Elevated inflammatory parameters and inflammation scores are associated with poor prognosis in patients undergoing pulmonary metastasectomy for colorectal cancer†

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Abstract

OBJECTIVES: Pulmonary metastasectomy (PM) has evolved to become a standard treatment for colorectal cancer lung metastases. However, biomarkers to estimate the prognosis after PM are currently missing. We therefore investigated the prognostic impact of inflammatory-related biomarkers and scores in patients undergoing curative PM for colorectal cancer.

METHODS: We analysed prospectively collected datasets of 52 patients treated in our institution between April 2009 and June 2014. Fibrinogen (cut-off 325 mg/dl), C-reactive protein (CRP, cut-off 0.5 mg/dl), the modified Glasgow prognostic score (mGPS) and the neutrophil-to-lymphocyte ratio (NLR) at the time of PM were tested for their prognostic power, and correlated to time to recurrence (TTR), time to lung-specific recurrence (TTLR) and overall survival (OS).

RESULTS: Median OS after PM of all patients (n = 52, 21 females, 31 males, mean age ± standard deviation: 62.65 ± 11.41 years) was 36 months [95% confidence interval (CI) 24.7–47.3 months, number of events: n = 20/38.5%]. In univariable survival analyses, high fibrinogen [hazard ratio (HR) 5.51, 95% CI 1.21–25.17], elevated CRP (HR 2.81, 95% CI 1.08–7.28), mGPS >0 (HR 2.81, 95% CI 1.08–7.28) and an NLR of 4 or higher (HR 3.05, 95% CI 1.02–9.13) was associated with poor OS. Median TTR was 15 months for all patients (number of events: n = 35/67.3%). Fibrinogen (HR 3.79, 95% CI 1.32–10.94) and NLR (HR 2.99, 95% CI 1.20–7.46) but not CRP (P = 0.102) and mGPS (P = 0.102) were found to indicate TTR. With regard to TTLR (number of events: n = 26/50%), only NLR predicted early lung recurrence (HR 3.02, 95% CI 1.06–8.564). After multivariable analyses, fibrinogen was the only significant OS predictor. However, all investigated inflammatory biomarkers and scores were prognostic for TTR in multivariable analyses. Finally, we divided the study population into an inflammatory phenotype (one or more inflammatory marker/score-elevated) and a non-inflammatory phenotype group. The inflammatory phenotype was prognostic in uni- and multivariable analyses for all three outcome parameters (OS, TTR and TTLR).

CONCLUSIONS: Inflammatory markers provided promising prognostic information in this cohort of curative PM patients after colorectal cancer. Further validation is needed to verify the prognostic role of these markers and establish them in clinical routine.

Keywords: Pulmonary metastasectomy • Biomarker • Prognostic • Fibrinogen • C-reactive protein • Neutrophil-to-lymphocyte ratio • Modified Glasgow prognostic score

INTRODUCTION

Pulmonary metastasectomy (PM) is nowadays a standard treatment for selected patients suffering from metastatic disease to the lungs. However, the number of prognostic biomarkers for patients undergoing PM lags far behind when compared with the corresponding primary malignancies. Currently, there are no recommended biomarkers for daily clinical routine in patients undergoing curative resection of pulmonary metastases regardless of their oncological origin [1].

Colorectal cancer (CRC) is the most common malignancy in non-smokers worldwide, in both males and females. Systemic recurrence of the disease is the main reason for CRC-associated mortality since approximately half of all patients develop metastases after resection of the primary tumour. The rate of patients developing metastases restricted to the lungs is estimated at 8% [2].
Various inflammation-related blood-derived biomarkers have been investigated for their prognostic impact in primary CRC. These biomarker studies mainly focused on acute phase response proteins. Fibrinogen is characterized by its significant increase in plasma concentrations in response to proinflammatory cytokines. Besides this acute phase response, fibrinogen plays a central role in the blood coagulation cascade and during wound healing [3]. In tumours, it stimulates tumour-associated neoangiogenesis, and thus directly promotes tumour progression. In patients suffering from primary CRC treated surgically, high-fibrinogen levels were found to be of prognostic value. Furthermore, an association of elevated plasma fibrinogen levels and distant metastases after resection was reported by Tang et al. [3–5]. The role of fibrinogen in the setting of curative PM is currently completely unknown.

