

## Original Article

# Dynamic $\gamma$ -H2AX response in blood lymphocytes for prediction of radiotherapy induced bladder toxicity in cervical cancer patients

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**Background and objectives:** Radiotherapy for advanced cervical cancer (CaCx) often results in unintended genitourinary toxicities, notably bladder damage. Predicting such radiation-induced toxicity remains challenging.  $\gamma$ -H2AX, a marker of DNA double-strand breaks (DSBs), offers promise as a predictive biomarker for radiosensitivity. This study aimed to evaluate  $\gamma$ -H2AX foci kinetics in peripheral blood lymphocytes (PBLs) as a surrogate for DNA damage response and a predictor of bladder toxicity in CaCx patients undergoing pelvic radiotherapy.

**Methods:** In this prospective study, 43 FIGO stage IIIB CaCx patients were enrolled. Stage I (n=31) assessed  $\gamma$ -H2AX induction post-CT simulation (2–6 mGy); Stage II (n=34) evaluated  $\gamma$ -H2AX kinetics across three radiotherapy fractions (FR1, FR13, FR25) during external beam radiotherapy (50 Gy in 25 fractions  $\pm$  cisplatin). Blood samples were collected at baseline, 1-, 4-, and 24-h post-irradiation.  $\gamma$ -H2AX foci were quantified via flow cytometry. Bladder toxicity was graded using Radiation Therapy Oncology Group (RTOG) criteria.

**Results:** CT and radiotherapy both induced significant  $\gamma$ -H2AX foci, peaking at 1 h. Patients without bladder toxicity showed higher foci induction and faster decay (1 $\rightarrow$ 4h: 48.9% vs. 39.4%; 1 $\rightarrow$ 24h: 43.6% vs. 12.8%) across all fractions. Persistent foci at 24 h correlated with increased toxicity risk, indicating deficient DNA repair capacity.

**Interpretation and conclusions:**  $\gamma$ -H2AX foci kinetics effectively reflect in vivo DNA repair efficiency and predict radiation-induced bladder toxicity. This minimally invasive biomarker may guide personalized radiotherapy, enabling early identification of high-risk patients and potential use of radioprotectors or treatment modifications.

**Keywords**  $\gamma$ -H2AX; Bladder toxicity; Cancer cervix; Chemoradiotherapy; CT scan; Peripheral blood lymphocytes