Annals of Oncology 23: 135–141, 2012
doi:10.1093/annonc/mdr062
Published online 29 April 2011

Prognosis of mucinous histology for patients with radically resected stage II and III colon cancer

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Received 2 October 2010; revised 5 February 2011; accepted 9 February 2011

Background: Previous studies investigating the prognostic role of mucinous histology of colorectal cancer produced conflicting results. This retrospective analysis was carried out in order to explore whether mucinous adenocarcinoma (MC) is associated with a comparatively worse prognosis than that of nonmucinous adenocarcinoma (NMC) for patients undergoing curative resection for stage II and III colon cancer.

Patients and methods: This study involved 1025 unselected patients who underwent curative surgery for sporadic colon cancer and follow-up procedures at six different oncology departments.

Results: MCs accounted for 17.4% (n = 178) of tumours. Patients with MC had 5- and 8-year overall survival rates of 78.6% and 68.8%, respectively, compared with 72.3% and 63.8%, respectively, for patients with nonmucinous tumours. Multivariate analysis using the Cox proportional hazards model showed that the clinically significant prognostic factors were stage of disease and adjuvant chemotherapy. No statistically significant interaction between mucinous histology and adjuvant chemotherapy was found.

Conclusions: For patients with stage II and III colon cancer who underwent curative surgery, mucinous histology has no significant correlation with prognosis compared with NMC. This retrospective analysis suggests a comparable benefit from adjuvant chemotherapy for MC compared with NMC.

Key words: adjuvant chemotherapy, colon cancer, mucinous adenocarcinoma, prognosis

introduction

Mucinous adenocarcinoma (MC) is a subset of histological subtypes of colorectal adenocarcinoma, accounting for 10%–20% of all colorectal cases [1–5]. This type of tumour contains cancer cells that produce a large amount of extracellular mucin with a ≥50% mucinous component of tumour volume that is required for the designation of MC [6]. Many retrospective analyses have shown an association between mucinous colorectal cancer and younger patients [7], the proximal colon as frequent primary site [1], and more advanced stage of disease [1, 8, 9]. Conversely, the prognostic significance of mucinous histology for colorectal cancer is still controversial. Many retrospective studies report a worse prognosis for patients with MC of the colorectum compared with nonmucinous adenocarcinoma (NMC) [1, 4, 8, 10, 11]. However, both the American Joint Committee on Cancer and the College of American Pathologists consider the mucinous subtype has not been proven as being a statistically significant prognostic factor independent of histological grade [12, 13]. The mucinous histology is to be differentiated from signet-ring cell carcinoma, which is constituted by single tumour cells with intracytoplasmic mucin displacing their nuclei aside with ≥50% of such component. Unlike MC, the signet-ring cell type of adenocarcinoma has been consistently found to have a stage-independent adverse effect on prognosis [12, 13]. Previous studies have often focused on patients with carcinoma of the colon and rectum and analysed the prognosis of the mucinous subtype in different stages of disease (e.g. from stage I to IV). Recently, in a retrospective study on patients with advanced colorectal cancer, our group found a high statistically significant poor survival rate and less responsiveness to first-line chemotherapy for patients with mucinous tumours compared with nonmucinous tumours [14]. All the patients included in the study were given treatments including irinotecan and/or oxaliplatin in addition to fluoropyrimidines. Similar results were also reported in a case-controlled study carried out by the Royal Marsden Hospital group [15]

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in which patients received only fluoropyrimidine-based chemotherapy.

No large-scale report of patients with MC who underwent curative surgery has been previously published. Generally, the conclusions for radically resected cancers are extrapolated from more general studies covering all stages of disease. Furthermore, different retrospective studies have linked the adverse outcome of MC to tumours arising in the rectosigmoid tract, and not in the remaining regions of the bowel [1, 4, 8, 16].

The overall survival (OS) benefit of adjuvant chemotherapy in stage III colon cancer has been well established [17–19]. Conversely, the value of adjuvant chemotherapy for patients with stage II colon cancer is still controversial [20], and a major issue in this regard is the definition of those subgroups of patients who will most likely benefit from adjuvant chemotherapy. As recommended by the American Society of Clinical Oncology, adjuvant chemotherapy for stage II colon cancer should be reserved for patients with high-risk tumours, e.g. T4 lesions, inadequate lymphadenectomy, poorly differentiated tumours, bowel obstruction or perforation, lymphovascular or perineural invasion [21].

