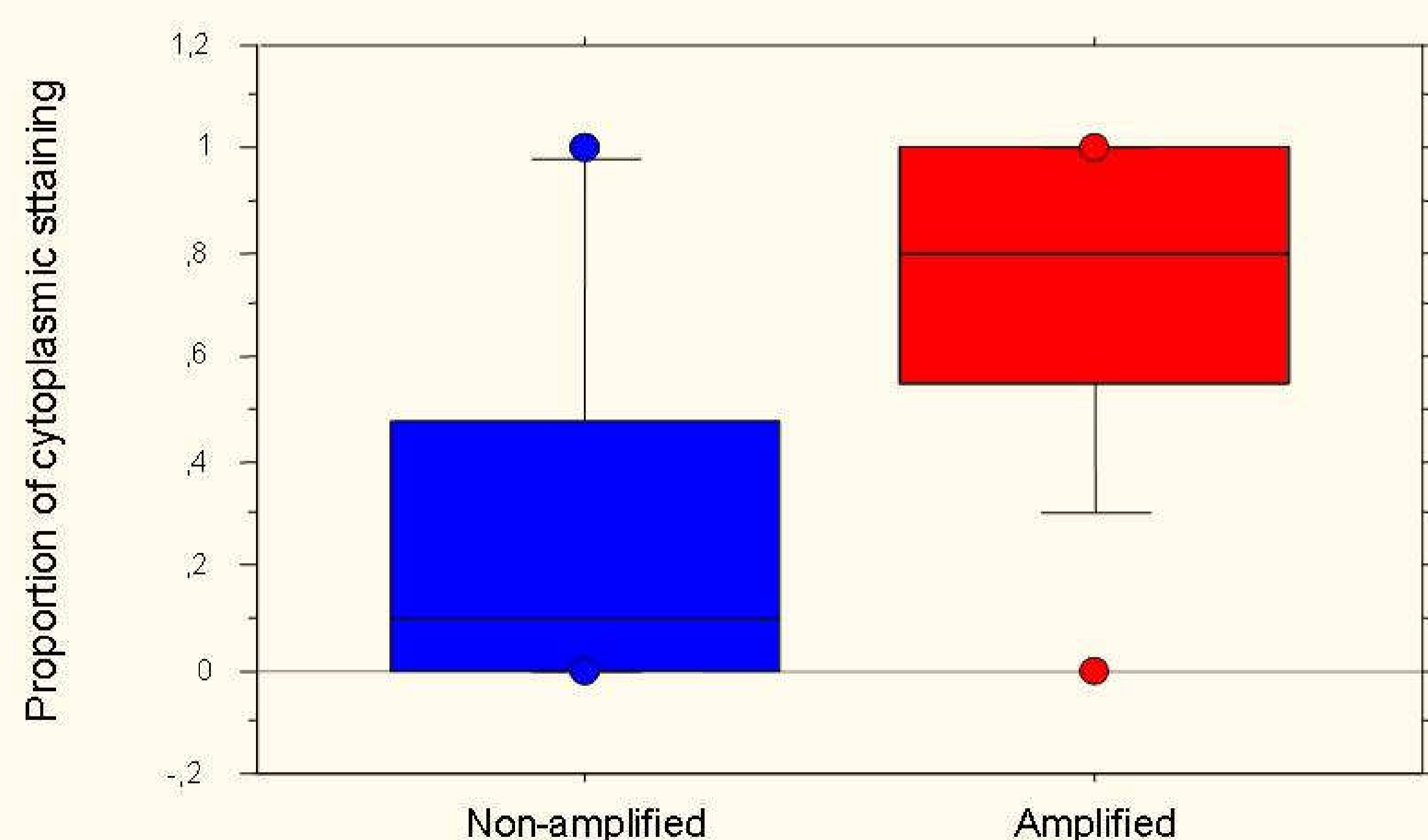
METHODS

We examined 38 cases of invasive colon carcinoma. Mdm2 IHC and FISH were performed on paraffin-embedded sections. FISH was performed by using mdm2 gene probes and CEP12 probes. Mdm2 protein expression was recorded based on staining pattern (cytoplasmic or nuclear), staining intensity (weak, moderate, or strong), and proportion of tumour cells stained. We then correlated mdm2 protein expressions with the FISH result.