C-reactive protein (CRP) is another important acute phase protein. CRP was reported to be of prognostic value in various malignancies including non-small-cell lung cancer and malignant pleural mesothelioma [6, 7]. With regard to primary CRC, a prognostic role of CRP has been described in patients undergoing curative resection [8]. The modified Glasgow prognostic score (mGPS) which is an inflammatory-related score that combines CRP (a positive acute phase response protein) and albumin (a negative acute phase response protein) also showed considerable prognostic power in primary CRC patients [9].

A high concentration of neutrophils is known to promote tumour progression, and it can suppress the antitumour effect of lymphocytes [10]. Thus, an imbalance of neutrophils and lymphocytes in peripheral blood can be associated with tumour development. The prognostic role of neutrophil-to-lymphocyte ratio (NLR) has been recently highlighted in a meta-analysis published by Jenkins and colleagues [11]. Again, data on NLR as prognosticator after PM for CRC are currently missing.

The aim of this study was to elucidate the impact of inflammatory-related markers in patients undergoing PM for CRC metastases. We therefore analysed preoperative levels of fibrinogen, CRP, the mGPS and NLR in a prospectively followed cohort of patients, and correlated them with clinical outcome parameters.

PATIENTS AND METHODS

Patients

A total of 52 consecutive patients, who underwent curative PM for CRC between April 2009 and June 2014 at the Department of Thoracic Surgery, Medical University of Vienna, were prospectively included in our institutional data base. All patients received their first PM (no re-metastasectomies). Inclusion criteria for PM were resectability of all pulmonary nodules, absence of any extra-pulmonary spreading, a controlled primary tumour site and an adequate functional status. Singular sub-pleural metastases were treated by a video-assisted thoracic surgical approach. All other patients underwent a muscle-sparing anterior or posterior thoracotomy to perform a bimanual palpation of the lung. Complete resection—defined by pathological report and intraoperative findings—was achieved in all patients. A total of 41 patients (78.8%) had received chemotherapy before metastasectomy, 38 patients (73.1%) underwent adjuvant chemotherapy after PM (5-fluorouracil/oxaliplatin ± bevacizumab). Patients were followed-up with a computed tomography (CT) scan every 3 months within the first year after PM. If no recurrence was detected within the first 12 months, follow-up intervals were prolonged to biannual controls. No patient was lost to follow-up. Overall survival (OS) was calculated as time from PM to date of last follow-up in patients alive or to date of death in all deceased patients. Time to recurrence (TTR) was defined as the time from PM to tumour recurrence irrespective of the recurrence site. Time to lung-specific recurrence (TTLR) was calculated from the time of PM to pulmonary recurrence of the disease identified by chest CT scan during prospective follow-up. Inflammatory parameters and scores were evaluated/calculated in a retrospective way using our prospectively followed patient cohort.

The study was approved by the Ethics Committee of the Medical University of Vienna (EK-No.: 1044/2012), and was conducted according to the Helsinki Declaration and the guidelines for good scientific practice of the Medical University of Vienna.

Measurement of fibrinogen and C-reactive protein levels

Fibrinogen and CRP were measured during routine preoperative work-up one day before PM (day of hospital admission) in order to rule out any unspecific alteration due to the surgical procedure. Blood samples were derived from peripheral venous punctures, and fibrinogen levels were measured according to the Claus method [3]. Serum CRP levels were measured using a modified latex-enhanced immunoturbidimetric assay (Olympus Life and Material Science Europe) as previously published [6]. Fibrinogen and CRP values were available in 51 patients (98% of the study population). In one patient fibrinogen and in another patient CRP levels were not available in the medical records, respectively (Supplementary material, Fig. S1). We used a cut-off value of 325 mg/dl to dichotomize the patients into high- and low-fibrinogen groups as previously reported by Son et al. [5]. The cut-off used at our clinic (0.5 mg/dl) was utilized to dichotomize patients into an elevated CRP and a normal CRP group.