To date, mucinous histology is not taken into account in the treatment choice of adjuvant chemotherapy for patients with early colon cancer and is not considered in the planning of adjuvant chemotherapy trials. There is no information on its possible clinical impact in early-stage colon cancer. Moving from this background, we tried to explore the prognostic role, if any, of MC patients with radically resected stage II and III colon cancer, paying attention to the role of adjuvant chemotherapy in addition to other well-known clinicopathological features.

patients and methods

The population consisted of 1025 consecutive unselected patients who underwent curative resection for stage II (T3 or T4,N0,M0) and III (any T,N1 or N2,M0) colon cancer at six oncology departments from September 1998 to 2006. All patients were diagnosed as having primary colon cancer after thorough work-up, including endoscopic examination. Clinicopathological and follow-up data for these patients were recorded in an electronic file in coded format.

Patient age, gender, tumour location, histology, lymphovascular or perineural invasion, depth of invasion, stage at presentation according to the TNM (tumour–node–metastasis) system [22], curative resection as well as adjuvant chemotherapy were recorded for each patient. The group did not include any patients who had undergone neoadjuvant treatments. Patients were excluded if they had had previous malignancy within 5 years (except for basal cell skin cancer or *in situ* carcinoma of the cervix) and were from families with familial adenomatous polyposis or hereditary nonpolyposis colorectal with a highly penetrant genetic predisposition to colorectal cancer. Patients with synchronous primary malignancies were also excluded.

The pathologists from the six referral hospitals were asked to review tumour specimens and assess the tumour type. In order to avoid evaluator variability in the patients, all the pathologists were not aware of the clinical results. In accordance with the classification of tumours by the World Health Organization (WHO) [6], a ≥50% mucinous component was required for the designation of mucinous colorectal carcinoma. After excluding tumours with signet-ring cells, the other tumours were classified as not otherwise specified adenocarcinoma. Grading was established according to the differentiation by predominant area [23].

Curative resection was defined as complete one-step removal of all gross tumours with negative surgical margins on microscopic examination. Distant metastases at the time of resection were excluded by preoperative abdomen ultrasonography or computed tomography (CT) scan, chest X-ray or CT scan, and intraoperative exploration. Proximal colon was defined as the large bowel proximal to the hepatic flexure, while distal colon was defined as the large bowel distal to the hepatic flexure.

Patients received adjuvant chemotherapy in accordance with local policy. Locoregional recurrence was defined as the growth of the tumour in and around the tumour bed, including the pericolic fat, the adjoining mesentery, and regional lymph nodes, or in the suture or staple line of the bowel anastomosis.

statistical analysis

The chi-squared test or Fisher's exact test was used to compare results between the groups that were given as percentages. The primary outcome was OS, defined as the interval between the date of surgical treatment and either the date of death or the censoring date for follow-up (31 December 2008), whichever was earlier. Death from any cause was regarded as an event and the subjects who were still alive at the end of follow-up were censored. Survival curves were generated according to the Kaplan–Meier method and survival distributions were compared with the use of the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for multivariate analyses were computed using the Cox proportional hazards regression models. All tests of significance were two tailed; differences at P values of <0.05 were considered to be significant. Ethical approval for the study was obtained from the local human ethics committee.

