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# MUCINOUS COMPONENT IN COLORECTAL CARCINOMA – INFLUENCE ON SURVIVAL

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**SUMMARY**

AIM. Clinical significance of mucin component in colorectal cancer is still unclear. We compared clinical and pathological features of mucinous and non-mucinous colorectal cancers and assessed the impact of mucinous differentiation and other specific features of colorectal cancer on survival. PATIENTS AND METHODS. We analyzed clinical and pathological data of 271 patients who underwent surgical resection of colorectal adenocarcinoma at our Department between 1994 and 2002. RESULTS. Patients with mucinous colorectal cancer had worse overall survival, but not statistically significant ($P$=0.296). In a multivariate model, only tumor size, the presence of hepatic metastases, and the presence of metastases in lymph nodes, but not mucinous differentiation, were found to be significant and independent predictors of survival. CONCLUSION. The results of this study confirm the frequent observation that mucinous colorectal cancer is associated with worse prognosis compared to non-mucinous type. However, these results do not provide evidence that mucinous differentiation is independently associated with more aggressive tumor behavior. Current findings justify surgical resection of all gross tumor deposits, together with the employment of perioperative intraperitoneal chemotherapy in the treatment of patients with mucinous colorectal cancer.

KEYWORDS: *adenocarcinoma, mucinous; colorectal neoplasms; survival analysis; colonic neoplasms/*pathology/surgery; rectal neoplasms/*pathology/surgery*

**MUCINOZNA KOMPONENTA U KOLOREKTALNOM KARCINOMU – UTJECAJ NA PREŽIVLJENJE**

**SAŽETAK**

CILJ. Klinička važnost mucinozne komponente u kolorektalnom karcinomu još nije jasan. Usporedili smo kliničke i patološke osobine kolorektalnog karcinoma mucinoznog i nemucinoznog tipa te mjerili utjecaj diferencijacije mucina i drugih specifičnih značajka kolorektalnog karcinoma na preživljenje. BOLESNICI I METODE. Analizirali smo kliničke i patološke podatke 271 bolesnika u kojih je na našem odjelu od 1994. do 2002. kirurškim putem uklonjen kolorektalni adenokarcinom. REZULTATI. Bolesnici s mucinoznim kolorektalnim karcinomom imaju lošije sveukupno preživljenje, ali to nije statistički značajno ($P$=0,296). Na multivarijatnom modelu uočeno je da su samo veličina tumora, prisutnost jetrenih metastaza i prisutnost metastaza u limfnim čvorovima, a ne i mucinozna diferencijacija, značajni i nezavisni prognostički faktori preživljenja. ZAKLJUČAK. Rezultati ovog ispitivanja potvrđuju ono što se često uočava, a to je da je prognoza za mucinozni kolorektalni karcinom lošija od prognoze za nemucinozni tip raka toga sijela. Međutim, tj. rezultati ne dokazuju da je mucinozna diferencijacija nezavisno povezana s agresivnijim ponašanjem tumora. Sadašnji nalazi opravdavaju kiruršku resekciju svih okom vidljivih tumorskih depozita uz primjenu perioperativne intraperitonejske kemoterapije u liječenju bolesnika s mucinoznim kolorektalnim karcinomom.

KLJUČNE RIJEČI: *adenokarcinom, mucinozni; kolorektalne neoplazme; analiza preživljenja; neoplazme kolona/*patologija/kirurgija; neoplazme rektuma/*patologija/kirurgija*

## INTRODUCTION

Colorectal cancer is the third most common cancer in the world, with over 600,000 new cases every year (1).

Mucinous adenocarcinoma represents a particular subtype of colorectal cancer with distinct features (2). This type of colorectal cancer accounts for approximately 5%-20% of all colorectal cancers (1, 3). It is characterized by accumulation of extracellular mucin that by definition comprises more than 50% of the tumor mass (4, 5). Mucinous colorectal cancer usually occurs more frequently in the right colon (5), in younger patients and presents in more advanced stage (3, 5). It is therefore considered to have worse prognosis compared to non-mucinous cancer (3, 5, 6).

