RLC score (R status, lymphovascular invasion, C-reactive protein) predicts survival following radical cystectomy for muscle-invasive bladder cancer

Der RLC-Score (R-Status, Lymphgefäßinfiltration, CRP) zur Vorhersage des Gesamtüberlebens bei Patienten mit muskel-invasivem Harnblasenkarzinom nach radikaler Zystektomie

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SCHRÄGTEXT

ZUSAMMENFASSUNG

Background CRP-based scoring systems were found to correlate with survival in patients with urooncologic diseases. Our retrospective single-centre study aimed to confirm CRP as a prognostic parameter in patients with bladder cancer (BCa) undergoing radical cystectomy (RC) and, based on the findings, to develop our own outcome score for muscle-invasive bladder cancer (MIBC) patients undergoing RC in order to identify patients with a high risk of mortality.

Material and methods A total of 254 patients who underwent RC at Hanover Medical School between 1996 and 2007 were reviewed with a follow-up until autumn 2013. The clinicopathologic parameters assessed included age, co-morbidities, pre-/postoperative serum levels of CRP, leukocytes, haemoglobin, creatinine, urinary diversion, tumour grading, staging, lymph node status, lymph node density (LND), lymphovascular invasion (LVI), metastases, and resection margin status. The Chi-square test was used for univariate analyses. Kaplan-Meier estimates and the log-rank test were used for survival analyses. Regarding outcome, overall survival (OS) was assessed.

Results The multivariate analysis excluding lymph node (LN)-positive and metastatic patients at time of RC showed a significant association of R status (R; p < 0.001), LVI (L; p = 0.021) and preoperative CRP level > 5 mg/l (C; p = 0.008) with OS. Based on these parameters, the RLC score was developed. The median OS in the intermediate, high-risk and very high-risk groups according to the RLC score was 62, 22, and 6.5 months, respectively. The score had a high predictive accuracy of 0.752.

Conclusion The RLC score identifies BCa patients at a higher risk of overall mortality after RC. Overall, our study supports the role of CRP in prognostic score models for BCa.

ZUSAMMENFASSUNG

Hintergrund In der Vergangenheit konnte für CRP basierte Klassifizierungssysteme bereits eine Korrelation mit dem Überleben bei Patienten mit uroonkologischer Erkrankung nachgewiesen werden. Unsere retrospektive, unizen-
trische Studie zielte darauf ab, CRP als prognostischen Parameter für Patienten mit Harnblasenkarzinom (BCa), die sich einer radikalen Zystektomie (RC) unterzogen, zu bestätigen und basierend auf diesen Beobachtungen ein eigenes Klassifizierungssystem für muskelinvasive Harnblasenkarzinome zu entwickeln, welches Patienten mit einem hohen Mortalitätsrisiko sicher identifizieren kann.

**Material and Methods**

Insgesamt wurden Daten von 254 Patienten der Medizinischen Hochschule Hannover, die sich zwischen 1996 und 2007 einer RC unterzogen und bis Herbst 2013 nachbeobachtet wurden, ausgewertet. Die ausgewerteten klinisch-pathologischen Parameter umfassten u. a. das Alter, Komorbiditäten, prä- und postoperative CRP-Spiegel, Tumorgrading und -staging, Lymphknotenstatus, die lymphovaskuläre Infiltration (LVI) sowie Metastasenstatus und Resektionsränder (R-Status). Univariate Analysen wurden mittels Chi-Quadrat-Test durchgeführt. Ausgewertet wurde das Gesamtüberleben (OS).

**Ergebnisse**

Die multivariate Analyse unter Ausschluss Lymphknoten positiver und metastasierter Patienten ergab eine signifikante Korrelation von R-Status (R; p < 0,001), LVI (L; p = 0,021) und praoperativ eleviertem CRP-Spiegel > 5 mg/l (C; p = 0,008) mit dem OS. Das mediane OS in den RLC-Riskogruppen betrug 62 Monate in der mittleren Riskogruppe, 22 Monate in der Hochrisikogruppe und 6,5 Monate in der Gruppe mit sehr hohem Risiko. Der Score hatte eine hohe Vorhersagengenauigkeit von 0,752.