results

The clinicopathologic features among patients with MC and NMC are shown in Table 1. MC accounted for 17.3% of patients. MC was found in 104 males (58.4%), whereas NMC was found in 455 males (53.7%) ($P = 0.287$). The median age of patients was 68 years for both MC (range 28–87) and NMC (range 29–85) ($P = 0.986$). MC was present in 3.0% of patients <40 years of age compared with 1.9% of NMC patients ($P = 0.330$). MC patients were more likely to have right-sided colon cancer than NMC (54.5% and 33.8%, respectively; $P < 0.0001$) and had more frequently T4 than NMC tumours (11.8% and 6.4%, respectively; $P = 0.026$). Conversely, more patients (23.5%) with NMC had vascular, lymphatic, or perineural invasion compared with patients (15.2%) with MC ($P = 0.020$). Stage II and III tumours were found in 46.4% and 53.6% of patients with NMC and 54.5% and 45.5% with MC, respectively ($P = 0.043$). The distribution among MC and NMC for adjuvant chemotherapy was not significantly different (Table 1). Adjuvant chemotherapy consisted of different regimens for 12, 8 or 6 cycles repeated every 2, 3 or 4 weeks, respectively. Median duration of adjuvant chemotherapy was 24 weeks both for patients with NMC (range 2–24 weeks) and MC (range 3–24 weeks). The planned 6 months of chemotherapy was received by 70.4% and 74.2% of patients in the MC and NMC groups, respectively ($P = 0.950$). In the NMC group, 123 (23.1%) patients discontinued adjuvant chemotherapy due to toxicity, 10 (1.8%) patients due to relapse, and 5 (0.9%) refused to continue treatment. In the MC group, 26 (24.8%) patients discontinued treatment due to

Table 1. Patient characteristics

Characteristic	Nonmucinous (n = 847), n (%)	Mucinous (n = 178), n (%)	P value	Overall (N = 1025)
Sex				
Male	455 (53.7)	104 (58.4)	0.287	559
Female	392 (46.3)	74 (41.6)		466
Median age (range), years	68 (29–85)	68 (28–87)	0.986	68 (28–87)
Patients ≤40 years old	16 (1.9)	6 (3.4)	0.339	22
Stage of disease				
II	393 (46.4)	98 (54.5)	0.043	491
III	454 (53.6)	80 (45.5)		534
Depth of invasion (pT)				
1	9 (1.1)	1 (0.6)	0.026	10
2	52 (6.1)	5 (2.8)		59
3	732 (86.4)	151 (84.8)		882
4	54 (6.4)	21 (11.8)		74
Grading[a]				
Well differentiated	647 (76.4)	122 (68.5)	0.229	769
Poorly differentiated	172 (20.3)	42 (23.6)		214
Invasion[b]				
Present	199 (23.5)	27 (15.2)	0.020	226
Absent	648 (76.5)	151 (84.8)		799
Primary tumour site				
Right sided	286 (33.8)	97 (54.5)	<0.0001	383
Left sided	559 (66.0)	80 (45.0)		639
Multiple	2 (0.2)	1 (0.5)		3
Adjuvant chemotherapy				
None	324 (38.3)	73 (41.0)	0.788	397
Fluoropyrimidine based	382 (45.1)	77 (43.3)		459
Oxaliplatin based	141 (16.6)	28 (15.7)		169

[a]Missing data for grading (28 patients with nonmucinous and 14 patients with mucinous histology).
[b]Invasion refers to lymphovascular or perineural invasion.

toxicity, 3 (2.9%) patients due to disease relapse, and 2 (1.9%) patients refused to continue treatment.

The median period of follow-up was 78 months for the MC group (range 2–134 months) and 77 months for the NMC group (range 2–140 months). Overall, there were 229 deaths (27.0%) in the NMC group and 39 deaths (21.9%) in the MC group. The vast majority of deaths were a result of relapse or recurrence (202 of 229 deaths for NMC patients and 35 of 39 deaths for MC patients). At the time of analysis, 268 patients in the NMC group (31.6%) had relapsed, as compared with 50 (28.0%) in the MC group. More patients with MC of colon cancer had local relapse (40.0% versus 22.0% of patients with NMC; $P = 0.012$), while liver metastasis was more frequent for patients with NMC (54.5% versus 32.0% for patients with MC; $P = 0.005$). No significant difference of the incidence of peritoneal metastasis was observed between MC and NMC patients (16.0% and 11.9%, respectively; $P = 0.574$).

Subsequent chemotherapy at relapse was given to 222 (82.8%) NMC patients compared with 37 (74.0%) MC patients ($P = 0.201$). Use of oxaliplatin, irinotecan, and biologic agents (bevacizumab) was balanced among the two groups. Surgical treatment (resection of local relapse or metastasectomy) was carried out in 35 (13.1%) and 12 (24.0%) patients, respectively ($P = 0.074$). Eleven (4.1%) NMC patients and 1 (2.0%) patient did not receive any treatment after the first recurrence. Among patients receiving chemotherapy at relapse, median OS was 19.2 months for NMC patients and 15.9 months for MC patients. Despite the difference of 3.3 months, this was not statistically significant ($P = 0.108$).

