Original article

Colorectal cancer, systemic inflammation and outcome: staging the tumor and staging the host

James H. Park MB ChB, David G. Watt MB ChB, Campbell S. D. Roxburgh PhD, Paul G. Horgan PhD, Donald C. McMillan PhD

Academic Unit of Colorectal Surgery, School of Medicine, University of Glasgow, Glasgow Royal Infirmary, Glasgow, United Kingdom

Corresponding author:

Mr James H. Park,

Academic Unit of Surgery, 2nd Floor, New Lister Building,

University of Glasgow, Glasgow Royal Infirmary,

10-16 Alexandra Parade

Glasgow, G31 2ER

United Kingdom

Tel: 00441412018676

Email: james.park@glasgow.ac.uk

Running head: colorectal cancer and systemic inflammation

Mini-Abstract

Of measures of the systemic inflammatory response, the modified Glasgow Prognostic Score has been most extensively validated in cancer. The present study examined its clinical utility in a large cohort of patients undergoing potentially curative resection of colorectal cancer.

Abstract

Objective

The present study aims to examine the clinical utility of the combination of TNM stage and modified Glasgow Prognostic Score (mGPS) in patients undergoing potentially curative resection of colorectal cancer (CRC).

Background

Of measures of the systemic inflammatory response, the mGPS has been most extensively validated in patients with cancer.

Methods

Data from 1000 consecutive patients undergoing potentially curative CRC resection from a single institution (January 1997 to May 2013) were included. The relationship between mGPS (0 – CRP ≤10mg/L, 1- CRP >10mg/L and albumin ≥35g/L, 2- CRP >10mg/L and albumin <35g/L), TNM stage and cancer-specific survival (CSS) and overall survival (OS) was examined using Kaplan-Meier and multivariate Cox regression analysis.

Results

An mGPS of 0, 1 and 2 was observed in 63%, 21% and 16% of patients. Median follow-up was 56 months (IQR: 28-107 months). TNM and mGPS were independently associated with CSS and OS (all P<0.001). In all patients, TNM and mGPS stratified five-year CSS and OS from 97% and 87% (stage I, mGPS=0) to 32% and 26% (stage III, mGPS=2) respectively. In patients undergoing elective resection of colon cancer (n=575), five-year CSS and OS ranged from 100% and 87% (stage I, mGPS=0) to 37% and 30% (stage III, mGPS=2), respectively.

Conclusions

The present study shows how the combination of TNM and mGPS effectively stratifies outcome in patients undergoing potentially curative resection of CRC. These data support routine staging of both the tumor and the host in patients with CRC.

INTRODUCTION

Colorectal cancer is the third most common cancer in the Western World and the second most common cause of cancer death.[1] Currently the need for adjuvant therapy is primarily based on pathological staging of the resected tumor using TNM criteria.[2] However, such a scheme may fail to accurately distinguish patients at high risk of recurrence and cancer death, particularly in the context of lymph node negative disease.[3]

Characteristics pertaining to the host, such as emergency presentation,[4] are also independently associated with poorer oncological outcome. Furthermore, the presence of an elevated systemic inflammatory response, as evidenced by changes in circulating acute phase proteins or myeloid cells, is an important unifying host characteristic and has been consistently associated with reduced survival, independent of stage, across a number of cancers including colorectal cancer.[5, 6] Systemic inflammation-based prognostic scores, such as the modified Glasgow Prognostic Score (mGPS) and the neutrophil:lymphocyte ratio (NLR) have been repeatedly reported to have prognostic value in a variety of operable cancers.[5, 6] Of these, the mGPS, a cumulative score based on the presence of an elevated serum C-reactive protein (CRP) and decreased serum albumin, has been reported to have superior prognostic value compared to the NLR in patients with operable colorectal cancer.[7-10]

Although the prognostic value of the mGPS has been widely reported, how it might be incorporated into the existing TNM-based staging of colorectal cancer, and how it might be implemented in the context of routine clinical practice and clinical trials is not clear. In the present study, the clinical utility of assessment of the systemic inflammatory response, utilizing pre-operative mGPS, was examined in a large cohort of patients undergoing potentially curative resection of colorectal cancer.

PATIENTS AND METHODS

Patients were identified from a prospectively collected and maintained database of elective and emergency colorectal cancer resections undertaken in a single surgical unit at Glasgow Royal Infirmary. Consecutive patients who had pre-operative measurement of serum CRP and serum albumin within 30 days prior to surgery and, who on the basis of preoperative abdominal computed tomography and laparotomy findings were considered to have undergone potentially curative resection for colorectal adenocarcinoma without distant metastases between January 1997 and May 2013 were included. Patients with inflammatory bowel disease-related cancer, who underwent resection with palliative intent or local resection only, or had not had pre-operative measurement of CRP or albumin, were excluded.

Tumors were staged using the fifth edition of the tumor, node and metastases classification,[2] with additional data taken from pathological reports issued following resection. Following surgery, all patients were discussed at a colorectal multidisciplinary meeting involving surgeons, oncologists, radiologists and pathologists with a colorectal cancer special interest; patients with stage III or high-risk stage II disease and no significant comorbidities precluding chemotherapy use were offered primarily 5-fluorouracil-based adjuvant chemotherapy on the basis of current guidelines at the time.

Pre-operative serum CRP and albumin were recorded prospectively. Patients undergoing elective resection had serum CRP and albumin concentrations measured routinely within 30 days prior to elective surgery. In patients undergoing emergency resection, CRP and albumin measured on admission were recorded. The mGPS was constructed as previously described;[5] patients with a CRP $\leq$10mg/L were allocated a score of 0, a CRP >10mg/L and albumin $\geq$35g/L a score of 1, and a CRP >10mg/L and albumin <35g/L a score of 2.

Patients were routinely followed up for five years following surgery. Date and cause of death was crosschecked with the cancer registration system and the Registrar General (Scotland). Death records were complete until 31st March 2014 that acted as the censor date. Cancer-specific survival was measured from date of surgery until date of death from recurrent or metastatic colorectal cancer. Overall survival was measured until the date of death from any cause.

The relationship between clinicopathological characteristics, pre-operative mGPS and five and ten-year survival was examined using Kaplan-Meier log-rank survival analysis and univariate Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI). Variables statistically significant on univariate analysis were subsequently entered into a multivariate model using a backwards conditional method. The relationship between mGPS and clinicopathological characteristics was examined using the χ^2 method for linear trend. A *P*-value ≤ 0.05 was considered statistically significant. All analyses were performed using SPSS version 22.0 (IBM SPSS, IL, USA). The West of Scotland Research Ethics Committee approved the study.

RESULTS

One thousand patients who underwent potentially curative resection of colorectal cancer were studied. Clinicopathological characteristics are shown in Table 1. Data on neoadjuvant therapy, adjuvant therapy and tumor differentiation were missing in 19, two and 10 patients respectively. Two-thirds of patients were older than 65 at time of surgery, 55% were male and over 90% of patients underwent elective resection. Two thirds of patients underwent resection of colon cancer. Ninety-three patients with rectal cancer and five patients with colon cancer received neoadjuvant therapy prior to surgery; of these, thirteen patients with rectal cancer had pathological confirmation of stage 0 disease (complete pathological response). Overall, 15% of patients had stage I disease, 46% had stage II disease and 38% had stage III disease. A quarter of patients received adjuvant chemotherapy following surgery; 16% of patients with stage II disease and 45% of patients with stage III disease received adjuvant therapy.