The modified Glasgow prognostic score

The mGPS was calculated as previously published [9]: patients with normal CRP (<0.5 mg/dl) and normal albumin (≥35 g/l) were allocated to mGPS 0, patients with either heightened CRP (>0.5 mg/dl) or low albumin (<35 g/l) were allocated to the mGPS 1 group and patients with both, high CRP and low albumin were allocated to the mGPS 2 group. mGPS was available in 51 patients (98% of the study population). As in 1 patient, CRP was not available mGPS could not be calculated.

The neutrophil-to-lymphocyte ratio

The NLR was calculated by dividing the neutrophil count by the lymphocyte count. Both the neutrophil and the lymphocyte counts were measured at the time of admission to the hospital before surgery or any other invasive diagnostic or therapeutic interventions. A cut-off of 4 was used for NLR as previously published [11]. NLR was available in 47 patients (90% of the study population). In 5 patients, the neutrophil and/or lymphocyte count was missing in the medical records, and accordingly, NLR could not be calculated in these patients.

The inflammatory phenotype

The inflammatory phenotype was calculated as follows: patients with no elevated inflammatory markers (fibrinogen and CRP) and
scores (mGPS and NLR) were allocated to the non-inflammatory phenotype group (n = 36). All patients with one or more elevated inflammatory markers and/or score were allocated to the inflammatory phenotype group resulting in 10 inflammatory phenotype patients. In 6 patients, the inflammatory phenotype could not be estimated because of missing values (in 1 patient the NLR and CRP was missing, in 1 patient fibrinogen was missing and in 4 patients the NLR could not be calculated, Supplementary material, Fig. S1).

**Statistical analysis**

The association of all analysed inflammatory-related biomarkers (fibrinogen, CRP, mGPS and NLR) with important categorical baseline patients’ characteristics (gender, early versus late pulmonary metastases, chemotherapy before and after PM, number of nodules and liver metastases before PM) was evaluated using the two-sided \( \chi^2 \) test. One-way ANOVA (for mGPS) and unpaired \( t \)-test (for fibrinogen, CRP and NLR) was used to compare markers with patients’ baseline characteristics. The Kaplan–Meier method was used for survival estimation, and the log-rank test was performed to investigate univariable impact on OS, TTR and TTLR. The Cox regression model was used for univariable and multivariable survival analyses. For the multivariable Cox regression analyses, the following clinical baseline characteristics were included: gender (dichotomized as male versus female), age (as continuous characteristic), number of nodules at the time of PM (dichotomized as singular versus multiple pulmonary nodules) and type of pulmonary metastases (early versus late pulmonary metastases after primary tumour diagnosis). \( P \)-values <0.05 were considered statistically significant. Statistical analyses were performed using the PASW Statistics 18.0 package (Predictive Analytics Software, SPSS, Inc., Chicago, IL, USA).

**RESULTS**

**General characteristics**

This prospective study cohort (n = 52, 21 females, 31 males, mean age ± standard deviation: 62.7 ± 11.4 years) consisted of 28 (53.8%) male patients. In 31 patients (59.6%), lymph node metastases (N1 and N2) were present at the time of resection of the primary tumour. Accordingly, the majority of our patients (n = 43, 82.7%) were in Stage III or IV at the time of diagnosis. Sixteen patients (30.8%) had liver metastases, which were resected prior to PM; 41 patients (78.8%) had already received chemotherapy before PM. Median time from primary CRC resection to PM was 28 months [(95% confidence interval (CI) 22.9–33.0 months)]. Thus, 27 patients (51.9%) were grouped into ‘early pulmonary spreading’ (<28 months) and 25 (48.1%) into ‘late pulmonary spreading’ (>28 months). A total of 34 (65.4%) patients were suffering from singular pulmonary nodules at the time of PM opposed to 18 (34.6%) patients with multiple nodules. Resection was complete for all 52 patients (100%). Four of the 52 patients suffered from mild/moderate postoperative complications. In 1 patient, a subcutaneous postoperative bleeding occurred, 2 patients experienced a prolonged postoperative air leak (>5 days) and 1 patient had wound healing problems.