However, some reports question the prognostic significance of mucinous differentiation of colorectal cancer, reporting on no significant difference in survival between mucinous and non-mucinous colorectal cancers when compared by stage or in multivariate analyses (2, 7-9). Furthermore, highly mucinous (or colloid) carcinomas of some organs (e.g. breast, pancreas) are found by some authors to have better prognosis than other types of cancers of respective organs (10, 11). Interestingly, MUC2 gene, which is highly expressed in mucinous colorectal cancer, is a tumor suppressor gene (12).

Therefore, the clinical significance of mucin component in colorectal cancer is still unclear (3), and there is ongoing controversy about its prognostic value.

In this study, we compared clinical and pathological features of mucinous and non-mucinous colorectal cancers and performed multivariate analysis to assess the impact of mucinous differentiation and other specific features of colorectal cancer on survival.

## PATIENTS AND METHODS

In this study, we analyzed clinical and pathological data of 271 patients with histological diagnosis of colorectal adenocarcinoma. All patients underwent surgical resection at our Department between 1994 and 2002.

Preoperative assessment included colonoscopy with biopsy for histological verification of adenocarcinoma as well as abdominal ultrasound for detection of hepatic metastases. In cases of emergency surgery, intraoperative inspection and palpation of the liver was accompanied by postoperative liver ultrasound.

For all patients, age and gender were obtained from admission records. Operating surgeon's report included information about tumor location and macroscopic signs of hepatic and peritoneal metastases. Pathology report included information about tumor size (diameter), local infiltration according to the 6$^{th}$ revision of TNM classification for colorectal cancer, number of positive lymph nodes, and the degree of tumor differentiation (well, moderate and poor).

By definition, tumors were considered to be mucinous if more than 50% of their volume was made of extracellular mucus (5, 13). Survival was analyzed using the data from the National Cancer Registry and hospital records.

In one patient with two metachronous tumors the location could not have been unequivocally determined.

Data analysis was performed using the Mann-Whitney U test and Fisher exact test as appropriate. Survival rates were calculated using the Kaplan-Meier method and compared using the Mantel-Cox test. Variables that were independently and significantly associated with survival were determined using the Cox proportional hazard regression method. Values of $p<0.05$ were considered statistically significant.

## RESULTS

Patients with mucinous and non-mucinous colorectal adenocarcinoma did not differ significantly in either age or proportion of genders (Table 1). Mucinous carcinomas were located significantly more often proximal to splenic flexure (Fisher exact test, $P$=0.018) and significantly less often in the rectum (Fisher exact test, $P$=0.026). Furthermore, mucinous carcinomas were significantly larger at the time of surgery (Mann-Whitney U test, $P$=0.023). However, there were no statistically significant differences in the proportions of patients with positive lymph nodes, hepatic metastases or peritoneal carcinosis (Fisher exact test, $P$>0.05) (Table 1).

In an univariate model, variables significantly associated with survival were tumor size ($P$=0.0001), the presence of hepatic metastases

