

ADJUVANT DRUG THERAPY IN THE TREATMENT OF NON-MUSCLE-INVASIVE BLADDER CANCER

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Abstract

Background: Urothelial carcinoma is the most common malignancy of the urinary tract, with a heterogeneous prognosis influenced by age, pathological stage, grade, and treatment response. Despite Bacillus Calmette–Guérin (BCG) being the gold standard for high-risk non-muscle-invasive bladder cancer (NMIBC), therapeutic limitations such as intolerance, recurrence, and worldwide shortages highlight the need for alternative adjuvant strategies.

Objectives: This thesis aimed to identify and validate clinico-pathological prognostic factors in urothelial carcinoma, with a focus on NMIBC and upper tract urothelial carcinoma (UTUC), and to evaluate the efficacy and safety of epirubicin, including device-assisted delivery (chemohyperthermia).

Methods: The research integrates five original studies: two multicenter retrospective international cohorts (CIS treated with BCG; UTUC after radical nephroureterectomy), one systematic review and meta-analysis on intravesical epirubicin, one unicentric pilot study on chemohyperthermia with epirubicin in recurrent NMIBC, and one long-term unicentric cohort (18 years) on NMIBC in real-life practice. Data analysis included Kaplan–Meier survival estimates, log-rank tests, and multivariate Cox regression models.

Results:

- Age impact: Patients >70 years showed significantly worse recurrence-free survival (HR 1.68) and progression-free survival (HR 2.82) in CIS, as well as reduced overall (HR 2.18) and cancer-specific survival (HR 2.31) in UTUC.
- Epirubicin efficacy: Comparable to mitomycin C and gemcitabine, but inferior to BCG in recurrence prevention. Device-assisted administration demonstrated oncological outcomes similar to MMC under hyperthermia.
- Chemohyperthermia pilot study: Feasible and safe in BCG-naïve recurrent NMIBC, with a 44.4% complete response at 24 months and no disease progression.
- Long-term NMIBC survival (18 years): Multiplicity of tumors (HR 3.94) and age predicted poor outcomes; RecScore and ProgScore correlated with recurrence and progression. The protective effect of BCG was marginal, possibly influenced by treatment administration disruptions during the pandemic period.

Conclusions: Advanced age and tumor multiplicity are strong independent predictors of poor outcomes in urothelial carcinoma. Epirubicin remains a valid alternative in cases of BCG intolerance or shortage, with promising results when combined with hyperthermia. The pilot Romanian study demonstrated feasibility of chemohyperthermia with epirubicin, supporting its further multicentric validation. Long-term real-world follow-up confirms the prognostic value of RecScore and ProgScore and highlights the need for resilient adjuvant treatment protocols in crisis settings.

Original contribution: This is the first Romanian pilot study on chemohyperthermia with epirubicin, combined with one of the longest follow-ups of NMIBC patients in the region, integrating local and international data to provide practical recommendations for individualized adjuvant therapy in Central and Eastern Europe.

Keywords: urothelial carcinoma, non-muscle-invasive bladder cancer, upper tract urothelial carcinoma, epirubicin, chemohyperthermia, prognostic factors, survival.