**Schlussfolgerung**

Der RLC-Score identifiziert BCa-Patienten nach RC mit einem höheren Risiko für eine erhöhte Mortalität. Insgesamt stützen unsere Daten die Rolle von CRP in prognostischen Vorhersagemodellen beim BCa.

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**ABBREVIATIONS**

| Abbreviation | Description |
|--------------|-------------|
| TNR-C        | tumor stage, lymph node density, resection margin status, and serum CRP |
| CSS          | cancer specific survival (CSS) |
| BCa          | bladder cancer |
| RC           | radical cystectomy |
| MIBC         | muscle-invasive bladder cancer |
| OS           | overall survival |
| LN           | lymph node |
| NMIBC        | non-muscle invasive BCa |
| EORTC        | European Organisation for Research and Treatment of Cancer |
| CIS          | carcinoma in situ |
| MHH          | Hanover Medical School |
| UCC          | urothelial carcinoma |
| LND          | lymph node density |
| AUC          | area under the curve |
| ROC          | Receiver Operating Characteristics |
| UTUC         | upper tract urothelial carcinoma |

**Introduction**

Bladder cancer (BCa) is estimated to be among the 10 leading cancer types regarding new cases (62,380) and deaths (12,520) among males in the United States in 2018, thus representing a frequent and lethal disease [1]. Current 5-year survival rates for BCa average 70% for localized disease, 35% for regional disease, and 5% for distant disease [1]. Approximately three-quarters of the newly diagnosed BCa patients present with non-muscle invasive BCa (NMIBC) [2]. As of now, the EORTC (European Organisation for Research and Treatment of Cancer) BCa risk calculator is the only routinely used score for outcome prediction. Within this score, parameters such as grading, tumor size, concomitant carcinoma in situ (CIS), T-stage, the number of tumors, and prior recurrence rate are used to predict the recurrence and progression of NMIBC Ta/T1 tumors [2, 3]. There are currently no clinically established score systems for outcome prediction in patients with locally advanced or metastasized BCa.

In 2011, Gakis et al. pointed out the prognostic potential of serum CRP (C-reactive protein level) for BCa patients [4]. The authors proposed the TNR-C score for the prediction of cancer-specific survival (CSS) for BCa patients undergoing radical cystectomy (RC), which was a new outcome prediction model including the variables tumor stage (T), lymph node density (N), resection margin status (R), and preoperative serum CRP level (C) [4].

CRP represents an acute-phase protein and indicates systemic inflammation. Currently discussed hypotheses for elevated CRP levels in cancer patients are CRP secretion by the tumor itself, which makes CRP intriguing as a tumor burden marker, and physiological CRP production by hepatocytes initiated by tumor-released cytokines [5, 6].

The primary aims of this retrospective single center study were to confirm CRP as a prognostic parameter in patients with BCa undergoing RC, and based on the findings, to develop our own outcome score for muscle-invasive bladder cancer (MIBC) patients undergoing RC that can identify patients with a high mortality risk.

**Material and Methods**

In the present retrospective study, 254 patients who underwent RC at the Department of Urology of Hanover Medical School (MHH) between 1996 and 2007 were reviewed with a follow-up till autumn 2013. The histological assessment was performed in the pathology department of MHH and was based on the TNM classification approved by the American Joint Cancer Committee. Positive surgical margins were defined as the microscopic presence of malignant cells at the resection margins. The clinicopathologic parameters assessed were: age, gender, pre-/postoperative serum CRP, pre-/postoperative leukocytes and hemoglobin, pre-/postoperative serum creatinine.
urinary diversion, WHO tumour grading (G1/G2/G3), tumor staging (T1-T4), lymph node (LN) status, lymph node density (LND), lymphovascular invasion, vascular invasion, tumor necrosis, concomitant CIS, the number of tumors, synchronous/mетachronous metastases, and the resection margin status. No systematic elevation of performance status was performed, but every patient was declared fit for RC. The CRP cut-off was set at >5 mg/L. The cut-off values for hemoglobin were set at 14–18 g/dl for men and 12–16 g/dl for women. For the creatinine levels, we defined cut-offs from 85 to 104 µmol/L [7]. All these cutoffs were defined following German standards for laboratory diagnostics. The clinical outcome was measured from the date of RC to date of death or date of last follow-up. Twenty-five patients were excluded due to histologically confirmed malignancies other than urothelial carcinoma (UC). During preoperative standard assessment for RC patients were checked for signs of infection by urine testing, physical and ultrasound examination, demonstration of CT or MRI scans, level of leucocytes, elevation of body temperature.