*Table 1.*

*CLINICAL AND PATHOLOGICAL FEATURES OF NON-MUCINOUS AND MUCINOUS COLORECTAL ADENOCARCINOMAS.*

| | Non-mucinous colorectal adenocarcinoma | | Mucinous colorectal adenocarcinoma | | *P* value |
|---|---|---|---|---|---|
| Patients | 237 | | 34 | | |
| Age (years) | 67 | (44-91) | 66 | (40-83) | 0.329 |
| Gender | | | | | |
| Female | 96 | 40.51% | 11 | 32.35% | 0.454 |
| Male | 141 | 59.49% | 23 | 67.65% | |
| Location | | | | | |
| Right | 53 | 22.36% | 14 | 41.18% | 0.031 |
| Left | 87 | 36.71% | 13 | 38.24% | 0.851 |
| Rectum | 96 | 40.51% | 7 | 20.59% | 0.036 |
| Unknown | 1 | | | | |
| Tumor diameter (cm) | 4.5 | (0.5-20) | 6.0 | (2-10) | 0.023 |
| Peritoneal metastases | | | | | |
| Yes | 11 | 4.64% | 4 | 11.76% | 0.103 |
| No | 226 | 95.36% | 30 | 88.24% | |
| Hepatic metastases | | | | | |
| Yes | 31 | 13.08% | 5 | 14.71% | 0.788 |
| No | 206 | 86.92% | 29 | 85.29% | |
| Lymph node metastases | | | | | |
| Yes | 103 | 43.46% | 14 | 41.18% | 0.855 |
| No | 134 | 56.54% | 20 | 58.82% | |
| Local infiltration | | | | | |
| T1 | 8 | 3.38% | 1 | 2.94% | 0.704 |
| T2 | 41 | 17.30% | 9 | 26.47% | 0.235 |
| T3 | 167 | 70.46% | 18 | 52.94% | 0.049 |
| T4 | 21 | 8.86% | 6 | 17.65% | 0.125 |
| Differentiation | | | | | |
| Well | 128 | 54.01% | 21 | 61.76% | 0.462 |
| Moderate | 93 | 39.24% | 13 | 38.24% | 0.911 |
| Poor | 16 | 6.75% | 0 | 0.00% | 0.234 |

Values are presented as median values with range given in parentheses.

*Table 2.*

*RESULTS OF UNIVARIATE REGRESSION ANALYSIS OF FACTORS INFLUENCING SURVIVAL.*

| | Beta | Wald | *P* value |
|---|---|---|---|
| Tumor size | 0.189 | 22.851 | 0.000 |
| Liver metastases | 1.336 | 28.807 | 0.000 |
| Gender | -0.157 | 0.415 | 0.519 |
| Age | 0.021 | 2.346 | 0.126 |
| Rectal vs. colon cancer | 0.124 | 0.275 | 0.600 |
| Right vs. left colon | -0.321 | 0.962 | 0.327 |
| Peritoneal metastases | -1.434 | 19.467 | 0.000 |
| Mucinous type | 0.090 | 0.321 | 0.571 |
| Grade | -0.062 | 0.081 | 0.776 |
| T stage | 0.714 | 13.615 | 0.000 |
| Nodal metastases | 0.901 | 12.823 | 0.000 |

Beta = regression coefficient, *P*=level of significance

*Table 3.*

*RESULTS OF COX MULTIPLE REGRESSION OF VARIABLES THAT INDEPENDENTLY INFLUENCE SURVIVAL OF PATIENTS WITH COLORECTAL CANCER.*

| | Beta | Wald | *P* value |
|---|---|---|---|
| Tumor size | 0.134 | 11.974 | 0.001 |
| Liver metastases | 0.978 | 8.559 | 0.003 |
| Peritoneal metastases | -0.762 | 2.230 | 0.135 |
| T stage | 0.268 | 1.661 | 0.198 |
| Nodal metastases | 0.559 | 3.656 | 0.056 |

$X^2 = 38.9413$ ; $\gamma = 5$ ; $P < 0.00001$

(*P*=0.0001), peritoneal carcinosis (*P*=0.0001), depth of local invasion (*P*=0.0001) and the number of positive lymph nodes (*P*=0.0001) (Table 2).

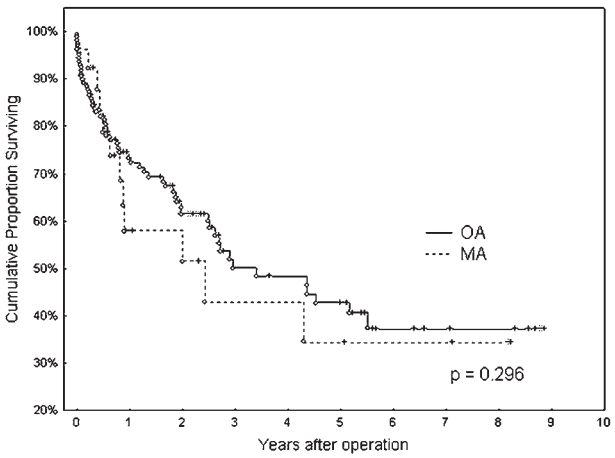


*Figure 1. Cummulative survival rates for patients with non-mucinous colorectal adenocarcinoma (OA) and those with mucinous colorectal adenocarcinoma (MA).*

In a multivariate model, only tumor size, the presence of hepatic metastases, and marginally the presence of metastases in lymph nodes were found to be significant and independent predictors of survival (Table 3).