**Inflammatory-related markers and scores in colorectal cancer metastasectomy patients**

Mean fibrinogen level of all patients prior to PM was 407.37 (±109.69) mg/dl. Forty patients (78.4%) had a fibrinogen higher than 325 mg/dl [5]. In 19 patients (37.3%), pre-metastasectomy CRP level was above the cut-off of 0.5 mg/dl. Mean CRP of all analysed patients was 0.87 (±1.65) mg/dl. Only 2 patients (3.9%) suffered from hypoalbuminaemia (albumin <35 g/l), and had elevated CRP values at the same time. Thus, 32 patients (62.7%) were allocated to mGPS 0, 17 patients (33.3%) to mGPS 1 and 2 patients (3.9%) to mGPS 2. Inflammatory parameters and inflammatory scores grouped by patients’ clinical characteristics are given in Table 1. Interestingly, female patients were more likely to have CRP levels below the cut-off when compared with male patients (\( P = 0.024 \)). Accordingly, there was a statistical trend for female patients to have lower mGPS than male patients (\( P = 0.065 \)). In contrast to these findings, the NLR was significantly lower in female patients to have lower mGPS than male patients (3.9%) to mGPS 2. Inflammatory-related markers and scores grouped by patients’ clinical characteristics are given in Table 1. Interestingly, female patients were more likely to have CRP levels below the cut-off when compared with male patients (\( P = 0.024 \)). Accordingly, there was a statistical trend for female patients to have lower mGPS than male patients (\( P = 0.065 \)). In contrast to these findings, the NLR was significantly lower in female patients to have lower mGPS than male patients (3.9%) to mGPS 2.

<table>
<thead>
<tr>
<th>Table 1: Patients’ characteristics and inflammatory markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (n)</strong></td>
</tr>
<tr>
<td><strong>Fibrinogen</strong></td>
</tr>
<tr>
<td>&lt;325 mg/dl</td>
</tr>
<tr>
<td>≥325 mg/dl</td>
</tr>
<tr>
<td>CRP</td>
</tr>
<tr>
<td>≥0.5 mg/dl</td>
</tr>
<tr>
<td>mGPS</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>NLR</td>
</tr>
<tr>
<td>≥4</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; mGPS: modified Glasgow Prognostic score; NLR: neutrophil-to-lymphocyte ratio; n: number of patients.
higher in female patients \((P = 0.024)\). Patients with low NLR were significantly younger than patients with high NLR \((P = 0.001)\).

**Impact of clinical factors on prognosis after pulmonary metastasectomy**

The prognostic impact of clinical characteristics on OS, TTR and TTLR is reported in Table 2. Median OS after PM was 36 months \((95\% \text{ CI} 24.7–47.3\text{ months}, \text{ number of events: } n = 20/38.5\%)\), median TTR was 15 months \((95\% \text{ CI} 11.3–18.7\text{ months number of events: } n = 35/67.3\%)\) and median TTLR for all analysed patients was 21 months \((95\% \text{ CI} 12.7–29.3\text{ months number of events: } n = 26/50\%)\). None of the baseline characteristics including gender, age, type of pulmonary metastasis (early versus late), time from primary tumour to PM (as continuous characteristic), chemotherapy before and after PM, number of pulmonary metastases (singular versus multiple pulmonary metastases) and liver metastases prior to PM influenced OS, TTR and TTLR in our patient cohort.

**Inflammatory markers/scores and outcome parameters**

In a further set of analyses, we evaluated the prognostic impact of inflammatory-related biomarkers and scores on outcome after PM for CRC (Table 3). All investigated inflammatory parameters were found to influence OS in patients undergoing curative PM for CRC. With regard to TTR, only fibrinogen and the NLR but not CRP and mGPS indicated early tumour recurrence after PM as shown in Fig. 1. When evaluating TTLR, only NLR was prognostic in univariable survival analyses.