The Kaplan–Meier survival curve for MC and NMC is shown in Figure 1. The overall 5- and 8-year survival rates for MC were 78.6% (95% CI 71.3–85.7) and 68.8% (95% CI 59.3–78.3), respectively, not significantly different from those for NMC, with 72.3% (95% CI 60.4–64.4) and 63.8% (95 CI 59.4–68.2), respectively ($P = 0.206$). When considering stage II tumours (Figure 2A), the overall 5- and 8-year survival rates for MC were 85.7% (95% CI 77.5–93.8) and 83.4% (95% CI 74.4–92.6) compared with 81.8% (95% CI 77.4–86.2) and 75.3% (95 CI 69.6–81.0) for NMC, respectively ($P = 0.147$). For patients with stage III disease (Figure 2B), the overall 5- and 8-year survival rates for MC were 68.9% (95% CI 55.9–81.5) and 46.3% (95% CI 28.5–64.1) compared with 64.0% (95% CI 58.7–69.3) and 53.6% (95 CI 47.2–60.0), respectively, for NMC ($P = 0.732$).

Differences in survival between patients treated with adjuvant chemotherapy and the group of patients receiving resection alone were found in the overall group ($N = 1025$) and in stage III colon cancer but not in patients with stage II colon cancer (Figure 3A–C). In the overall group (Figure 3A), 5- and 8-year OS rates for the adjuvant chemotherapy group and for the control group were 76.9%, 68.1%, 68.1%, and 59.7%, respectively (HR = 0.74; 95% CI 0.58–0.94; $P = 0.014$). Similarly, patients with stage III colon cancer (Figure 3B) had a survival benefit when they were treated with adjuvant chemotherapy (5- and 8-year OS of 70.4% and 59.0%, respectively) compared with the surgery-alone group (5- and 8-year OS of 50.6% and 38.6%, respectively) ($P < 0.0001$). However, for patients with stage II colon cancer (Figure 3C), the differences between patients receiving adjuvant chemotherapy and those receiving follow-up alone were not of statistical significance (5- and 8-year OS, 87.2% and 78.5% versus 81.7% and 72.9%, respectively; $P = 0.112$).

To adjust the curves taking into account any other factors that might have influenced the OS of MC patients and NMC patients, we used the Cox proportional hazards model in a forward stepwise manner. Covariates were mucinous histology, age, gender, stage at diagnosis, invasion and adjuvant chemotherapy. The multivariate analysis confirmed no prognostic significance for the mucinous histology (Table 2). Stage at diagnosis and adjuvant chemotherapy were the most significant factors affecting survival (Table 2).

Cox model for survival analysis allows to include some interaction terms; by this way, we could evaluate any statistical interactions among different variables, such as histology (MC versus NMC) and adjuvant chemotherapy (yes versus none). Each regression coefficient (referring to interaction terms) was estimated according to maximum likelihood method and then statistically tested against the hypothesis to be equal to 0.

The Cox model excluded any significant interaction between these two variables (HR = 0.76; 95% CI 0.38–1.53; $P = 0.456$).

discussion

Many clinicopathological features of MC are well recognised, e.g. young age at onset, advanced stage at presentation, higher lymph node involvement, peritoneal spread and lower curative resectability [9, 11, 24–28]. However, the prognostic value of mucinous histology in colorectal cancer is still a point of discussion. Many studies have pointed to the adverse prognostic role of the mucinous histology of colorectal cancer, but at the same time other studies found the opposite. In the present analysis, we did not observe any negative prognostic role for patients with radically resected stage II and III mucinous colon cancer compared with NMC. The large and homogeneous sample size gives strength to the present report, especially when compared with many previous studies that included patients with radically resected and metastatic disease, colon and rectal cancer.