Thirty-seven percent of patients had CRP >10mg/L and 26% had an albumin <35g/L prior to surgery. Almost two thirds of patients were mGPS=0, whereas 21% and 16% were mGPS=1 and mGPS=2 respectively. An elevated mGPS was associated with advancing age, emergency presentation (both $\leq$0.001), less frequent use of neoadjuvant therapy (P<0.05), colonic primary, advancing T stage, advancing TNM stage, poor tumor differentiation, surgical margin involvement, peritoneal involvement and tumor perforation (all $P\leq$0.001).

The median follow-up of survivors was 56 months (range 10-206 months; interquartile range 28-107 months), with 242 colorectal cancer-related deaths and 193 non-cancer deaths. Cancer-specific survival at five and ten years was 75% and 67% respectively, and overall survival at five and ten years was 64% and 43%. The relationship between clinicopathological characteristics, pre-operative mGPS and survival is shown in Table 2.

The following clinicopathological characteristics were associated with reduced cancer-specific survival on univariate analysis: mGPS (P<0.001), advancing age (P<0.01), emergency presentation (P<0.01), T stage (P<0.001), N stage (P<0.001), poor differentiation (P<0.01), venous invasion (P<0.001), margin involvement (P<0.001) and peritoneal involvement (P<0.001). On multivariate survival analysis, mGPS was associated with reduced cancer-specific survival (HR 1.28 P=0.003), independent of age (P<0.01), T stage (P<0.001), N stage (P<0.001) and margin involvement (P<0.001). Poor differentiation and venous invasion showed a trend towards reduced survival on multivariate analysis (P=0.086 and P=0.094, respectively), whereas emergency presentation, peritoneal involvement and tumor perforation were not associated with survival.

The following clinicopathological characteristics were associated with reduced overall survival on univariate analysis: mGPS (P<0.001), advancing age (P<0.001), emergency presentation (P<0.05), no adjuvant therapy (P<0.05), T stage (P<0.001), N stage (P<0.001), poor differentiation (P=0.001), venous invasion (P<0.01), margin involvement (P<0.001) and peritoneal involvement (P<0.001). On multivariate analysis mGPS was associated with reduced overall survival (HR 1.28, P<0.001), independent of age (P<0.001), adjuvant therapy use (P<0.05), T stage (P<0.05), N stage (P<0.001), differentiation (P<0.05) and margin involvement (P<0.001). Venous invasion showed a trend towards reduced overall survival (P=0.066), whereas emergency presentation, peritoneal involvement and tumor perforation were not associated with survival.

The relationship between pre-operative mGPS, TNM stage and cancer-specific and overall survival is shown in Figure 1 and Table 3. Cancer-specific survival at five years varied from 100% in patients with stage 0 colorectal cancer to 61% in patients with stage III disease and from 80% in patients with mGPS=0 to 61% in patients with mGPS=2. When combined, cancer-specific survival at five years varied from 100% in patients with stage 0

disease and mGPS=0, to 32% in patients with stage III disease and mGPS=2 (P<0.001). A similar relationship between TNM stage, mGPS and ten-year cancer-specific survival was also observed; whereas survival ranged from 100% to 52% and from 70% to 52% with TNM stage or mGPS alone, the combination of TNM and mGPS stratified ten-year survival from 100% (TNM 0, mGPS=0) to 32% (TNM III, mGPS=2). The synergistic nature of the relationship between TNM stage and mGPS is, for example, shown for TNM stage III in Figure 2a (P<0.001).

Overall survival at five years varied from 92% (stage 0) to 51% (stage III) and from 70% (mGPS=0) to 46% (mGPS=2). Ten year overall survival varied from 92% (stage 0) to 35% (stage III) and from 49% (mGPS=0) to 30% (mGPS=2). Utilizing both TNM stage and mGPS, five-year overall survival ranged from 92% (TNM 0, mGPS=0) to 26% (stage III, mGPS=2) and ten-year overall survival ranged from 92% (TNM 0, mGPS=0) to 17% (TNM III, mGPS=2) (P<0.001). The synergistic effect of the combination of TNM stage and mGPS on overall survival is again evident in Figure 2b (P<0.001).

As mGPS was associated with emergency resection and a colonic primary, to control for any confounding of these variables the relationship between TNM stage, mGPS and survival was examined for 575 patients undergoing elective resection of colon cancer. In patients undergoing elective resection of colon cancer, an elevated mGPS was associated with advancing age, advancing T stage and TNM stage, poor differentiation, surgical margin and peritoneal involvement and tumor perforation (Table 4). The median follow-up of survivors was 56 months (range 10-206 months; interquartile range 27-107 months), with 122 cancer-related deaths and 124 non-cancer deaths. Cancer-specific and overall survival was 79% and 66% respectively at five years and 70% and 43% at ten years. On multivariate analysis, mGPS was associated with reduced cancer-specific survival (HR 1.61, 95% CI 1.28-2.02, P<0.001), independent of age (P<0.05), T stage (P=0.001), N stage (P<0.001), and

reduced overall survival (HR 1.52, 95% CI 1.29-1.78, $P<0.001$), independent of age ($P<0.001$), no adjuvant therapy ($P<0.05$), N stage ($P<0.001$) and margin involvement ($P=0.001$) (Supplementary Table 1). Venous invasion, peritoneal involvement and tumor perforation were not associated with cancer-specific or overall survival on multivariate analysis.

In patients undergoing elective resection of colon cancer, cancer-specific survival at five years ranged from 96% in patients with stage I disease to 63% in patients with stage III disease and from 86% in patients with mGPS=0 to 64% in patients with mGPS=2 (both $P\leq0.001$) (Figure 3a-b, Table 5a). Cancer-specific survival at ten years ranged from 96% (stage I) to 54% (stage III) and from 76% (mGPS=0) to 49% (mGPS=2). The combination of TNM stage and mGPS stratified both five and ten-year cancer-specific survival from 100% (stage I, mGPS=0) to 37% (stage III, mGPS=2) ($P<0.001$). Overall survival ranged from 79% (stage I) to 54% (stage III) and from 75% (mGPS=0) to 46% (mGPS=2) at five years, and from 44% (stage I) to 38% (stage III) and 54% (mGPS=0) to 24% (mGPS=2) at ten years (both $P\leq0.001$) (Figure 3c-d, Table 5b). The combination of TNM stage and mGPS stratified overall survival at five years from 87% (stage I, mGPS=0) to 30% (stage III, mGPS=2) and at ten years from 53% (stage I, mGPS=0) to 17% (stage III, mGPS=2) ($P<0.001$).

Subgroup analysis was subsequently performed to examine the relationship between mGPS, use of adjuvant chemotherapy and cancer-specific survival of 205 patients undergoing elective resection of stage III colon cancer. Use of adjuvant chemotherapy was associated with younger age ($P<0.001$), less advanced T stage and a lower mGPS (both $P<0.05$) but no other clinicopathological characteristics. The median follow-up of survivors was 61 months (range 11-205 months; interquartile range 31-107 months), with 71 cancer-related deaths. Cancer-specific survival was 79% at five years and 64% at ten years for patients with stage III colon cancer who received adjuvant chemotherapy, compared to 51% and 47%

respectively for patients who did not receive adjuvant therapy (*P*=0.002) (Table 6a). The mGPS stratified survival of patients with stage III colon cancer irrespective of adjuvant therapy status; for example, five-year survival varied from 91% (mGPS=0) to 61% (mGPS=1) for patients who received adjuvant therapy (*P*=0.003), and varied from 60% (mGPS=0) to 34% (mGPS=2) for patients who did not receive adjuvant therapy (*P*=0.114). Furthermore, whereas use of adjuvant therapy was associated with increased survival in patients with mGPS=0 (P=0.003), it was not associated with improved survival in patients with an elevated mGPS (*P*=0.357).