For development of our scoring system from the remaining 229 patients, 74 patients were additionally excluded due to synchronous metastases, suspected other reasons for CRP elevation (e.g. urosepsis or other cancer entities) and radiologically node-positive status at the time of RC because these groups bear a high progression risk. Patients receiving neoadjuvant, adjuvant or palliative chemotherapy after developing metastatic disease during follow-up had been included as long as there weren’t any signs of synchronous metastatic disease or radiologically node-positive status at time of RC. The remaining cohort of 155 patients was named the “development cohort”. The RLC score is based on a multivariate analysis and on previous work by limura et al [8]. By using cox regression [9], we developed a risk stratified model for patients with negative LN and no sign of synchronous metastasis after RC based on the significant parameters associated with survival in multivariate analysis – the RLC score. Patients with positive resection margins received 3 points due to the observed hazard ratio (HR 5.151). Patients with preoperatively elevated CRP ≥5 mg/L received 1 point (HR 1.670), and patients with lymphatic vessel invasion also received 1 point (HR 1.729). Taking the the 5-year OS rates into account we defined 3 risk groups. The intermediate risk group (group 1, n=134) was defined as 0–1 points, the high risk group (group 2, n=13) as 2–3 points, and the very high risk group (group 3, n=8) as 4–5 points. Equivalent to Gakis et al., we analysed the parameters T stage, LND, R-status, and preoperative CRP-level via multivariate analyses. We chose OS as the outcome parameter for multivariate analyses.

The Chi-square test was used for univariate analyses. Kaplan-Meier estimates and the log-rank test were used for survival analyses. Statistical analyses were performed with IBM SPSS Statistics version 21 and 22. The significance level was set as α = 5%, thus p-values < 0.05 were considered statistically significant. Approval of the Ethics Committee of Hanover Medical School was obtained for this study (vote nr. 2044–2014).

Results

Descriptive statistics

The majority of the development cohort (n = 155) was male (78.1%). Their median age at the time of RC was 65.9 years (CI 64.6–67.2); the women were 2.5 years older on average (CI 65.5–71.3). Adjuvant chemotherapy was administered in 2.6% of cases. A total of 54.8% of the patients received an ileum conduit, 28.4% received an orthotopic bladder substitution, 11.6% a ureterosigmoidostomy (Mainz-II-pouch), and 2.6% an ileocecal pouch (Mainz-I-pouch) as urinary diversions. The prevalence of tumor stages was 1.3% for pT0, 6.5% for pTa and pTis, 15.5% for pT1, 34.8% for pT2, 27.7% for pT3, and 7.7% for pT4. Another 23.9% developed metachronous distant metastases. ▶Table 1 and ▶Table 2 describe the patient and tumor characteristics of the development cohort.

| ▶Table 1 Patient characteristics of development cohort (n = 155) |
| Parameters | |
| Age (median; in years) | 95% CI |
| *Male* | 65.9 | 64.6–67.2 |
| *Female* | 68.4 | 65.5–71.3 |
| Gender (n) | |
| *Male* | 121 (78.1%) |
| *Female* | 34 (21.9%) |
| Urinary diversion | |
| Neobladder | 44 (28.4%) |
| Ileumconduit | 85 (54.8%) |
| Mainz-I-pouch | 4 (2.6%) |
| Mainz-II-pouch | 18 (11.6%) |
| None (nephrectomy) | 4 (2.6%) |
| Chemotherapy | |
| none | 137 (88.4%) |
| adjuvant | 4 (2.6%) |
| neoadjuvant | 0 (0%) |
| palliative | 14 (9%) |
| Radiotherapy | |
| adjuvant | 7 (4.5%) |
| Overall survival (mean, months) | p = 0.17 |
| ≤65 years of age | 95.9 |
| >65 years of age | 68.7 |
| Sex | p = 0.72 |
| Male | 81.3 |
| Female | 76.5 |

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Associations with elevated CRP levels

Based on the previous work of other groups [4, 10], the cut-off for preoperatively evaluated CRP levels was set at 5 mg/L following German standards for laboratory diagnostics. Overall, an elevated preoperative CRP level was found in 49.8% of all cases. Leukocytosis of > 10,000/µL was found in 28.8% of all cases.