In contrast with the present findings, in two previous retrospective series, patients with advanced colorectal cancer of

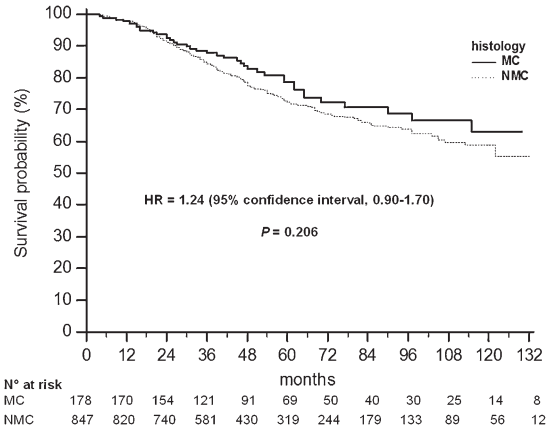

Figure 1. Cumulative overall survival of patients with MC and NMC. MC, mucinous adenocarcinoma; NMC, nonmucinous adenocarcinoma.

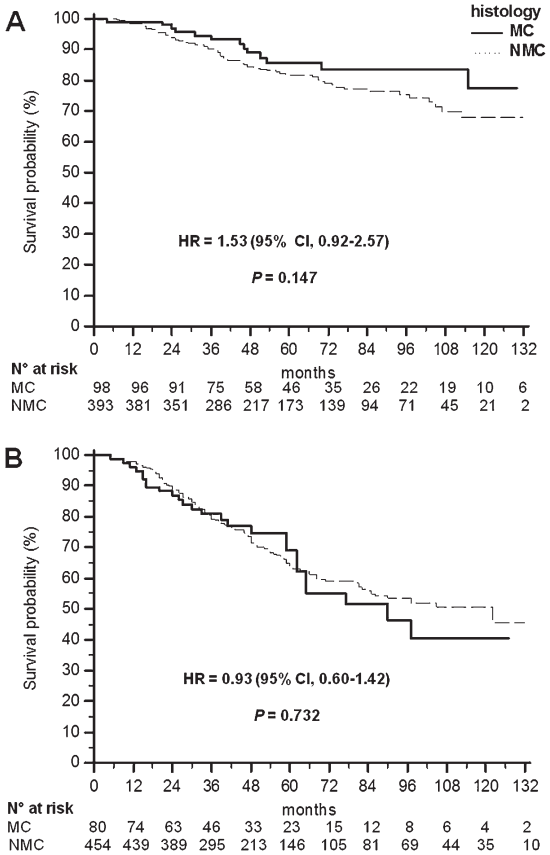

Figure 2. Cumulative survival of patients with MC and NMC, according to stage II (A) and stage III (B) colon cancer. MC, mucinous adenocarcinoma; NMC, nonmucinous adenocarcinoma.