**Inflammatory markers and scores and their independent prognostic impact after multivariable analyses**

We evaluated the independent prognostic role of inflammatory-related biomarkers for OS, TTR and TTLR. We therefore utilized a multivariable Cox regression model including known clinical prognostic factors e.g. gender (male versus female), age (as continuous characteristic), number of nodules at the time of PM (singular versus multiple) and type of pulmonary metastases (early versus late pulmonary metastases). Only fibrinogen proved to be an independent OS predictor, whereas CRP, the NLR and the mGPS failed to reach statistical significance (Table 4). With regard to TTR, all markers proved to significantly indicate early recurrence independent of age, gender, number of nodules and type of metastases (early versus late pulmonary metastases). However, every tested marker failed to indicate early lung-specific recurrence (TTLR).

**Inflammatory phenotype influences overall survival, disease-free survival and time to lung recurrence**

Since inflammatory-related biomarkers predicted outcome after PM in CRC patients, we summarized all markers and scores, and defined an inflammatory and a non-inflammatory phenotype. Patients with either elevated CRP, high fibrinogen or an elevated inflammatory score (NLR, mGPS) were allocated to the inflammatory phenotype group \((n = 36)\), and patients without any signs of systemic inflammation were allocated to the non-inflammatory phenotype group \((n = 10)\). The inflammatory phenotype...
phenotype group had significantly worse OS [hazard ratio (HR) 4.81, 95% CI 1.06–21.73, \(P = 0.041\)], shorter TTR (HR 6.20, 95% CI 1.83–21.02, \(P = 0.003\)) and decreased TTLR (HR 3.21, 95% CI 1.37–7.49, \(P = 0.007\)) as also illustrated in Fig. 2. In multivariable survival analyses, the inflammatory phenotype proved to indicate poor OS (HR 9.03, 95% CI 1.51–54.06, \(P = 0.016\)), short TTR (HR 7.01, 95% CI 1.98–24.79, \(P = 0.003\)) and worse TTLR (HR 4.10, 95% CI 1.62–10.40, \(P = 0.003\)) independent from age.

### Table 3: Univariable analyses: prognostic impact of inflammatory markers and scores

<table>
<thead>
<tr>
<th>Univariable survival analyses</th>
<th>Overall survival</th>
<th>Time to recurrence</th>
<th>Time to pulmonary recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (CI)</td>
<td>(P)-value</td>
<td>HR (CI)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metric</td>
<td>1.005 (1.001–1.008)</td>
<td>0.012</td>
<td>1.003 (1.000–1.005)</td>
</tr>
<tr>
<td>&lt;325 mg/dl</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>≥325 mg/dl</td>
<td>5.512 (1.207–25.172)</td>
<td>0.028</td>
<td>3.794 (1.315–10.943)</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metric</td>
<td>1.290 (1.039–1.601)</td>
<td>0.017</td>
<td>1.126 (0.959–1.322)</td>
</tr>
<tr>
<td>&lt;0.5 mg/dl</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>≥0.5 mg/dl</td>
<td>2.806 (1.082–7.277)</td>
<td>0.034</td>
<td>1.816 (0.889–3.709)</td>
</tr>
<tr>
<td>mGPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2.682 (1.009–7.124)</td>
<td>0.048</td>
<td>2.233 (1.057–4.675)</td>
</tr>
<tr>
<td>2</td>
<td>5.070 (0.578–44.447)</td>
<td>0.143</td>
<td>0.604 (0.081–4.523)</td>
</tr>
<tr>
<td>0 + 2</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1 + ≥2</td>
<td>2.806 (1.082–7.277)</td>
<td>0.034</td>
<td>1.816 (0.889–3.709)</td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>≥4</td>
<td>3.045 (1.016–9.128)</td>
<td>0.047</td>
<td>2.994 (1.202–7.461)</td>
</tr>
</tbody>
</table>

HR: hazard ratio; CI: confidence interval; CRP: C-reactive protein; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio.