Finally, subgroup analysis was performed to examine the relationship between mGPS, ASCO high-risk pathological criteria (presence of a T4 tumor, lymph node yield <10 nodes, poor tumor differentiation, tumor perforation or venous invasion) and cancer-specific survival of 239 patients undergoing elective resection of stage II colon cancer without subsequent adjuvant therapy. The median follow-up of survivors was 63 months (range 10-205 months; interquartile range 28-111 months), with 41 cancer-related deaths. Five and ten-year survival of patients with no high-risk pathological characteristics was 91% and 85% respectively, compared to 83% and 70% for patients with one or more high-risk characteristic (*P*=0.138) (Table 6b). An elevated mGPS was associated with reduced survival of patients with both low and high-risk stage II colon cancer; ten-year survival of patients with low-risk disease was stratified from 88% (mGPS=0) to 68% (mGPS=2) (*P*=0.035), and ten-year survival of patients with high-risk disease varied from 71% to 51% (*P*=0.042).

DISCUSSION

The results of the present study show how the combination of TNM and mGPS effectively stratifies outcome in patients undergoing potentially curative resection of colorectal cancer. These data support the routine staging of both the tumor and the host systemic inflammatory response in patients with colorectal cancer.

In the present study, an increasing mGPS was associated with the presence of high-risk clinicopathological characteristics pertaining to both the host and the tumor. Even so, the pre-operative mGPS was prognostic independent of TNM stage and routinely reported adverse tumour characteristics, such as peritoneal involvement and tumor perforation. Furthermore, although associated with emergency presentation and a colonic primary, which may potentially reflect site-specific tumor heterogeneity,[11] it was of interest that the mGPS retained independent prognostic utility in the context of elective resection of colon cancer. Indeed, the combination of TNM stage and mGPS increased the range of survival compared to either TNM or mGPS alone. For example, whereas five-year cancer-specific survival of all patients undergoing elective resection of stage III colon cancer was 63%, the addition of mGPS stratified survival from 75% to 37%. Furthermore, within stage II disease, it was possible to identify a fifth of patients undergoing resection at higher risk than that afforded by TNM criteria alone.

The present study was able to provide further insight regarding the relationship between systemic inflammatory responses and use of adjuvant chemotherapy for stage III colon cancer. Patients with an elevated mGPS prior to elective resection were less likely to receive adjuvant therapy. At the time of data collection, however, it was unlikely to have been a factor in the multidisciplinary team's decision to recommend chemotherapy. Furthermore, although an elevated mGPS was associated with advancing age, over 40% of patients who did not receive chemotherapy were younger than 75 at time of surgery. With

such observational studies, there is a concern that one might be examining a population with an associated but unrelated (to cancer) chronic inflammatory state which also was associated with a lower rate of adjuvant therapy. However, the common chronic inflammatory conditions, such as rheumatoid arthritis, do not normally preclude adjuvant chemotherapy. It is therefore of interest that an elevated mGPS has previously been associated with co-morbid status[12, 13] and the presence of post-operative infectious complications.[14] However, although both may preclude use of adjuvant chemotherapy and explain the present inverse association between mGPS and use of adjuvant therapy,[15] it is important to note that the relationship between mGPS and oncological outcome has previously been shown to be independent of underlying patient co-morbidity. [13, 16]

Of interest, the mGPS stratified the survival of patients who received adjuvant chemotherapy following resection of stage III colon cancer. Although the present analysis must be interpreted with caution, it is consistent with previous reports.[5] Indeed in the present study, although patients with mGPS=0 had a 50% relative increase in survival at five years with adjuvant therapy, patients with mGPS≥1 appeared to derive no benefit. The underlying mechanism responsible for this lack of benefit is unclear; whereas it may be indicative of reduced tolerance to chemotherapy leading to subsequent dose reduction or cessation of treatment,[17] it may simply represent a lack of efficacy in the systemically inflamed patient. Certainly, although secondary analyses of reported trials of adjuvant chemotherapy may provide further insight, it is clear that future studies of adjuvant therapies should incorporate assessment of the pre-operative systemic inflammatory response.

Although there is clear rationale for the use of adjuvant chemotherapy in patients with stage III colon cancer, the post-operative management of lymph node negative disease is problematic.[3] Other high-risk pathological characteristics, such as the presence of venous invasion, have been shown to effectively stratify outcome within TNM and may predict need

for adjuvant therapy.[18] However, the recent inclusion of venous invasion, alongside other high risk pathological characteristics as additional prognostic factors in tumor staging does not negate the utility of host characteristics, such as the mGPS, in the effective stratification of outcome. Indeed, in the present study, patients with mGPS=2 undergoing elective resection for otherwise low-risk stage II colon cancer had five and ten-year survival comparable to that of patients with stage III disease. Although the small number of patients receiving adjuvant therapy for stage II colon cancer precluded meaningful analysis in the present study, whether the mGPS may aid in the selection of patients with stage II colon cancer likely to benefit from adjuvant therapy would be of considerable interest. Furthermore, whereas assessment of pathological characteristics are often subjective and may be underreported,[19] the components of the mGPS, CRP and albumin, are objectively measured and routinely available.

The present study was limited by its single centre nature; however this was a large, prospectively collected cohort of patients. Although a population whose mGPS reverted to normal following surgery would be of interest, the majority of patients do not, in terms of their mGPS, change their inflammatory state. Indeed of those patients with an elevated mGPS, up to 80% may remain systemically inflamed following potentially curative resection of colorectal cancer.[9] As such, any changes to the operative and peri-operative management of patients over the time period studied, for example the introduction of enhanced recovery protocols to our centre in 2011, are unlikely to have had a significant effect on the mGPS. Furthermore, the small number of patients undergoing resection for stage I colon cancer and patients with rectal cancer precluded meaningful analysis within these subsets. Given that earlier stage disease is likely to predominate in the context of colorectal cancer screening programmes,[20] whether mGPS may aid in the decision between local excision and formal resection in patients presenting with early stage disease would be an important area for future

research. Finally, as mGPS was only recorded prior to surgery, it was not possible to examine the impact of neoadjuvant chemoradiotherapy on the mGPS of patients with rectal cancer. This would also be of considerable interest.

Although representing only "the tip of a far larger iceberg" in inflammation-associated tumor progression and dissemination,[21] the use of routinely available biomarkers, such as the mGPS, allows us to utilise our current understanding of the systemic inflammatory responses in patients with cancer. This has several far-reaching implications for clinical practice. As demonstrated, alongside guiding long-term prognosis, the incorporation of the mGPS into routine assessment may also identify patients less likely to tolerate, or benefit from, adjuvant systemic therapy. Furthermore, routine use of the mGPS may also direct future therapeutic strategies, targeted at the systemic inflammatory response itself. Indeed, it is now appreciated that systemic inflammation is complicit in cancer cachexia,[22] and may be attenuated by the use of non-steroidal anti-inflammatory drugs (NSAIDs).[23] A similar scheme may also be applied to patients undergoing potentially curative surgery. For example, in patients with stage III disease, those with mGPS=0 may benefit from adjuvant chemotherapy alone, whereas those with an elevated mGPS may also benefit from the addition of an anti-inflammatory agent, such as aspirin or other NSAID.[24, 25] Certainly, it is clear that randomised controlled trials, incorporating both routine assessment of the systemic inflammatory response and use of anti-inflammatory agents, are required.

In conclusion, the mGPS provides complimentary prognostic information to current TNM-based staging and may also aid in directing future therapeutic strategies, targeting the systemic inflammatory response. Given that the combination of TNM stage and the mGPS are routinely available worldwide, this staging system for patients undergoing potentially curative resection of colorectal cancer has much to commend it.