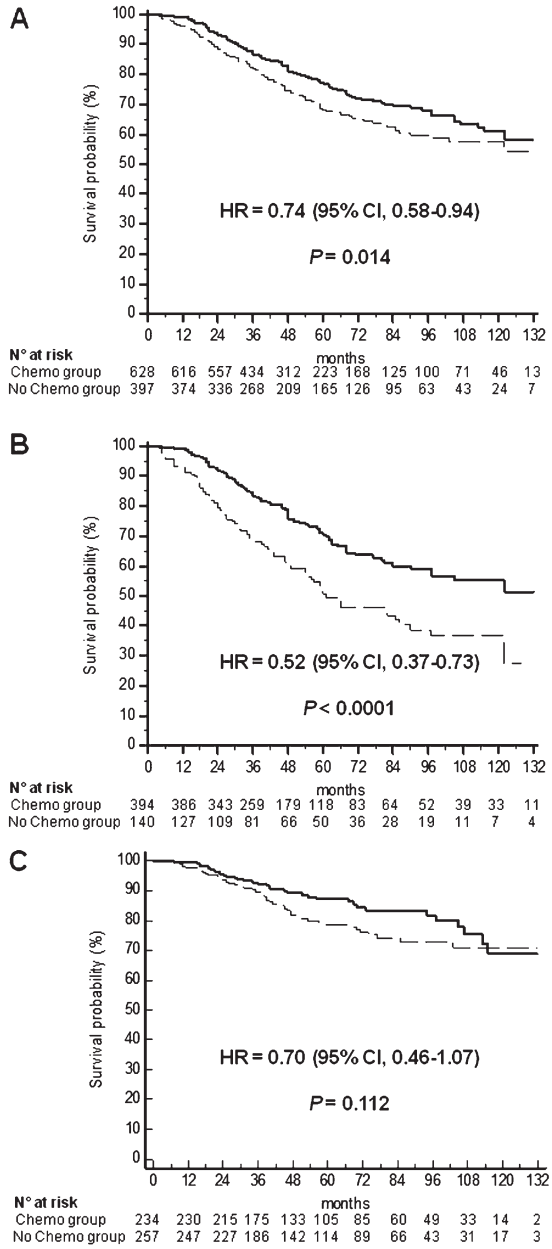

Figure 3. Cumulative survival of colon cancer patients receiving (–) or not (……) adjuvant chemotherapy, overall group (A), stage III (B), and stage II (C).

mucinous histology treated with first-line chemotherapy showed worse prognosis than patients with nonmucinous subtype [14, 15]. We revised our study population [14] finding the presence of about two-third of patients with metastatic disease at diagnosis and therefore differing from the present population composed by patients who had radically resected disease and who underwent chemotherapy for relapse during follow-up. Also, in the present study, we observed fewer patients with peritoneal metastasis and a higher frequency of patients with local relapse than previously reported [14, 15]. All these characteristics suggest the existence of subtypes of mucinous colorectal carcinoma, with patients presenting with advanced stage at diagnosis likely expressing a more aggressive disease, with less sensitivity to chemotherapy. All these aspects may supply, at least in part, a possible explanation for different results in previous reports.

Other possible explanations for the conflicting findings on prognosis of MC could be the inclusion of rectal tumours in many previous analyses and the lack of data on the role of adjuvant therapy for radically resected cancer patients. In the present study, we focused on patients with colon cancer only with data on adjuvant chemotherapy being collected carefully. As expected, >50% of patients with MC had right-sided primary tumours. This tendency is well recognised in unselected colorectal cancer showing more frequently microsatellite instability in proximal location [29–31] and in hereditary nonpolyposis colorectal cancer especially when mucinous right-sided colon cancers have poor differentiation and prominent tumour-infiltrating lymphocytes [23]. However, it has been suggested that prognosis for patients with MC has a different biology also for MC according to the site as mucinous rectal cancer patients have more often been associated with poor prognosis than those from colonic site [1, 4, 8, 16]. Rectal cancer shows higher recurrence rates than colon cancer [32]. This is largely due to the more extensive lymphatic drainage in the pelvic than in the abdominal colon [33]. Therefore, the greater propensity of MC to have nodal metastases, to be diagnosed at an advanced stage, and the low resectability of tumours could be greater in the rectum than in the colon, thus leading to a worse prognosis of mucinous rectal carcinomas. These features may explain why the prognosis for patients with MC occurring in the rectum faired worse compared with patients with NMC [16].

Other aspects accounting for the different and conflicting results on the prognostic significance of the mucinous pattern in colorectal cancer may be the different geographical distribution and molecular biology of this subset of tumour. MCs are generally considered to account for 10%–15% of all colorectal cancers [34], ranging from 4%–5% in studies from Asiatic countries [16, 28] to 12%–14% in studies from Sweden, Taiwan, and Argentina [5, 9, 35] and reaching up to 30% in studies from Greece and Italy [31, 36]. The coexistence of two main subtypes of MC has been postulated on the basis of genetic pathways, clinicopathological features, and behaviour [31, 37, 38]. Thus, the different distribution of these two mucinous subtypes worldwide may account for the controversial prognostic significance of mucinous histology.

A limitation to the interpretation of the published results may include the existence of diagnostic heterogeneity in the definition of the mucinous colorectal cancer [10, 11, 24, 25]. Some degree of mucin production is characteristic of all colorectal carcinoma. In the present study, we have followed the same standard definition of mucinous histology as that produced by the WHO [6]. Only those tumours showing a mucinous component in at least 50% of tumour volume were to be considered as mucinous. Patients whose tumours showed a focally mucinous component or should it in <50% of tumour volume were not considered mucinous carcinomas.