Figure 1: Differences in TTR after PM according to the investigated inflammatory parameters. As shown in (A) and (D), fibrinogen and the NLR were predicting early recurrence after PM, whereas CRP and mGPS had no impact on TTR (B and C). TTR: time to tumour recurrence; PM: pulmonary metastasectomy; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; mGPS: modified Glasgow prognostic score.
(continuous), gender (female versus male), number of nodules (singular versus multiple) and type of pulmonary metastases (early versus late).

**DISCUSSION**

In this study, we were able to show for the first time that inflammatory-related markers and scores including fibrinogen, CRP, mGPS and NLR provided prognostic information in patients undergoing curative PM after CRC. Although PM is nowadays a standard procedure in the treatment of pulmonary spreading of CRC, there is a considerable lack of evidence [12]. The decision if PM should be offered to a patient is still based on clinical prognostic factors, which have been proposed in the late 1970s (e.g. number of metastases, tumour-doubling time) and have recently been challenged. Lately, much effort has been made to find genetic and biological markers in order to characterize tumour

**Table 4: Multivariable analyses: prognostic impact of inflammatory markers and scores**

<table>
<thead>
<tr>
<th>Markers</th>
<th>P-value</th>
<th>Time to recurrence (CI)</th>
<th>P-value</th>
<th>Time to pulmonary recurrence (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;325 mg/dl</td>
<td>0.011</td>
<td>4.923 (1.631–14.857)</td>
<td>0.005</td>
<td>3.404 (0.587–19.719)</td>
<td>0.172</td>
</tr>
<tr>
<td>≥325 mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5 mg/dl</td>
<td>0.052</td>
<td>3.403 (1.329–8.715)</td>
<td>0.011</td>
<td>3.427 (0.650–18.063)</td>
<td>0.146</td>
</tr>
<tr>
<td>≥0.5 mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.065</td>
<td>3.813 (1.492–9.741)</td>
<td>0.005</td>
<td>3.614 (0.703–18.580)</td>
<td>0.124</td>
</tr>
<tr>
<td>1</td>
<td>0.111</td>
<td>1.220 (0.139–10.705)</td>
<td>0.858</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NLR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>0.106</td>
<td>5.099 (1.608–16.169)</td>
<td>0.006</td>
<td>3.618 (0.619–21.168)</td>
<td>0.154</td>
</tr>
<tr>
<td>≥4</td>
<td></td>
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</table>

HR: hazard ratio; CI: confidence interval; CRP: C-reactive protein; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio.

**Figure 2**: The prognostic impact of the inflammatory status (reflecting fibrinogen, C-reactive protein, the modified Glasgow prognostic score and the neutrophil to lymphocyte ratio) on overall survival (A), time to recurrence (B) and time to lung recurrence (C).
aggressiveness [1, 13, 14]. However, many of these studies are based on retrospective analyses limited by a long observation period, changes of diagnostic tools and surgical techniques as well as available chemotherapeutic regimes. The basis of this study is a well-defined prospectively followed up patient cohort with a complete follow-up for all included patients. This allowed us to evaluate different inflammatory markers/scores and correlate them to clinical outcome parameters and patients’ baseline characteristics.

Inflammatory-related biomarkers were found to be prognostic in a number of malignancies, including malignant thoracic diseases e.g. lung cancer and malignant pleural mesothelioma but also extrathoracic tumours like primary CRC [3, 6–9]. Furthermore, persistence of a high NLR after systemic therapy was reported to correlate to poor chemotherapy response in CRC [15]. Thus, an activated systemic immune response seems to be associated with an aggressive and treatment-resistant biological cancer phenotype translating into poor overall and disease-free survival. The exact biological background of these findings still remains elusive. However, tumour cells are known to produce inflammatory cytokines as autocrine growth signals. Furthermore, an activated immune response and its signals promote angiogenesis, and thus might also contribute to malignant progression [15]. Besides the prognostic value of inflammatory biomarkers in cancer patients in general, an activated systemic immune response was reported to impact patients’ performance status, and was associated with tumour cachexia [16]. Of note, monoclonal antibody therapy against interleukin 6—the major initiator of CRP and fibrinogen expression in the liver—led to reduced CRP levels and improved cancer cachexia in various malignancies [17].