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REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int. J. Cancer* 2010; 127:2893-917.
2. Fleming ID, American Joint Committee on Cancer., American Cancer Society., et al. AJCC cancer staging manual. 5th ed / ed. Philadelphia: Lippincott-Raven, 1997.
3. Horgan PG, McMillan DC. Surgeons and selection of adjuvant therapy for node-negative colonic cancer. *Br. J. Surg.* 2010; 97:1459-1460.
4. Oliphant R, Mansouri D, Nicholson GA, et al. Emergency presentation of node-negative colorectal cancer treated with curative surgery is associated with poorer short and longer-term survival. *Int. J. Colorectal Dis.* 2014; 29:591-8.
5. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat. Rev.* 2013; 39:534-40.
6. Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit. Rev. Oncol. Hematol.* 2013; 88:218-30.
7. Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. *Eur. J. Cancer* 2011; 47:2633-2641.
8. Leitch EF, Chakrabarti M, Crozier JEM, et al. Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer. *Br. J. Cancer* 2007; 97:1266-1270.
9. Guthrie GJ, Roxburgh CS, Farhan-Alanie OM, et al. Comparison of the prognostic value of longitudinal measurements of systemic inflammation in patients undergoing curative resection of colorectal cancer. *Br. J. Cancer* 2013; 109:24-8.
10. Choi KW, Hong SW, Chang YG, et al. Inflammation-based score (Glasgow prognostic score) as an independent prognostic factor in colorectal cancer patients. *Ann. Surg. Treat. Res.* 2014; 86:309-13.
11. Powell AG, Wallace R, McKee RF, et al. The relationship between tumour site, clinicopathological characteristics and cancer-specific survival in patients undergoing surgery for colorectal cancer. *Colorectal Dis.* 2012; 14:1493-9.
12. Richards CH, Leitch EF, Horgan PG, et al. The relationship between patient physiology, the systemic inflammatory response and survival in patients undergoing curative resection of colorectal cancer. *Br. J. Cancer.* 2010; 103:1356-1361.
13. Roxburgh CSD, Platt JJ, Leitch EF, et al. Relationship Between Preoperative Comorbidity, Systemic Inflammatory Response, and Survival in Patients Undergoing Curative Resection for Colorectal Cancer. *Ann. Surg. Oncol.* 2011; 18:997-1005.
14. Mohri Y, Miki C, Kobayashi M, et al. Correlation between preoperative systemic inflammation and postoperative infection in patients with gastrointestinal cancer: a multicenter study. *Surg. Today* 2014; 44:859-67.
15. Roxburgh C, McDonald A, Salmond J, et al. Adjuvant chemotherapy for resected colon cancer: comparison of the prognostic value of tumour and patient related factors. *Int. J. Colorectal Dis.* 2011; 26:483-492.
16. Michigan A, Johnson TV, Master VA. Preoperative C-reactive protein level adjusted for comorbidities and lifestyle factors predicts overall mortality in localized renal cell carcinoma. *Mol. Diagn. Ther.* 2011; 15:229-34.

17. Sharma R, Zucknick M, London R, et al. Systemic inflammatory response predicts prognosis in patients with advanced-stage colorectal cancer. *Clin. Colorectal Cancer* 2008; 7:331-7.
18. Loughrey MB, Quirke P, Shepherd NA. Dataset for colorectal cancer histopathology reports. 3 ed: The Royal College of Pathologists, 2014.
19. Morris EJ, Maughan NJ, Forman D, et al. Who to treat with adjuvant therapy in Dukes B/stage II colorectal cancer? The need for high quality pathology. *Gut* 2007; 56:1419-25.
20. Mansouri D, McMillan DC, Crighton EM, et al. Screening for colorectal cancer: what is the impact on the determinants of outcome? *Crit. Rev. Oncol. Hematol.* 2013; 85:342-9.
21. McAllister SS, Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. *Nat. Cell Biol.* 2014; 16:717-27.
22. Douglas E, McMillan DC. Towards a simple objective framework for the investigation and treatment of cancer cachexia: the Glasgow Prognostic Score. *Cancer Treat. Rev.* 2014; 40:685-91.
23. McMillan DC, Wigmore SJ, Fearon K, et al. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. *Br. J. Cancer* 1999; 79:495.
24. Park JH, McMillan DC, Horgan PG, et al. The impact of anti-inflammatory agents on the outcome of patients with colorectal cancer. *Cancer Treat. Rev.* 2014; 40:68-77.
25. Roxburgh CS, McMillan DC. Cancer and systemic inflammation: treat the tumour and treat the host. *Br. J. Cancer* 2014; 110:1409-12.

Figure 1. A, Relationship between TNM stage and cancer-specific survival of patients undergoing resection of colorectal cancer (P<0.001). B, Relationship between mGPS and cancer-specific survival of patients undergoing resection of colorectal cancer (P<0.001). C, Relationship between TNM stage and overall survival of patients undergoing resection of colorectal cancer (P<0.001). D, Relationship between mGPS and overall survival of patients undergoing resection of colorectal cancer (P<0.001).

Figure 2. A, Relationship between mGPS and TNM stage and cancer-specific survival of patients undergoing resection of stage III colorectal cancer (P<0.001). B, Relationship between mGPS and overall survival of patients undergoing elective resection of colon cancer (P<0.001).

Figure 3. A, Relationship between TNM stage and cancer-specific survival of patients undergoing elective resection of colon cancer (P<0.001). B, Relationship between mGPS and cancer-specific survival of patients undergoing elective resection of colon cancer (P<0.001). C, Relationship between TNM stage and overall survival of patients undergoing elective resection of colon cancer (P<0.001). D, Relationship between mGPS and overall survival of patients undergoing elective resection of colon cancer (P<0.001).

Table 1. The relationship between modified Glasgow Prognostic Score and clinicopathological characteristics in patients undergoing potentially curative resection of colorectal cancer

		All	mGPS=0	mGPS=1	mGPS=2	
Clinicopathological Characteristic		***n*=1000 (%)**	***n*=635 (%)**	***n*=207 (%)**	***n*=158 (%)**	***P***
Age						0.001
	<65	330 (33)	218 (34)	66 (32)	46 (29)	
	65-74	347 (35)	238 (38)	73 (35)	36 (23)	
	>75	323 (32)	179 (28)	68 (33)	76 (48)	
Sex						0.137
	Female	452 (45)	274 (43)	102 (49)	76 (48)	
	Male	548 (55)	361 (57)	105 (51)	82 (52)	
Presentation						<0.001
	Elective	913 (91)	610 (96)	174 (84)	129 (82)	
	Emergency	87 (9)	25 (4)	33 (16)	29 (18)	
Neoadjuvant therapy [a]						0.020
	No	883 (88)	544 (88)	199 (97)	140 (91)	
	Yes	98 (10)	77 (12)	7 (3)	14 (9)	
Adjuvant therapy [b]						0.805
	No	750 (75)	483 (76)	145 (70)	122 (78)	
	Yes	248 (25)	151 (24)	62 (30)	35 (22)	
Tumor site						<0.001
	Colon	656 (66)	380 (60)	152 (73)	124 (79)	
	Rectum	344 (34)	255 (40)	55 (27)	34 (22)	
T stage						<0.001
	0	13 (1)	13 (2)	0 (0)	0 (0)	
	1	66 (7)	56 (9)	7 (3)	3 (2)	
	2	112 (11)	95 (15)	11 (5)	6 (4)	
	3	550 (55)	354 (56)	111 (54)	85 (54)	
	4	259 (26)	117 (18)	78 (38)	64 (41)	
N stage						0.470
	0	618 (62)	396 (62)	118 (57)	104 (66)	
	1	274 (27)	182 (29)	58 (28)	34 (22)	
	2	108 (11)	57 (9)	31 (15)	20 (13)	
TNM stage						0.001
	0	13 (1)	0 (0)	0 (0)	0 (0)	
	1	148 (15)	126 (20)	14 (7)	8 (5)	
	2	457 (46)	257 (41)	104 (50)	96 (61)	
	3	382 (38)	239 (38)	89 (43)	54 (34)	
Less than 10 lymph nodes retrieved						0.267
	No	824 (82)	518 (82)	171 (83)	135 (85)	
	Yes	176 (18)	117 (18)	36 (17)	23 (15)	
Differentiation [c]						<0.001
	Mod/well	894 (89)	584 (93)	181 (87)	129 (82)	
	Poor	96 (10)	42 (7)	26 (13)	28 (18)	
Venous invasion						0.747
	No	493 (49)	312 (49)	108 (52)	73 (46)	
	Yes	507 (51)	323 (51)	99 (48)	85 (54)	
Margin involvement						0.001
	No	929 (93)	605 (95)	183 (88)	141 (89)	
	Yes	71 (7)	30 (5)	24 (12)	17 (11)	
Peritoneal involvement						<0.001
	No	773 (77)	531 (84)	138 (67)	104 (66)	