Table 3 illustrates the preoperative CRP values in relation to T stage, LN status, and R-status. Thirteen patients (5.7%) had to be excluded due to missing CRP. The association of preoperative elevated CRP levels with the overall T stage (NMIBC vs MIBC) showed no statistical significance (p = 0.582), although the subgroup analysis of MIBC alone (pT2 11.6 % vs pT3–4 31 %) showed a significant association (p = 0.002). Nodal status was significantly associated with elevated CRP levels (17.5 % vs 8.5%; p = 0.006), whereas no significant association could be found for the CRP level and R-status (p = 0.061). Instead, there was a significant association between the preoperative elevated CRP level and OS (61.7 months vs 86.2 months; p = 0.020).

RLC-score

The univariate analysis revealed a significant association between OS and T-stage (pT2 vs pT3 or higher, p = 0.001), R-status (p = 0.001), LVI (p = 0.011), and preoperative CRP levels (p = 0.02). All significant parameters of the univariate analysis were then included in the multivariate analysis, which identified R-status, LVI, and preoperative CRP level as independent prognostic markers for OS in the development cohort (n = 155), as shown in Table 4.

In the intermediate risk group, 77 (49.7%) patients showed a preoperative elevated CRP level. The mean preoperative CRP level in the intermediate risk group was 12.85 mg/L. Fifteen (9.7%) patients showed LVI and 30 (19.4%) patients showed progressive disease during follow-up. The median OS after RC was 62 months. The high risk group contained 13 patients. The mean preoperative CRP level in the high risk group was 18.92 mg/L. The median OS time was 22 months. In cases of metachronous metastases, the median OS decreased to 18.2 months. All of the 8 very high risk group patients showed a T stage of pT3 or higher and 6 patients (75 %) showed an elevated preoperative CRP level. The mean preoperative CRP level in the very high risk group was 45.11 mg/L. The median OS time was 6.5 months. Median age in RLC very high risk group exceeded the other two groups by around five years (73.5 years vs 67.5 and 68.9 years). Kaplan-Meier-curves for OS in RLC risk groups are shown in Fig. 1. The area under the curve (AUC) of the Receiver Operating Characteristics (ROC-) curve, which demonstrates the diagnostic ability of RLC-score for OS was 0.752 (p = 0.056, 95 % CI 0.485 – 1.000).
**Table 4** Multivariate analysis and design of the RLC Score in the development cohort (endpoint OS)

| Parameter                  | Regression coefficient | Significance (p value) | Hazard Ratio | 95% CI      |
|----------------------------|------------------------|------------------------|--------------|-------------|
| R-status (R)               | 1.639                  | <0.001                 | 5.151        | 2.755 – 9.631 |
| Lymphovascular invasion (L)| 0.548                  | 0.021                  | 1.729        | 1.088 – 2.748 |
| CRP (C)                    | 0.513                  | 0.008                  | 1.670        | 1.142 – 2.443 |

**Figure 1** Kaplan-Meier-plot for RLC score regarding OS.

**Discussion**

BCa is an aggressive disease and is associated with high morbidity and mortality rates if not treated optimally [11]. Even though BCa is common, it is often mismanaged. Despite RC with extended lymph node dissection, there is a high risk of tumor progression [12–14]. Approximately 50% of the patients with a T stage higher than T2 and/or LVI develop metastases within 5 years [12] and up to 15% present with local recurrent disease [15]. It is assumed that these patients already bear lymphogenous and haematogenous micro-metastases at time of surgery [16]. Several meta-analyses of adjuvant treatment trials have shown a 22 to 25% reduction in the risk of death with cisplatin-based adjuvant treatment [17, 18], however, they might have been underpowered to draw final conclusions. The selection of patients with a higher risk of disease progression after RC and a valuable tool to predict the outcome for OS in patients after RC and to identify those patients who will benefit from early adjuvant treatment are therefore needed.

