

PROGNOSTIC BIOMARKERS AND MULTIMODAL TREATMENT OUTCOMES IN UROTHELIAL AND SMALL-CELL BLADDER CANCER

Ph.D. Thesis Booklet

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1.Introduction

5.1.1. What is the topic?

This thesis addresses two interrelated challenges in contemporary uro-oncology: the identification of reliable circulating biomarkers for prognostication in urothelial carcinoma and the evaluation of multimodal treatment strategies for aggressive bladder cancer variants.

5.1.2. What is the problem to solve?

Despite advances in surgery and systemic therapy, conventional clinicopathological parameters frequently fail to identify biologically aggressive disease or occult metastatic spread. This limitation results in suboptimal risk stratification and treatment selection.

5.1.3. What is the importance of the topic?

Urothelial carcinoma is associated with substantial morbidity and mortality, particularly in muscle-invasive and high-risk disease. Improved prognostic tools are required to support individualized treatment decisions and avoid both overtreatment and undertreatment.

5.1.4. What would be the impact of our research results?

The integration of circulating biomarkers into clinical decision-making may enable earlier identification of high-risk patients and support more personalized perioperative management strategies.

2. Objectives

2.1. Study I. – A comprehensive analysis of the prognostic value of circulating MMP-7 levels in urothelial carcinoma: a combined cohort analysis, systematic review and meta-analysis

Our research aimed to evaluate further the prognostic relevance of preoperative serum MMP-7 levels in two independent UC cohorts. Furthermore, we also assessed two additional new aspects of serum MMP-7: (1) its potential value for the decision-making regarding limited versus extended LND, and (2) its utility for therapeutic monitoring aimed at the early detection of disease progression. Finally, we performed a systematic review and meta-analysis to provide a comprehensive overview of the clinical value of circulating MMP-7 levels in UC.

2.2. Study II.

Study II. – Radical Surgery Compared to Bladder-Preserving Approaches for Limited Stage Small-Cell Bladder Cancer: Systematic Review and Meta-Analysis

In this study, we conducted a systematic review and meta-analysis of retrospective studies to evaluate the efficacy of radical surgical intervention (CBMMT) compared with bladder-preserving RBMMT, with a particular focus on chemotherapy, in patients diagnosed with LS-SCBC.

3.Methods

3.1. Study I.

Pretreatment serum samples were collected from two independent cohorts of patients with urothelial carcinoma undergoing radical cystectomy or transurethral resection. Circulating MMP-7 concentrations were measured using a standardized enzyme-linked immunosorbent assay (ELISA). Overall survival was defined as the interval from surgery to death from any cause or last follow-up.

Associations between MMP-7 levels, clinicopathological parameters, lymph node status, and survival outcomes were analyzed using Kaplan–Meier methods and Cox proportional hazards regression models, including multivariable adjustment for established prognostic factors.

In addition, a systematic review and meta-analysis were conducted to comprehensively assess the prognostic significance of circulating MMP-7 in urothelial carcinoma. Hazard ratios for overall survival were extracted or reconstructed from published studies and

pooled using random-effects models. Heterogeneity, publication bias, and sensitivity analyses were assessed in accordance with PRISMA guidelines.

3.2. Study II.

A systematic review and meta-analysis of retrospective studies comparing cystectomy-based and bladder-preserving multimodal therapy in patients with limited-stage small-cell bladder cancer was conducted using random-effects models.

4.Results

4.1. Study I.

Elevated pretreatment serum MMP-7 levels were significantly associated with adverse pathological features, including muscle-invasive disease and lymph node metastases. High MMP-7 levels independently predicted shorter overall survival in both institutional cohorts.

Notably, lymph node–negative patients with elevated pretreatment MMP-7 levels had survival outcomes comparable to those of lymph node–positive patients, suggesting the presence of occult metastatic disease undetected by conventional staging.

Postoperative analyses revealed a marked decline in circulating MMP-7 levels following radical cystectomy, supporting the tumor as the primary source of the biomarker. Persistently elevated postoperative levels were associated with lymph node positivity and inferior survival.

The meta-analysis confirmed the robustness of these findings. Across multiple independent cohorts and treatment settings, elevated pretreatment MMP-7 levels were associated with a significantly increased risk of mortality, with consistent effect estimates and stable results in sensitivity analyses.

4.2. Study II

No significant difference in overall survival was observed between cystectomy-based and bladder-preserving multimodal treatment strategies in patients with limited-stage small-cell bladder cancer.

5. Conclusions

This thesis demonstrates that circulating MMP-7 is a robust and reproducible prognostic biomarker in urothelial carcinoma. Pretreatment serum MMP-7 assessment identifies patients at increased risk of lymph node involvement, occult metastatic disease, and inferior survival, and may support individualized perioperative decision-making.

In limited-stage small-cell bladder cancer, bladder-preserving multimodal therapy provides oncological outcomes comparable to radical cystectomy, supporting risk-adapted and patient-centered treatment selection.

6. Bibliography - Publications related to the thesis:

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