Tumor perforation	**Yes**	227 (23)	104 (16)	69 (33)	54 (34)	<0.001
	No	973 (97)	630 (99)	195 (94)	148 (94)	
	Yes	26 (3)	5 (1)	11 (6)	10 (6)	

[a] Data missing for 19 patients, [b] Data missing for 2 patients, [c] Data missing for 10 patients

Table 2. The relationship between clinicopathological characteristics and survival of patients undergoing potentially curative resection of colorectal cancer

	Cancer-specific survival				Overall survival			
Clinicopathological Characteristic	**Univariate analysis**	***P***	**Multivariate analysis**	***P***	**Univariate analysis**	***P***	**Multivariate analysis**	***P***
Age (<65/ 65-74/ >75)	1.28 (1.09-1.50)	0.002	1.24 (1.06-1.46)	0.007	1.69 (1.50-1.91)	<0.001	1.57 (1.39-1.79)	<0.001
Sex (Female/ male)	1.08 (0.84-1.40)	0.534	-	-	1.14 (0.94-1.37)	0.189	-	-
Presentation (Elective/ emergency)	1.75 (1.20-2.55)	0.004	-	0.893	1.37 (1.01-1.88)	0.046	-	0.654
Neoadjuvant therapy (No/ yes)	1.16 (0.76-1.78)	0.485	-	-	0.84 (0.58-1.21)	0.349	-	-
Adjuvant therapy (No/ yes)	1.08 (0.81-1.44)	0.617	-	-	0.75 (0.59-0.96)	0.020	0.73 (0.56-0.95)	0.017
Tumor site (Colon/ rectum)	1.12 (0.86-1.45)	0.416	-	-	0.96 (0.79-1.17)	0.694	-	-
T stage (0/ 1/ 2/ 3/ 4)	1.98 (1.63-2.40)	<0.001	1.48 (1.21-1.82)	<0.001	1.37 (1.20-1.56)	<0.001	1.16 (1.01-1.33)	0.042
N stage (0/ 1/ 2)	1.88 (1.60-2.21)	<0.001	1.58 (1.33-1.88)	<0.001	1.42 (1.25-1.62)	<0.001	1.39 (1.21-1.60)	<0.001
Less than 10 lymph nodes retrieved (No/ yes)	1.28 (0.95-1.72)	0.110	-	-	1.15 (0.92-1.44)	0.227	-	-
Differentiation (Mod-well/ poor)	1.81 (1.25-2.63)	0.002	-	0.086	1.63 (1.22-2.17)	0.001	1.36 (1.02-1.82)	0.038
Venous invasion (No/ yes)	1.69 (1.31-2.19)	<0.001	-	0.094	1.36 (1.12-1.65)	0.002	-	0.066
Margin involvement (No/ yes)	3.74 (2.67-5.23)	<0.001	2.63 (1.86-3.73)	<0.001	2.51 (1.87-3.36)	<0.001	2.06 (1.52-2.80)	<0.001
Peritoneal involvement (No/ yes)	2.12 (1.63-2.76)	<0.001	-	0.593	1.51 (1.22-1.86)	<0.001	-	0.733
Tumor perforation (No/ yes)	1.75 (0.93-3.29)	0.084	-	-	1.48 (0.88-2.47)	0.138	-	-
mGPS (0/ 1/ 2)	1.51 (1.29-1.76)	<0.001	1.28 (1.09-1.52)	0.003	1.43 (1.27-1.61)	<0.001	1.28 (1.13-1.45)	<0.001

Table 3a. The relationship between modified Glasgow Prognostic Score and five and ten-year cancer-specific survival in patients undergoing potentially curative resection of stage I-III colorectal cancer

	mGPS = 0 (CRP ≤10 mg/L)		**mGPS = 1 (CRP >10mg/L and albumin ≥35 g/L)**		**mGPS = 2 (CRP >10mg/L and albumin <35g/L)**		**All (mGPS = 0-2)**	
	n	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**
Stage 0	13	100 (0)	0	-	0	-	13	100 (0)
Stage I	126	97 (2)	14	72 (14)	8	-	148	94 (2)
Stage II	257	83 (3)	104	84 (4)	96	76 (5)	457	82 (2)
Stage III	239	68 (4)	89	56 (6)	54	32 (8)	382	61 (3)
All (Stage 0-III)	635	80 (2)	207	71 (3)	158	61 (5)	1000	75 (2)
	n	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**
Stage 0	13	100 (0)	0	-	0	-	13	100 (0)
Stage I	126	86 (5)	14	57 (17)	8	-	148	83 (5)
Stage II	257	75 (3)	104	76 (5)	96	61 (8)	457	73 (3)
Stage III	239	56 (4)	89	53 (6)	54	32 (8)	382	52 (3)
All (Stage 0-III)	635	70 (2)	207	65 (4)	158	52 (6)	1000	67 (2)

CSS - cancer-specific survival. Survival not calculated if $n<10$

Table 3b. The relationship between modified Glasgow Prognostic Score and five and ten-year overall survival in patients undergoing potentially curative resection of stage I-III colorectal cancer

	mGPS = 0 (CRP ≤10 mg/L)		mGPS = 1 (CRP >10mg/L and albumin ≥35 g/L)		mGPS = 2 (CRP >10mg/L and albumin <35g/L)		All (mGPS = 0-2)	
	n	**5-yr OS % (SE)**	***n***	**5-yr OS % (SE)**	***n***	**5-yr OS % (SE)**	***n***	**5-yr OS % (SE)**
Stage 0	13	92 (7)	0	-	0	-	13	92 (7)
Stage I	126	87 (4)	14	59 (14)	8	-	148	80 (4)
Stage II	257	74 (3)	104	74 (5)	96	57 (6)	457	70 (2)
Stage III	239	59 (4)	89	45 (5)	54	26 (7)	382	51 (3)
All (Stage 0-III)	635	70 (2)	207	60 (4)	158	46 (5)	1000	64 (2)
	n	**10-yr OS % (SE)**	***n***	**10-yr OS % (SE)**	***n***	**10-yr OS % (SE)**	***n***	**10-yr OS % (SE)**
Stage 0	13	92 (7)	0	-	0	-	13	92 (7)
Stage I	126	56 (8)	14	16 (14)	8	-	148	49 (7)
Stage II	257	53 (4)	104	44 (6)	96	38 (7)	457	48 (3)
Stage III	239	40 (4)	89	33 (5)	54	17 (7)	382	35 (3)
All (Stage 0-III)	635	49 (3)	207	38 (4)	158	30 (5)	1000	43 (2)