The aim of this study was to evaluate CRP as a prognostic parameter in patients with BCa undergoing RC and based on the findings, to develop a new score to predict OS in patients with BCa after RC. In univariate analysis, the OS was significantly associated with T-stage (pT2 vs pT3 or higher, p = 0.001), R-status (p ≤ 0.001), and LVI (p = 0.011). All of these pathologic parameters have been identified as being of prognostic importance in MIBC [12] and were therefore used for the multivariate analysis and score development. Furthermore, elevated preoperative CRP levels showed a significant association (p = 0.002) with the later T stage (pT2 11.6% vs pT3 – 31%) in MIBC after RC, LN infiltration (17.5% vs 8.5% p = 0.006), and an unfavorable OS (61.7 vs. 86.2 months, p = 0.02). Recently, several other groups identified CRP as a prognostic predictor in cancer patients [5, 19–22]. High CRP levels yielded a worse survival in renal cell carcinoma, prostate cancer, BCa, and upper tract urothelial carcinoma (UTUC). The main advantages of CRP as a serum biomarker are its widespread availability due to its routine use as an inflammation marker and its inexpensive assessment. The main disadvantage is the possibility of false negative results due to true infectious inflammation [21].

In multivariate analysis, R-status, LVI, and the preoperative CRP level were independent prognostic markers for OS. The final model consisting of these three parameters, the RLC score, yielded a high predictive accuracy of 0.752. Our model used OS as an endpoint instead of CSS, in contrast to other score systems such as the TNR-C score of Gakis et al. [4] or the TNM-C score of Limura et al. [8] Despite intense analysis of multiple sources, such as the central German cancer registry, the given clinical chart data, and data from the patients’ general practitioners, no robust CSS data were assessable. Whereas Gakis et al. included LN positive patients, our RLC-score excluded this group. This limits the direct comparison of results but might be an advantage of the RLC score at the same time as we assessed a patient group with a lower risk to develop a metastatic disease.

In the intermediate risk group of our RLC score, more than a third (55.4%) showed tumour progression. In comparison to the aforementioned scores, the survival rates showed a significantly lower OS for RLC high risk and very high risk group members compared to the intermediate group. The R-status represented the most important independent prognostic factor. It is noteworthy that CRP is, per se, a marker for inflammation processes and occurs ubiquitously in the human body. However, it has clinical relevance because it is a standard parameter of the preoperative evaluation of patients with BCa in most urologic clinics. Overall, the RLC score can identify patients with a higher risk of mortality who would benefit from a close follow-up or early adjuvant chemotherapy. The RLC score now needs an external validation.

Due to the retrospective nature with a small cohort, this study bears limitations. In the RLC high risk group, 75% of the patients showed metachronous metastases, whereas in the very high risk group, only one patient was diagnosed with metastases. This can be explained by the short OS (median 6.5 months) of the very high risk group.
Furthermore, the developmental cohort counted 155 patients which is rather low compared to other studies in the field. Additionally, the majority of patients (134/155) belonged to the intermediate risk RLC group, thus patient allocation is not even. This is partially due to our intentional exclusion of patients with synchronous metastases and radiologically suspected, node-positive disease at the time of RC for our development cohort. Still, it is a major limitation to our scoring system.

The median age in the RLC very high risk group exceeded the other two groups by around five years (73.5 years vs 67.5 and 68.9 years). A correlation of age at the time of RC and OS has been detected before by other study groups [23–25], although comorbidities were found to be more important in this regard. In our study, comorbidities were not assessable and therefore could not be analysed.

Although our data is based on a retrospective RC cohort from 1996 to 2007, we do not believe this to be a relevant limitation to our study since the surgical technique for RC does not differ to date.

Conclusion

The RLC-score identifies BCa patients undergoing RC with a higher mortality risk, that means a reduced OS. Overall, our study supports the role of CRP in prognostic score models for BCa. Furthermore, there is a need for prospective trials confirming these findings.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Conflict of interests

Hupe MC: Vorträge für und Honorare/Reisekosten von Ipsen, Novartis, Sanofi, Solution Akademie.
Struck JP: Vorträge für und Berater/Advisory für Bayer, BMS, Eusai, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Roche. Merseburger AS: Vorträge und Berater/Advisor für Amgen, Apogephra, Astellas, Bayer, BMS, Clovis, Ferring, Hexal, Ipsen, Janssen, Merck, MSD, Novartis, Roche, Sanofi, Takeda, TEV.

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