RESULTS

Of the 38 cases, 11 (29%) showed mdm2 amplification. Mdm2 nuclear positivity was seen in 12 cases (32%). In most cases, nuclear staining was low. There was no correlation between mdm2 gene amplification and mdm2 nuclear positivity.

Cytoplasmic expression was present in 28 cases (74%) and was seen more frequently in amplified cases (10 cases, 91%) than in non-amplified cases (18 cases, 67%). Interestingly, we observed a significant correlation between mdm2 cytoplasmic staining and mdm2 gene amplification ($p = 0.0029$).

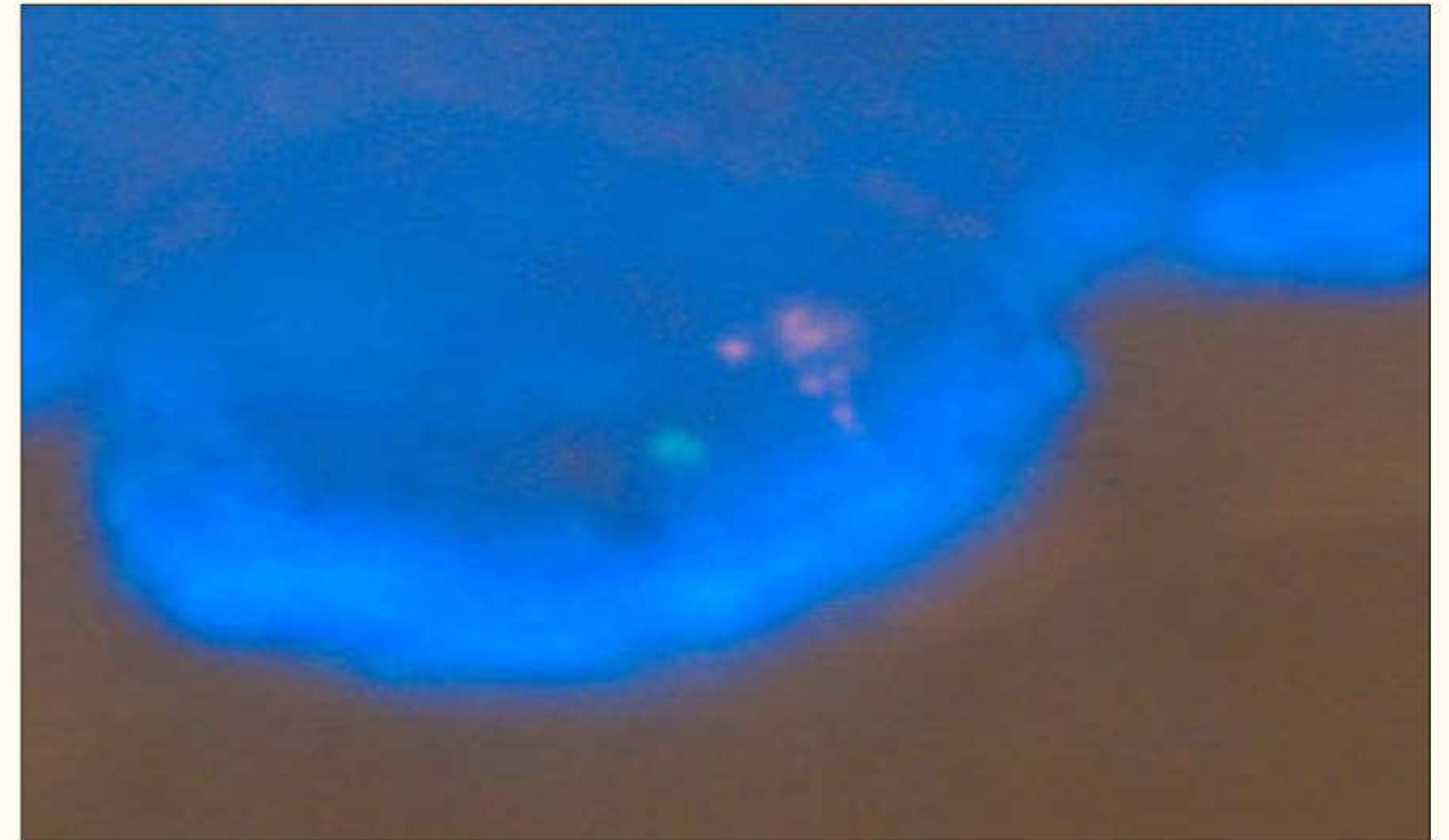


Correlation between mdm2 gene amplification and mdm2 cytoplasmic staining

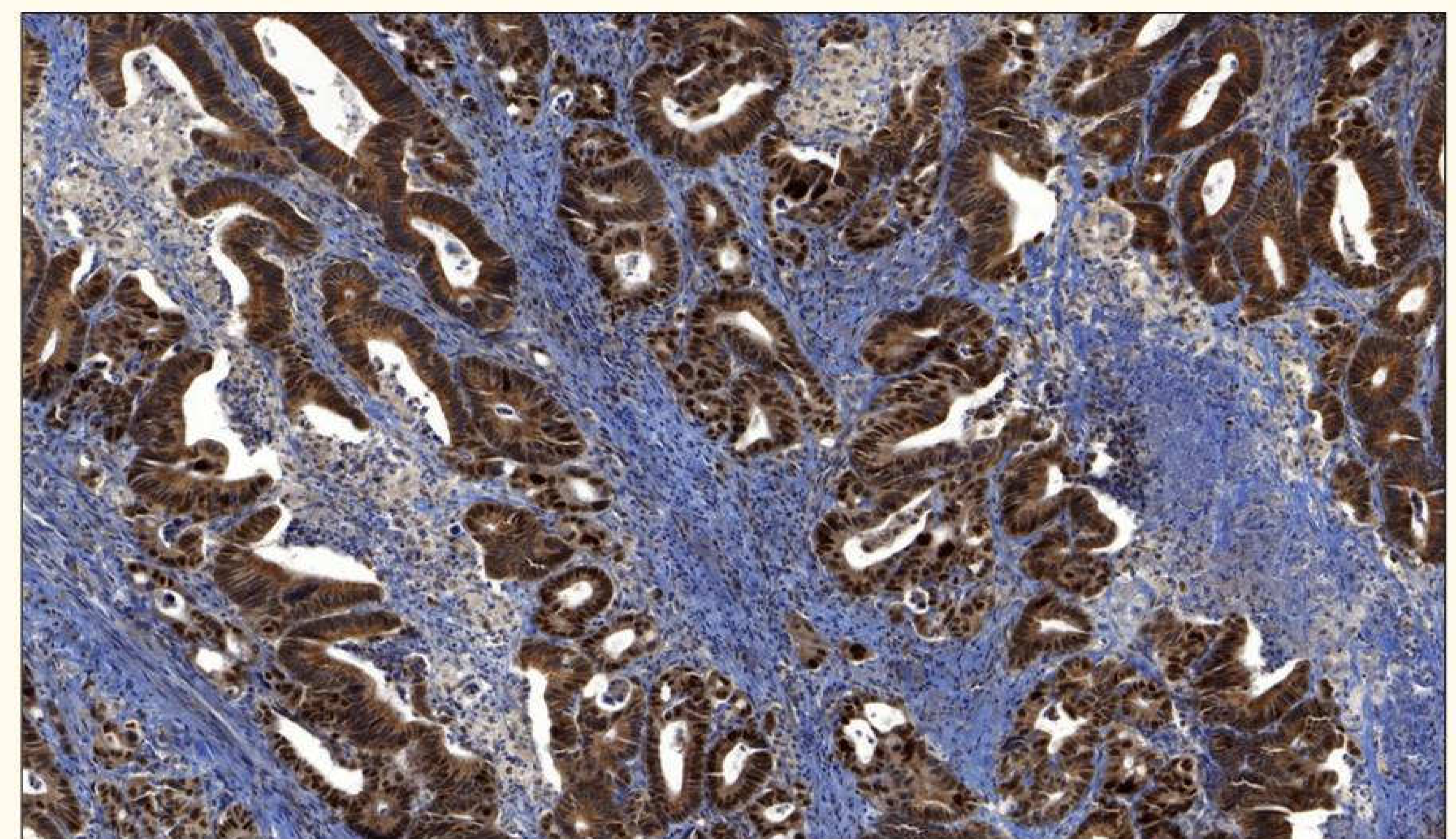
CONCLUSIONS

Contrary to published results, we showed the presence of mdm2 amplification in 29% of cases of colon carcinoma. We also observed a significant positive correlation between mdm2 gene amplification and cytoplasmic staining, regardless of the staining intensity.