The retrospective nature of the studies could be a confounding factor that may explain the conflicting results. Notably, the primary end point of the present analysis was OS. The choice of this end point can avoid all possible misleading conclusions that are linked to other end points, such as disease-free survival for which the assessment of progression is crucial. Furthermore, in the present study, the follow-up was sufficiently long and complete to support the conclusion.

Carrying out a multivariate analysis is a more reliable method for better selecting those factors with independent prognostic relevance. In the present study, the multivariate analysis showed the independent prognostic role for stage of disease (stage II versus III) and for adjuvant chemotherapy and excluded any significant role for the mucinous histology. In the past, only three studies provided a multivariate analysis when considering MC. Two studies [9, 25] failed to show any independent prognostic factor for the mucinous histology. However, the relatively low sample size in each stage grouping may have prevented the identification of any statistically significant differences. In the retrospective study by Wu et al. [9], only 53 patients fulfilled the criteria for MC. Moreover, Halvorsen and Seim [25] identified 165 tumours containing some mucinous component of 534 resected colorectal adenocarcinomas. However, of 165 MCs, 11 were signet-ring cell carcinomas and only 56 tumours contained predominating

Table 2. Multivariate survival analysis using Cox's model

Variable	Deaths/cases	Hazard ratio	95% Confidence interval	*P*
Age, years				
≤68	139/539	1.01	0.99–1.02	0.0868
>68	129/486	1		
Gender				
Male	146/560	0.96	0.76–1.22	0.7842
Female	122/465	1		
Histology				
Mucinous	39/178	0.89	0.59–1.69	0.5324
Nonmucinous	229/847	1		
Stage				
II	87/490	2.61	1.87–3.56	<0.0001
III	181/535	1		
Invasion[a]				
Present	66/228	1.08	0.81–1.44	0.5809
No	202/797	1		
Adjuvant				
Yes	144/628	2.73	1.71–3.78	0.0002
No	124/397	1		

[a]Invasion refers to lymphovascular or perineural invasion.

areas of mucinous histology. This is in contrast with the worldwide-accepted definition of MC [6]. In the third study by Kanemitsu et al. [28] carrying out a multivariate analysis, mucinous histology was shown as an independent predictor of decreased survival. However, the authors compared MC with an NMC group of well or moderately well-differentiated tumours, whereas tumours with poorly differentiated carcinomas were excluded from the analysis. A single widely accepted and employed standard for grading is lacking and subjectivity and imprecision in grading may be related in some degree to tumour heterogeneity. However, given its proven prognostic value, it is possible that by excluding poorly differentiated NMC a significant difference could be seen in favour of well or moderately NMC compared with MC. This concept has led our group to consider all patients with NMC of any grading. Moreover, another point of discussion of the study reported by Kanemitsu et al. [28] is that among patients receiving a radical resection of the tumour, only a percentage of them (nearly one-third of all patients) received adjuvant chemotherapy. The value of adjuvant chemotherapy for patients who undergo successful surgery for stage III colon cancer has been clearly demonstrated [17–19]. The optimal adjuvant treatment of stage II colon cancer remains controversial, while adjuvant chemotherapy for high-risk stage II disease is highly recommended [17, 20, 21]. Previously, reports investigating the prognostic role of MC rarely addressed the influence of adjuvant chemotherapy. In our analysis, we have not omitted to address this point as clearly it may influence the prognosis for patients with stage II and III colon cancer. Though considering the retrospective and non-randomised nature of the study, the multivariate analysis showed that patients receiving adjuvant chemotherapy had a survival benefit compared with those who were not treated at all. The benefit was shown among patients with MC and NMC as the Cox model excluded any interaction between histology and adjuvant chemotherapy.

To the best of our knowledge, this is the first large report that addressed the influence of mucinous histology in stage II and III colon cancer. This study supports the role of adjuvant chemotherapy in early-stage colon cancer regardless of the presence of mucinous histology.

acknowledgements

The authors would like to thank Sarah Helen Baulk for her improvements to the English in the manuscript.

funding

The authors have received no funds related to this study.

disclosure

The authors declare no conflict of interest.

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