OS - overall survival. Survival not calculated if $n<10$

Table 4. The relationship between modified Glasgow Prognostic Score and clinicopathological characteristics in patients undergoing elective, potentially curative resection of colon cancer

		mGPS=0	mGPS=1	mGPS=2	
Clinicopathological Characteristic		***n*=358 (%)**	***n*=121 (%)**	***n*=96 (%)**	***P***
Age					0.020
	<65	112 (31)	35 (29)	25 (26)	
	65-74	129 (36)	39 (32)	24 (25)	
	>75	117 (33)	47 (39)	47 (49)	
Sex					0.364
	Female	165 (46)	62 (51)	48 (50)	
	Male	193 (54)	59 (49)	48 (50)	
Neoadjuvant therapy [a]					0.456
	No	348 (99)	119 (98)	93 (99)	
	Yes	2 (1)	2 (2)	1 (1)	
Adjuvant therapy					0.640
	No	271 (76)	89 (74)	76 (79)	
	Yes	87 (24)	32 (26)	20 (21)	
T stage					<0.001
	1	32 (9)	1 (1)	2 (2)	
	2	53 (15)	6 (5)	3 (3)	
	3	196 (55)	68 (56)	54 (56)	
	4	77 (22)	46 (38)	37 (39)	
N stage					0.957
	0	231 (65)	73 (60)	66 (69)	
	1	99 (28)	34 (28)	21 (22)	
	2	28 (8)	14 (12)	9 (9)	
TNM stage					0.021
	1	76 (21)	7 (6)	4 (4)	
	2	155 (43)	66 (55)	62 (65)	
	3	127 (36)	48 (40)	30 (31)	
Less than 10 lymph nodes retrieved					0.286
	No	295 (82)	97 (80)	85 (89)	
	Yes	63 (18)	24 (20)	11 (11)	
Differentiation [b]					<0.001
	Mod/well	332 (93)	105 (87)	72 (76)	
	Poor	24 (7)	16 (13)	23 (24)	
Venous invasion					0.733
	No	185 (52)	64 (53)	47 (49)	
	Yes	173 (48)	57 (47)	49 (51)	
Margin involvement					0.015
	No	349 (98)	113 (93)	89 (93)	
	Yes	9 (3)	8 (7)	7 (7)	
Peritoneal involvement					0.005
	No	287 (80)	80 (66)	67 (70)	
	Yes	71 (20)	41 (34)	29 (30)	
Tumor perforation					0.001
	No	356 (99)	116 (96)	91 (95)	
	Yes	2 (1)	5 (4)	5 (5)	

[a] Data missing for 10 patients, [b] Data missing for 3 patients

Table 5a. The relationship between modified Glasgow Prognostic Score and five and ten-year cancer-specific survival in patients undergoing elective, potentially curative resection of stage I-III colon cancer

	mGPS = 0 (CRP ≤10 mg/L)		**mGPS = 1 (CRP >10mg/L and albumin ≥35 g/L)**		**mGPS = 2 (CRP >10mg/L and albumin <35g/L)**		**All (mGPS = 0-2)**	
	n (%)	**5-yr CSS % (SE)**	***n (%)***	**5-yr CSS % (SE)**	***n (%)***	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**
Stage I	76	100 (0)	7	-	4	-	87	96 (3)
Stage II	155	89 (3)	66	86 (5)	62	78 (6)	283	86 (2)
Stage III	127	75 (4)	48	53 (8)	30	37 (10)	205	63 (4)
All (Stage I-III)	358	86 (2)	121	72 (5)	96	64 (6)	575	79 (2)
	n (%)	**10-yr CSS % (SE)**	***n (%)***	**10-yr CSS % (SE)**	***n (%)***	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**
Stage I	76	100 (0)	7	-	4	-	87	96 (3)
Stage II	155	79 (4)	66	81 (6)	62	55 (11)	283	76 (3)
Stage III	127	62 (6)	48	49 (8)	30	37 (10)	205	54 (5)
All (Stage I-III)	358	76 (3)	121	68 (5)	96	49 (8)	575	70 (3)

CSS - cancer-specific survival. Survival not calculated if $n<10$

Table 5b. The relationship between modified Glasgow Prognostic Score and five and ten-year overall survival in patients undergoing elective, potentially curative resection of stage I-III colon cancer

	mGPS = 0 (CRP ≤10 mg/L)		**mGPS = 1 (CRP >10mg/L and albumin ≥35 g/L)**		**mGPS = 2 (CRP >10mg/L and albumin <35g/L)**		**All (mGPS = 0-2)**	
	n	**5-yr OS % (SE)**	***n***	**5-yr OS % (SE)**	***n***	**5-yr OS % (SE)**	***n***	**5-yr OS % (SE)**
Stage I	76	87 (5)	7	-	4	-	87	79 (5)
Stage II	155	77 (4)	66	73 (6)	62	57 (7)	283	72 (3)
Stage III	127	66 (5)	48	39 (7)	30	30 (9)	205	54 (4)
All (Stage 0-III)	358	75 (3)	121	58 (5)	96	46 (6)	575	66 (2)
	n	**10-yr OS % (SE)**	***n***	**10-yr OS % (SE)**	***n***	**10-yr OS % (SE)**	***n***	**10-yr OS % (SE)**
Stage I	76	53 (12)	7	-	4	-	87	44 (1)
Stage II	155	56 (5)	66	42 (7)	62	30 (9)	283	47 (4)
Stage III	127	50 (6)	48	24 (7)	30	17 (9)	205	38 (4)
All (Stage 0-III)	358	54 (4)	121	32 (5)	96	24 (7)	575	43 (3)

OS - overall survival. Survival not calculated if $n<10$

Table 6a. The relationship between modified Glasgow Prognostic Score, adjuvant chemotherapy use and five and ten-year overall survival in patients undergoing elective, potentially curative resection of stage III colon cancer

	mGPS = 0 (CRP ≤10 mg/L)		**mGPS = 1 (CRP >10mg/L and albumin ≥35 g/L)**		**mGPS = 2 (CRP >10mg/L and albumin <35g/L)**		**All (mGPS = 0-2)**	
	n	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**
Adjuvant therapy	64	91 (4)	23	61 (11)	8	-	95	79 (5)
No adjuvant therapy	63	60 (7)	25	47 (11)	22	34 (11)	110	51 (5)
All	127	75 (4)	48	53 (8)	30	37 (10)	205	63 (4)
	n	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**
Adjuvant therapy	64	72 (9)	23	53 (12)	8	-	95	64 (7)
No adjuvant therapy	63	53 (8)	25	47 (11)	22	34 (11)	110	47 (6)
All	127	62 (6)	48	49 (8)	30	37 (10)	205	54 (5)

CSS – cancer-specific survival. Survival not calculated if *n*<10

Table 6b. The relationship between modified Glasgow Prognostic Score, ASCO high-risk pathological criteria and five and ten-year cancer-specific survival in patients undergoing elective, potentially curative resection of stage II colon cancer