In our study cohort, preoperative CRP levels were elevated more frequently in the male population when compared with females. On the other hand, NLR was higher in the female population. These findings indicate that gender might have an influence on the distribution of inflammatory-related biomarkers in metastatic CRC patients. Furthermore, patients with low NLR were significantly younger than patients with high NLR (P = 0.001). This might be explained not only by the physiological senescence of the immune system during the process of ageing but also by alterations of the immune response by other, non-cancer-specific comorbidities in the elderly as discussed by Rembach et al. [18].

Patients with multiple pulmonary nodules had statistically lower levels of CRP when compared with patients with a singular metastasis. This finding was surprising, since tumours with multiple pulmonary spreading were traditionally considered more aggressive and associated with decreased survival rates [19]. In our cohort, the number of pulmonary metastases did not show prognostic impact. This observation is in line with reported series from Japan, showing that the number of metastatic nodules is not a negative prognostic factor in PM for CRC as long as complete resection of all nodules can be achieved [20–23]. However, it has to be pointed out that the number of patients evaluated in this study is relatively small, especially when subdividing the cohort into different subgroups. Therefore, our study might be statistically underpowered to detect and recapitulate the prognostic impact of already published baseline clinical characteristics including the number of nodules [24].

Another drawback of this study is that the measurement of inflammatory markers is limited to a single time point—preoperatively before PM. Since this is a retrospective analysis, data on inflammatory markers after resection of the primary tumour, adjuvant chemotherapy regimens or changes of these markers during the post-PM follow-up period were only sparsely available. This study also lacks a control group of patients with comparable clinical baseline characteristics, who were treated by chemotherapy instead of undergoing PM. These questions remain to be clarified by future studies.

One cornerstone of PM with curative intent is the ‘cascade spread hypothesis’. Metastatic disease first appears in a single organ or tissue compound followed by a generalized, disseminated metastatic spreading. Interrupting this cascade of tumour spreading by removing the first site of metastasis therefore would be a potentially curative treatment.

The concept, however, has recently been challenged by the observation that certain tumour phenotypes/genotypes are characterized by a lung-specific recurrence pattern. Lung metastases carrying a KRAS mutation are associated with an early recurrence to the lungs [25]. We therefore decided to use TTR as well as TTLR as end-points in our study. Interestingly, an inflammatory phenotype seemed to be associated with a decreased TTR. On the other hand, inflammatory markers had only little impact on lung-specific recurrence (TTLR).

A better knowledge on prognostic factors in PM from CRC could have a strong impact on the practice of PM. It is generally agreed that the identification of patients who will benefit from PM is difficult. Risk factors indicating early tumour recurrence might help the surgeon to weigh a local surgical approach against a systemic chemotherapeutic regimen. In addition to that, information on the aggressiveness of a tumour might change the post-metastasectomy patient care. It could be sufficient for ‘low-malignant’ tumours to follow a surveillance-only strategy whereas aggressive tumours should be treated by a pseudo-adjuvant chemotherapy.

The inflammatory markers/scores evaluated here have several advantages over previously published prognostic parameters. Their measurement is non-invasive, and can be performed without the need of tumour tissue. Tests are widely available and relatively cheap, and can be easily embedded in the preoperative routine work-up. This study was limited by the relative small number of patients, and by its single-centre nature. However, it gives first evidence that—similar to primary colorectal cancer [9]—a proinflammatory patient status, reflected by high fibrinogen, elevated CRP and high inflammatory scores (mGPS, NLR), is a negative prognostic factor in patients undergoing curative PM for CRC. Further validation studies with larger patient cohorts in a multicentre setting are warranted to verify our findings.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

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