Generally, patients with mucinous colorectal cancer had worse overall survival. However, no significant difference in survival was observed between patients with mucinous adenocarcinoma as compared to those with non-mucinous (ordinary) adenocarcinoma (Mantel-Cox test, $P$=0.296) as shown in Figure 1.

## DISCUSSION

Mucinous colorectal cancer may represent a distinct type of colorectal malignancy. This type of colorectal cancer is generally thought to proliferate and metastasize more rapidly than ordinary, non-mucinous cancers, and these clinicopathological features result in lower curability and increased rate of recurrence; due to these characteristics, mucinous colorectal cancers are thought to have worse prognosis (14-16). However, other reports claim no significant difference in prognosis between mucinous and non-mucinous colorectal cancer (9), especially when compared by stage (17) or in multivariate analysis (8, 18).

In our study, we found worse overall 5-year survival of patients with mucinous colorectal cancer compared to those with non-mucinous cancer, but this difference was not statistically significant.

Distribution of mucinous colorectal cancer within the colorectum in our study showed tendency for proximal colon. Most mucinous cancers were located in the right colon, followed by the left colon and rectum. Non-mucinous cancers were most frequently located in the rectum, followed by the left colon and the right colon (Table 1). Patients with mucinous colorectal cancer were also younger than patients with non-mucinous cancer, with no significant difference according to the gender. This is in accordance with findings of other authors, who also found that mucinous colorectal cancer occurred more frequently in younger patients (19) and in the proximal colon (2).

Mucinous colorectal cancer is also found to be more frequently associated with peritoneal dissemination (20), distant metastases (21) and increased stage at diagnosis (3). In our study, we found that mucinous cancers had significantly greater diameter at the time of diagnosis compared to non-mucinous cancers. The frequency of lymph node metastases and hepatic metastases was similar in both groups, but peritoneal carcinosis was more than twice more common in patients with mucinous cancer. Frequency of T1 and T2 stages was similar in both groups. Patients with non-mucinous cancer had significantly greater frequency of T3 stage compared to patients with mucinous cancer. However, frequency of T4 stage in patients with mucinous cancer was two times greater than in patients with non-mucinous cancer. The production of mucus under pressure may allow tumor to more frequently gain access to the peritoneal cavity (20). It can only be hypothesized that mucinous cancer, once it penetrates the bowel wall, is more likely to spread through the serosa to adjacent organs (resulting in T4 stage or peritoneal carcinosis) compared to non-mucinous cancer; this hypothesis, however, needs further investigation.

In univariate analysis, we found that tumor size, presence of liver metastases, peritoneal carcinosis, T stage and presence of nodal metastases were statistically significant predictors of survival. In multivariate model, only tumor size, presence of liver metastases and nodal involvement independently influenced survival.

Mucinous differentiation was not significantly associated with survival in neither univariate nor multivariate model. Similar results were also reported by Sasaki et al. (18) in an analysis of 316 mucinous and 413 non-mucinous carcinomas; they found that mucinous differentiation was not

independently associated with survival in multivariate analysis (18). Purdie et al. also found that mucinous differentiation of colorectal cancer has no prognostic significance (9), and Berg and Godwin reached the same conclusion (17).

Lack of clear evidence for the worse prognosis of mucinous colorectal cancer may also be, at least in part, due to technical differences in published studies.

One of the difficulties in determining the clinical significance of mucinous component in colorectal cancer may also be the problem of defining uniform criteria for defining mucinous cancer (1). Histologically, it is characterized by lakes of mucin where tumor cells are floating unattached to the stroma (10). While some authors define mucinous cancer as one composed of acini secreting lakes of mucus deep within the infiltrating portion of the tumor (3, 14), others use criteria based on the minimum percentage of mucinous component, that ranges from 50% to 75% (1, 5, 22). Clearly, further research is required to determine uniform criteria for mucinous adenocarcinoma of the colon and rectum (10).