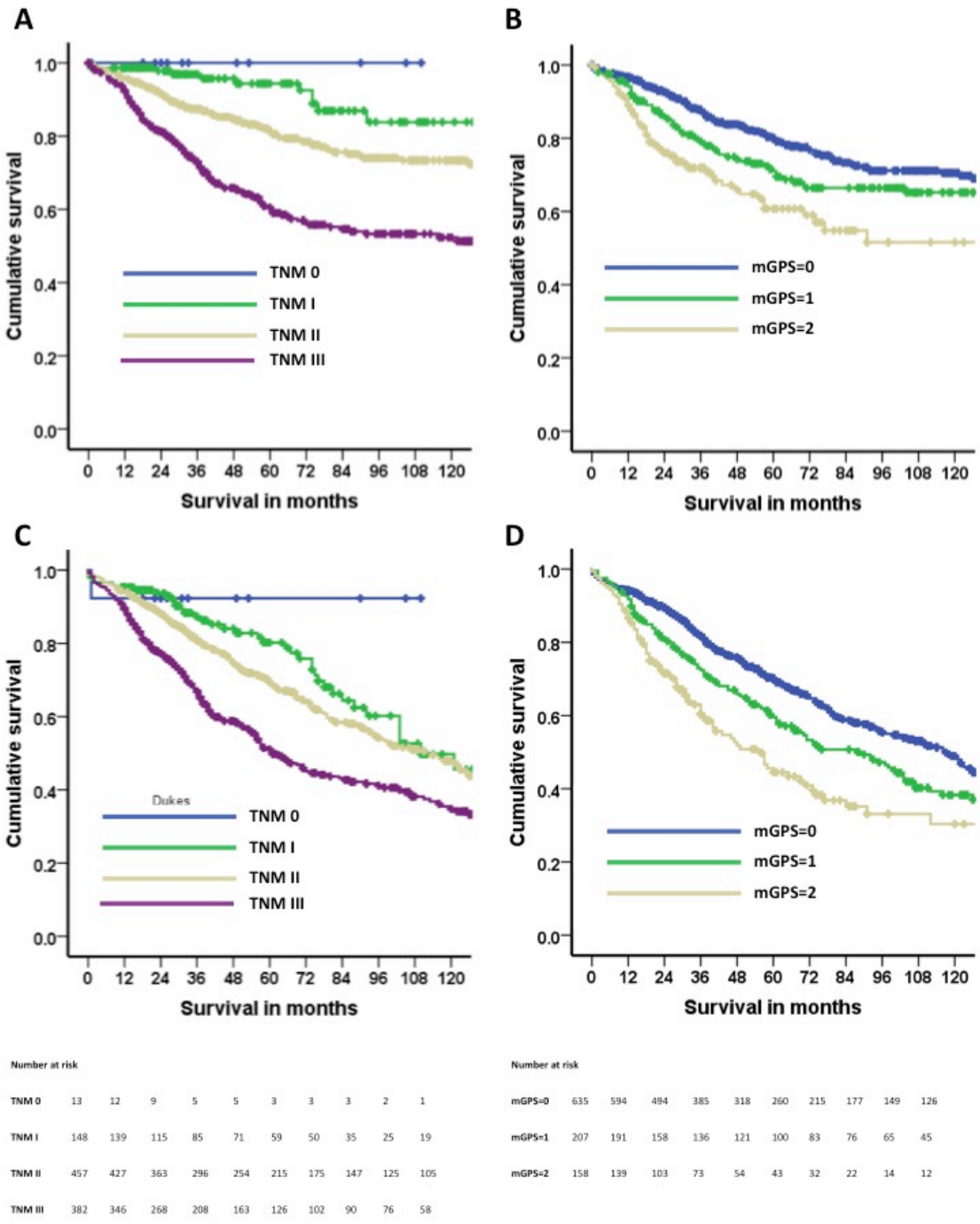
	mGPS = 0 (CRP ≤10 mg/L)		**mGPS = 1 (CRP >10mg/L and albumin ≥35 g/L)**		**mGPS = 2 (CRP >10mg/L and albumin <35g/L)**		**All (mGPS = 0-2)**	
	n (%)	**5-yr CSS % (SE)**	***n (%)***	**5-yr CSS % (SE)**	***n (%)***	**5-yr CSS % (SE)**	***n***	**5-yr CSS % (SE)**
Low risk	48	93 (4)	30	100 (0)	13	68 (13)	91	91 (3)
High risk[a]	84	85 (5)	27	84 (8)	37	78 (8)	148	83 (4)
All (Low and high-risk)	132	88 (3)	57	92 (4)	50	75 (7)	239	86 (3)
	n (%)	**10-yr CSS % (SE)**	***n (%)***	**10-yr CSS % (SE)**	***n (%)***	**10-yr CSS % (SE)**	***n***	**10-yr CSS % (SE)**
Low risk	48	88 (6)	30	89 (7)	13	68 (13)	91	85 (5)
High risk	84	71 (7)	27	84 (8)	37	51 (14)	29	70 (5)
All (Low and high-risk)	132	78 (5)	57	87 (5)	50	54 (12)	239	76 (4)

[a] High-risk stage II colon cancer denoted by presence of one or more of the following: T4 tumor, lymph node yield <10 nodes, poor tumor differentiation, tumor perforation or venous invasion. CSS- cancer-specific survival

Table S1. The relationship between clinicopathological characteristics and survival of patients undergoing potentially curative, elective resection of colon cancer

	Cancer-specific survival				Overall survival			
Clinicopathological Characteristic	**Univariate analysis**	***P***	**Multivariate analysis**	***P***	**Univariate analysis**	***P***	**Multivariate analysis**	***P***
Age (<65/ 65-74/ >75)	1.35 (1.08-1.69)	0.009	1.34 (1.07-1.68)	0.011	1.83 (1.55-2.15)	<0.001	1.04 (1.03-1.06)	<0.001
Sex (Female/ male)	0.89 (0.63-1.27)	0.531	-	-	1.00 (0.77-1.28)	0.967	-	-
Neoadjuvant therapy (No/ yes)	0.86 (0.12-6.17)	0.882	-	-	0.40 (0.06-2.87)	0.364	-	-
Adjuvant therapy (No/ yes)	1.06 (0.71-1.60)	0.774	-	-	0.61 (0.44-0.85)	0.004	0.65 (0.45-0.95)	0.025
T stage (0/ 1/ 2/ 3/ 4)	2.44 (1.81-3.28)	<0.001	1.77 (1.28-2.46)	0.001	1.36 (1.13-1.63)	0.001	-	0.383
N stage (0/ 1/ 2)	2.09 (1.66-2.64)	<0.001	1.86 (1.45-2.37)	<0.001	1.42 (1.18-1.70)	<0.001	1.62 (1.34-1.97)	<0.001
Less than 10 lymph nodes retrieved (No/ yes)	1.02 (0.65-1.59)	0.946	-	-	1.00 (0.73-1.36)	0.976	-	-
Differentiation (Mod-well/ poor)	1.49 (0.88-2.52)	0.140	-	-	1.53 (1.06-2.20)	0.022	-	0.437
Venous invasion (No/ yes)	1.88 (1.31-2.70)	0.001	-	0.151	1.31 (1.01-1.69)	0.041	-	0.140
Margin involvement (No/ yes)	3.86 (2.17-6.87)	<0.001	-	0.065	2.98 (1.86-4.77)	<0.001	2.24 (1.38-3.62)	0.001
Peritoneal involvement (No/ yes)	2.46 (1.72-3.53)	<0.001	-	0.928	1.43 (1.09-1.88)	0.010	-	0.242
Tumor perforation (No/ yes)	2.78 (1.14-6.82)	0.025	-	0.254	2.30 (1.13-4.65)	0.021	-	0.089
mGPS (0/ 1/ 2)	1.76 (1.42-2.18)	<0.001	1.61 (1.28-2.02)	<0.001	1.64 (1.40-1.91)	<0.001	1.52 (1.29-1.78)	<0.001