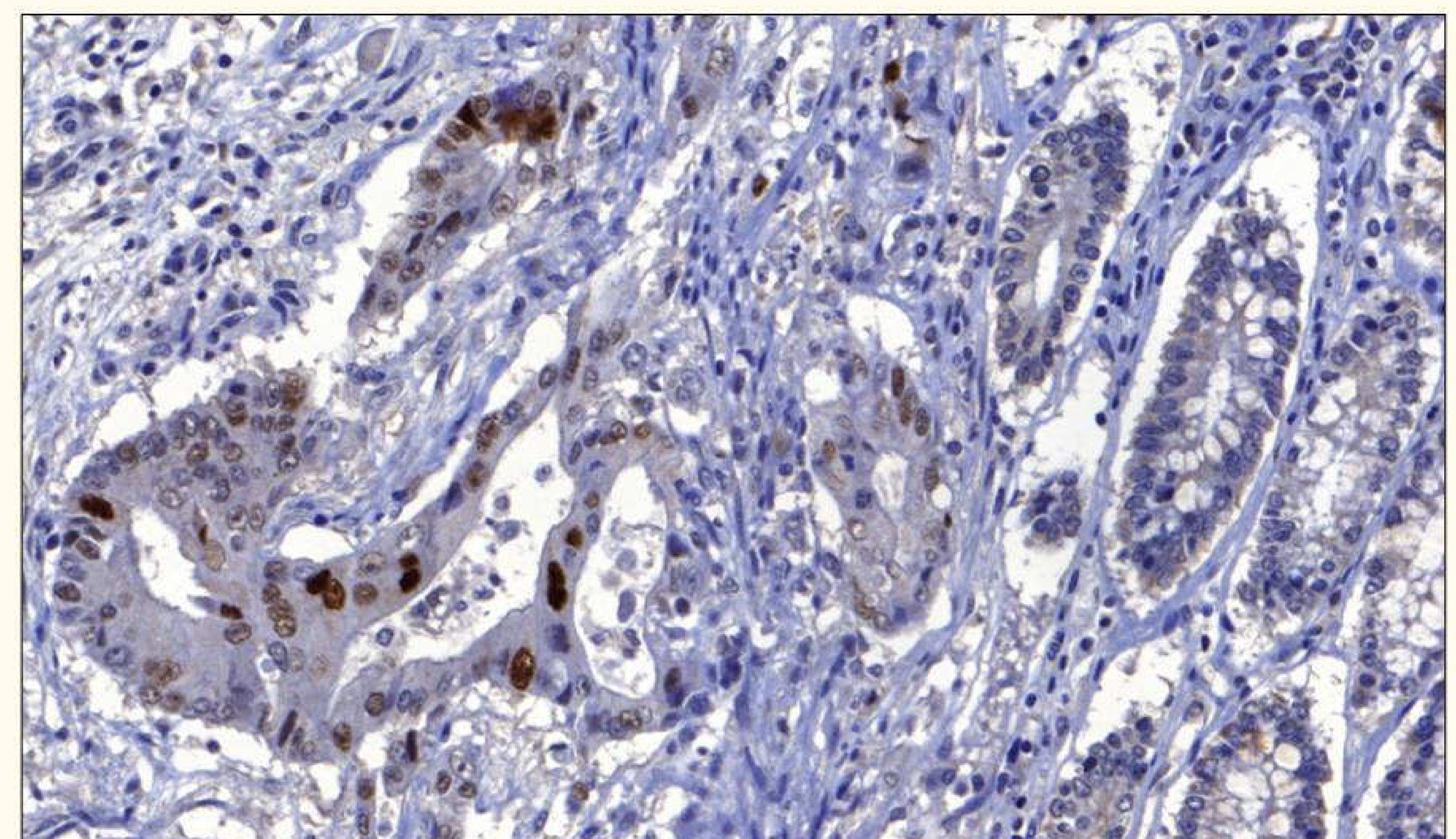
Mdm2 amplification and different staining patterns