Another issue is the inclusion criteria for analysis. Some authors included only well and moderately differentiated non-mucinous colorectal adenocarcinomas, and excluded poorly differentiated non-mucinous adenocarcinomas from survival analysis because of its proven worse prognosis (3). Other authors included cancers with well, moderate and poor differentiation (23). On the other hand, some authors analyzed mucinous adenocarcinoma together with signet-cell carcinomas, that are today recognized as two distinct subtypes of colorectal cancer (14).

Another reason for the worse survival of patients with mucinous colorectal cancer, although not statistically significant, may be the fact that the majority of mucinous cancers are located in the proximal colon. It takes more time for tumors of the proximal colon to develop symptoms, so that could be the reason for revealing the diagnosis in more advanced stage of tumor growth comparing to the tumors of the distal colon, and so worse overall survival.

Finally, it should be noted that mucinous colorectal cancer may not represent one uniform subgroup of colorectal malignancy.

Excessive accumulation of mucin within the stroma is shown to be due to the reversed polarity of cells, leading to secretion of mucus into the stroma (12). This pattern of mucin secretion is named colloid or "pure mucinous" (10). These colloid cancers are thought to have better prognosis because mucin in the stroma may act as a barrier to the tumor spread (10). However, the presence of even a small component of ordinary carcinoma means that cell have acquired properties that allow them to overcome mucin barrier and independently invade stroma, thus resulting in more aggressive behavior (10). Kazama et al. found that mucinous colorectal cancers with chromosomal instability (CSI) represent a subgroup of mucinous colorectal cancers that have worse prognosis (24).

The results of this study confirm the frequent observation that mucinous colorectal cancer is associated with worse prognosis compared to non-mucinous type. However, these results do not provide evidence that mucinous differentiation is independently associated with more aggressive tumor behavior. Further studies of the significance of the percentage of mucin (10), different molecular changes (4, 13, 24, 25) and the biomechanical role of mucin component (10) may provide more information.

Current findings, as well as the results of other studies (20, 26, 27), justify surgical resection of all gross tumor deposits, together with the employment of perioperative intraperitoneal chemotherapy in the treatment of patients with mucinous colorectal cancer.

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REFERENCES

1. Du W, Mah JT, Lee J, Sankila R, Sankaranarayanan R, Chia KS. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. Dis Colon Rectum 2004; 47:78-85.
2. Consorti F, Lorenzotti A, Midiri G, Di Paola M. Prognostic significance of mucinous carcinoma of colon and rectum: a prospective case-control study. J Surg Oncol. 2000;73:70-4.
3. Nozoe T, Anai H, Nasu S, Sugimachi K. Clinicopathological characteristics of mucinous carcinoma of the colon and rectum. J Surg Oncol. 2000; 75:103-7.
4. Byrd JC, Bresalier RS. Mucins and mucin binding proteins in colorectal cancer. Cancer Metastasis Rev 2004;23:77-99.