1



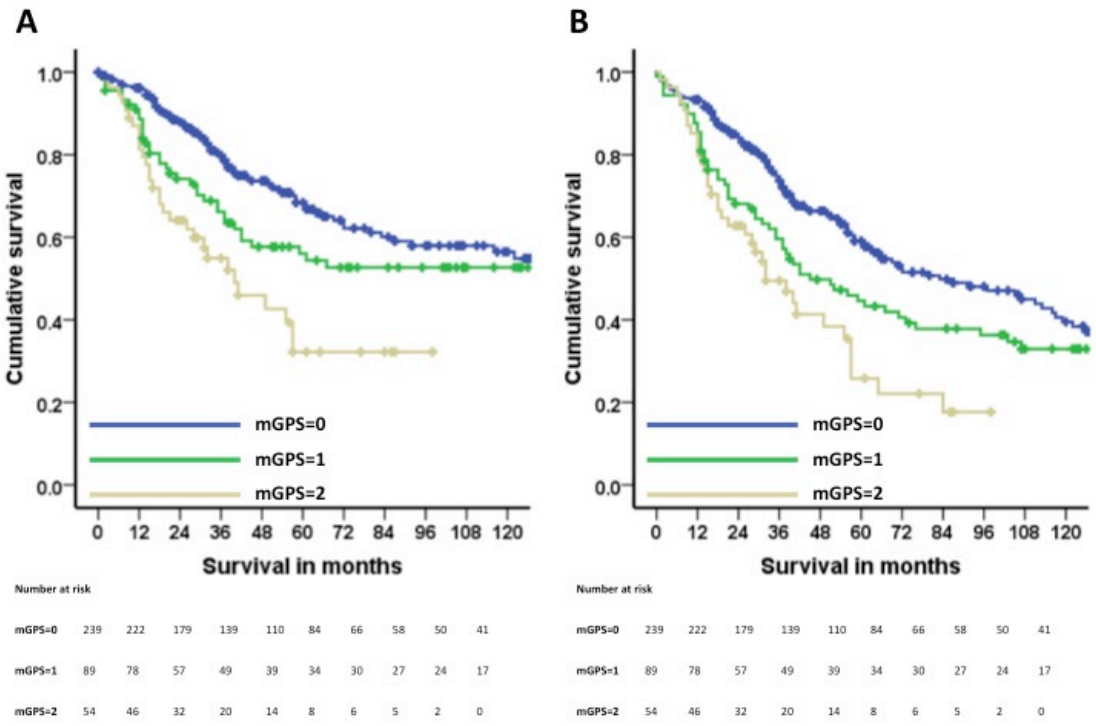
Number at risk

TNM 0	13	12	9	5	5	3	3	3	2	1
TNM I	148	139	115	85	71	59	50	35	25	19
TNM II	457	427	363	296	254	215	175	147	125	105
TNM III	382	346	268	208	163	126	102	90	76	58

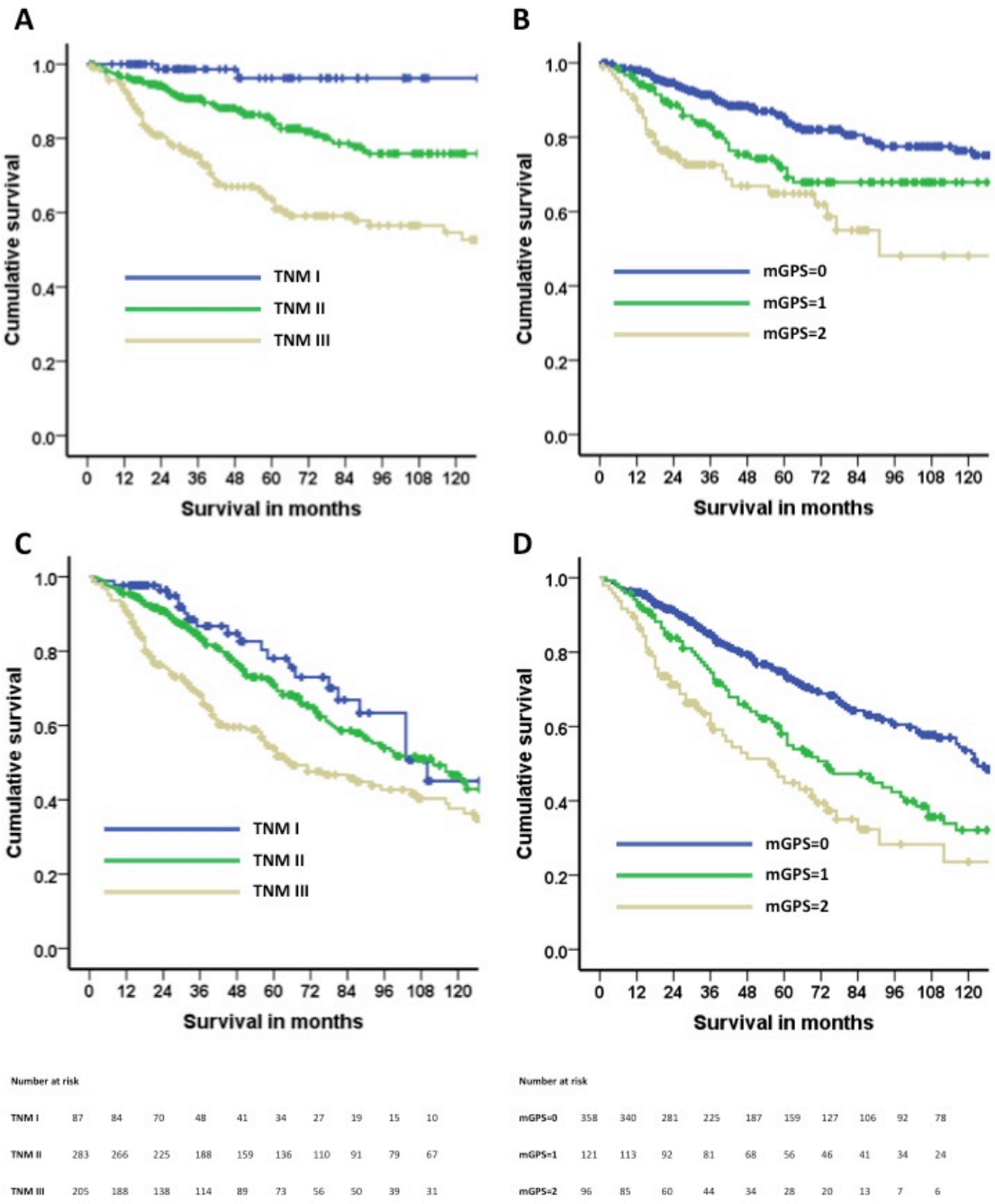
Number at risk

mGPS=0	635	594	494	385	318	260	215	177	149	126
mGPS=1	207	191	158	136	121	100	83	76	65	45
mGPS=2	158	139	103	73	54	43	32	22	14	12

2


A
B
Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
mGPS=0
mGPS=1
mGPS=2
0 12 24 36 48 60 72 84 96 108 120
Survival in months
Number at risk
mGPS=0 239 222 179 139 110 84 66 58 50 41
mGPS=1 89 78 57 49 39 34 30 27 24 17
mGPS=2 54 46 32 20 14 8 6 5 2 0

3



Number at risk

TNM I	87	84	70	48	41	34	27	19	15	10
TNM II	283	266	225	188	159	136	110	91	79	67
TNM III	205	188	138	114	89	73	56	50	39	31

Number at risk

mGPS=0	358	340	281	225	187	159	127	106	92	78
mGPS=1	121	113	92	81	68	56	46	41	34	24
mGPS=2	96	85	60	44	34	28	20	13	7	6