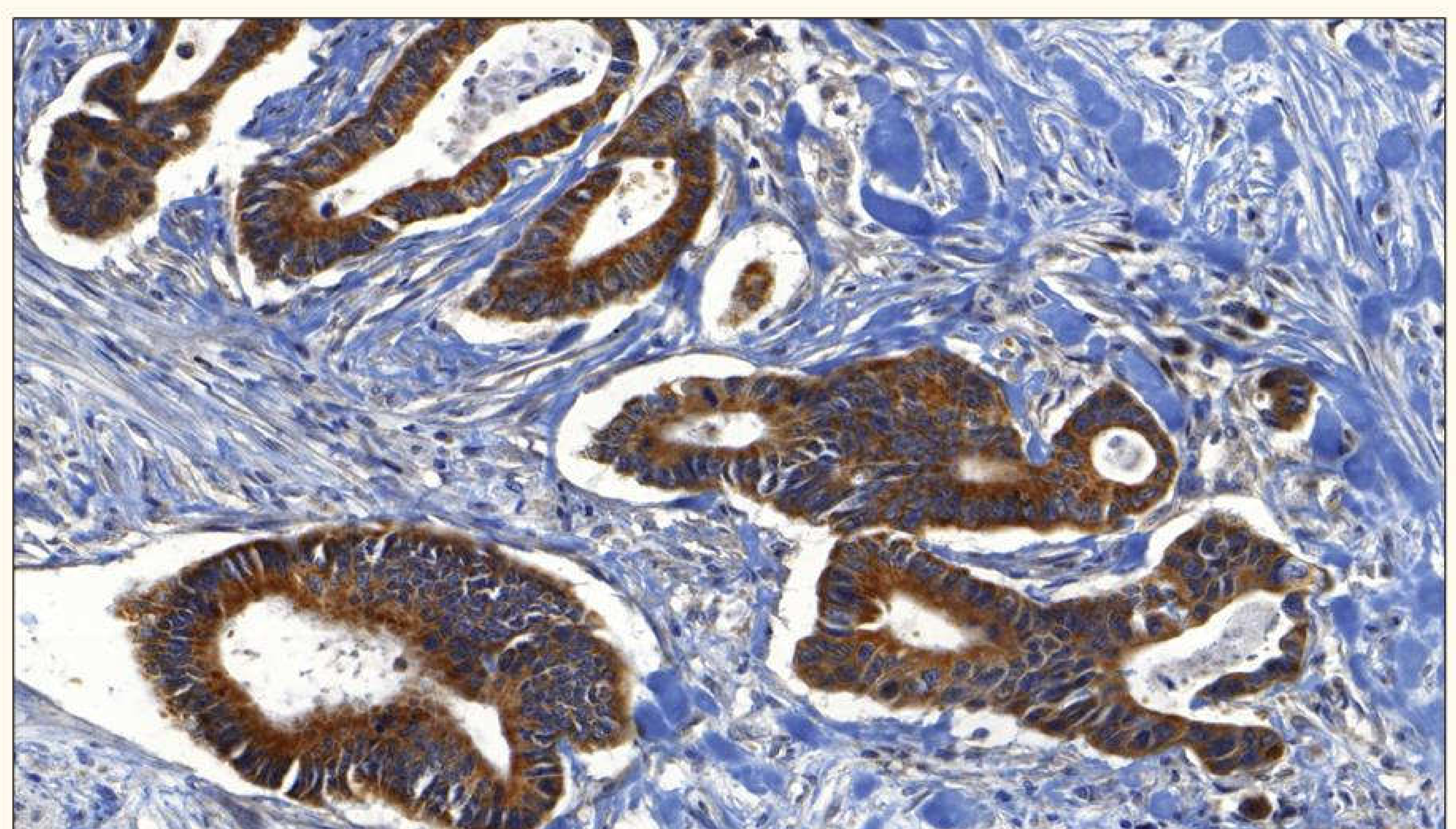
A case showing mdm2 gene amplification



Strong nuclear and cytoplasmic staining



Nuclear expression without cytoplasmic staining (with negative control of normal colonic glandular epithelium in the right field)



Cytoplasmic expression without nuclear staining