5. Papadopoulos VN, Michalopoulos A, Netta S, Basdanis G, Paramythiotis D, Zatagias A, Berovalis P, Harlaftis N. Prognostic significance of mucinous component in colorectal carcinoma. Tech Coloproctol 2004; 8:123-5.
6. Green JB, Timmcke AE, Mitchell WT, Hicks TC, Gathright JB, Jr., Ray JE. Mucinous carcinoma--just another colon cancer? Dis Colon Rectum. 1993;36:49-54.
7. Okuno M, Ikehara T, Nagayama M, Kato Y, Yui S, Umeyama K. Mucinous colorectal carcinoma: clinical pathology and prognosis. Am Surg. 1988;54:681-5.
8. Halvorsen TB, Seim E. Influence of mucinous components on survival in colorectal adenocarcinomas: a multivariate analysis. J Clin Pathol. 1988;41:1068-72.
9. Purdie CA, Piris J. Histopathological grade, mucinous differentiation and DNA ploidy in relation to prognosis in colorectal carcinoma. Histopathology. 2000;36: 121-6.
10. Adsay NV, Klimstra DS. Not all "mucinous carcinomas" are equal: time to redefine and reinvestigate the biologic significance of mucin types and patterns in the GI tract. Virchows Arch 2005;447:111-2.
11. Solcia E, Luinetti O, Tava F, Klersy C, Grillo F, Pandolfo N, Fiocca R. Identification of a lower grade muconodular subtype of gastric mucinous cancer. Virchows Arch. 2004;445:572-9.
12. Adsay NV, Merati K, Nassar H, Shia J, Sarkar F, Pierson CR, Cheng JD, Visscher DW, Hruban RH, Klimstra DS. Pathogenesis of colloid (pure mucinous) carcinoma of exocrine organs: Coupling of gel-forming mucin (MUC2) production with altered cell polarity and abnormal cell-stroma interaction may be the key factor in the morphogenesis and indolent behavior of colloid carcinoma in the breast and pancreas. Am J Surg Pathol 2003;27:571-8.
13. Kakar S, Aksoy S, Burgart LJ, Smyrk TC. Mucinous carcinoma of the colon: correlation of loss of mismatch repair enzymes with clinicopathologic features and survival. Mod Pathol 2004;17:696-700.
14. Symonds DA, Vickery AL. Mucinous carcinoma of the colon and rectum. Cancer. 1976;37:1891-900.
15. Umpleby HC, Ranson DL, Williamson RC. Peculiarities of mucinous colorectal carcinoma. Br J Surg. 1985; 72:715-8.
16. Pihl E, Nairn RC, Hughes ES, Cuthbertson AM, Rollo AJ. Mucinous colorectal carcinoma: immunopathology and prognosis. Pathology. 1980;12:439-47.
17. Berg JW, Godwin JD, 2nd. The epidemiologic pathology of carcinomas of the large bowel. J Surg Oncol. 1974;6:381-400.
18. Sasaki O, Atkin WS, Jass JR. Mucinous carcinoma of the rectum. Histopathology. 1987;11:259-72.
19. Kanemitsu Y, Kato T, Hirai T, Yasui K, Morimoto T, Shimizu Y, Kodera Y, Yamamura Y. Survival after curative resection for mucinous adenocarcinoma of the colorectum. Dis Colon Rectum 2003;46:160-7.
20. Sugarbaker PH. Mucinous colorectal carcinoma. J Surg Oncol. 2001;77:282-3.
21. Doci R, Bignami P, Montalto F, Gennari L. Prognostic factors for survival and disease-free survival in hepatic metastases from colorectal cancer treated by resection. Tumori. 1995;81:143-6.
22. Connelly JH, Robey-Cafferty SS, Cleary KR. Mucinous carcinomas of the colon and rectum. An analysis of 62 stage B and C lesions. Arch Pathol Lab Med. 1991; 115:1022-5.
23. Glasgow SC, Yu J, Carvalho LP, Shannon WD, Fleshman JW, McLeod HL. Unfavourable expression of pharmacologic markers in mucinous colorectal cancer. Br J Cancer. 2005;92:259-64-
24. Kazama Y, Watanabe T, Kanazawa T, Kazama S, Tada T, Tanaka J, Nagawa H. Mucinous colorectal cancers with chromosomal instability: a biologically distinct and aggressive subtype. Diagn Mol Pathol. 2006;15: 30-4.
25. Kazama Y, Watanabe T, Kanazawa T, Tada T, Tanaka J, Nagawa H. Mucinous carcinomas of the colon and rectum show higher rates of microsatellite instability and lower rates of chromosomal instability: a study matched for T classification and tumor location. Cancer. 2005;103:2023-9.
26. Sugarbaker PH. Managing the peritoneal surface component of gastrointestinal cancer. Part 1. Patterns of dissemination and treatment options. Oncology (Williston Park). 2004;18:51-9.
27. Sugarbaker PH. Managing the peritoneal surface component of gastrointestinal cancer. Part 2. Perioperative intraperitoneal chemotherapy. Oncology (Williston Park). 2004;18:207-19.

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