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Original article

Galectin-9 as a prognostic and predictive biomarker in bladder urothelial carcinoma

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Abstract

Purpose: Galectin-9, a member of the "tandem repeat" type galectins performing as animal lectins with an affinity for β-galactosides, has been well documented to exert crucial functions in immunomodulation, survival, and growth of various tumors. This study aims to reveal the clinical significance of galectin-9 in urothelial carcinoma of the bladder (UCB) postoperatively.

Materials and methods: We retrospectively included 202 patients with UCB who underwent radical cystectomy at a single institute from 2002 to 2014. Galectin-9 expression was assessed by immunohistochemistry on tissue microarrays. The Kaplan-Meier method was conducted to plot survival curves. Prognostic nomograms were constructed via integrating all the independent indicators from multivariate Cox analysis for recurrence-free survival (RFS) and cancer-specific survival (CSS). In addition, we evaluate whether patients with increased or decreased galectin-9 expression might benefit from adjuvant chemotherapy.

Results: Low galectin-9 expression was significantly correlated with lymphovascular invasion ($P = 0.002$), early recurrence ($P = 0.010$), and short CSS ($P = 0.002$). Furthermore, multivariate analysis identified galectin-9 expression as a potential independent indicator for RFS (hazard ratio = 0.62; 95% CI: 0.40–0.95; $P = 0.030$) and CSS (hazard ratio = 0.46; 95% CI: 0.26–0.81; $P = 0.008$). Moreover, the benefit associated with adjuvant chemotherapy was superior among galectin-9 low patients than among galectin-9 high patients ($P = 0.014$).

Conclusions: Expression of galectin-9 is an independent prognostic factor for RFS and CSS in patients with UCB. Evaluation of galectin-9 expression may predict the benefit from adjuvant chemotherapy.

Keywords: Bladder cancer; Galectin-9; Prognosis; Predictive biomarker; Adjuvant chemotherapy

1. Introduction

Bladder cancer is the ninth most commonly diagnosed cancer worldwide [1] and is the most common genitourinary malignancy in China [2]. The most common histological type of bladder cancer is urothelial carcinoma of the bladder (UCB), accounting for over 93% of all cases [3]. The standard treatment for localized muscle-invasive UCB and non–muscle-invasive UCB at high risk of progression is radical cystectomy. The positive role of adjuvant chemotherapy for UCB has been strengthened with the most recent meta-analysis [4,5]. According to recently updated European Association of Urology guidelines [5], Cisplatin-based combination chemotherapy is recommended to patients with pT3/4 or pN+ disease or both if no neoadjuvant chemotherapy has been given

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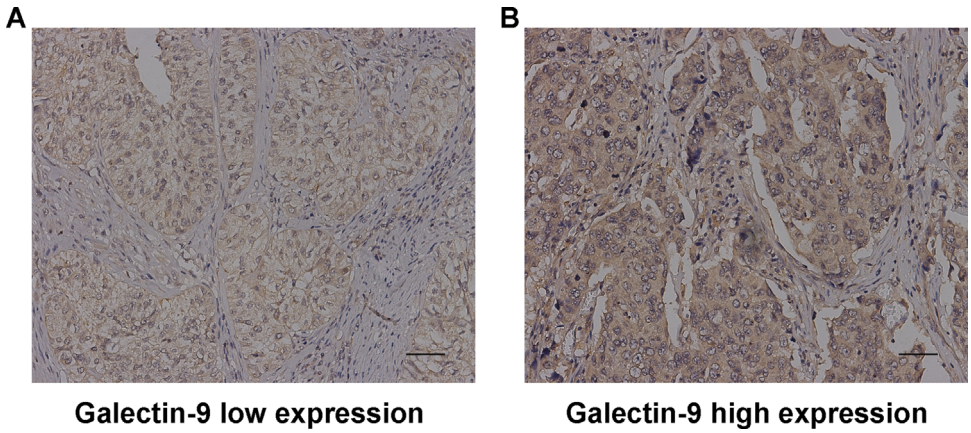

Fig. 1. Representative immunohistochemistry staining pictures of galectin-9 expression in UCB tissues. (A) Intratumor low galectin-9 expression. (B) Intratumor high galectin-9 expression. Scale bar: 50 μm (original magnification ×200). (Color version of figure is available online.)

(grade C). But currently no marker can predict outcomes or avoid overtreatment.

Galectins is a subgroup of the lectin family, known for the ability to bind to N-linked or O-linked glycosylated β-galactoside sugars. Galectins also participate in cell signaling, cell-cycle progression, and apoptosis [6,7]. Altered expression of galectins has been frequently associated with malignant tumors [8]. In the field of cancer, galectin-1 and galectin-3 are the most concerned among the galectin family. Compounds targeting galectin-1 and galectin-3 have been developed and have showed antitumor ability in vitro as well as in vivo [9].

Galectin-9, a family member of galectins, is reported to be associated with many critical processes of cancer, including cell-cycle control [10], escape of immune surveillance [11], angiogenesis [12], and metastatic potential [13]. The expression of galectin-9 is frequently negatively correlated with tumor stage, grade, or nodal involvement, and it is emerging as a marker of improved disease outcome in most of the studied cancer [9]. Yet, the expression pattern of galectin-9 and its functions in patients with UCB remain unknown. Hence, the current study aimed to explore the clinical significance of galectin-9 in UCB.

In this study, we evaluated the expression of galectin-9 in clinical specimens of patients with UCB by immunohistochemical analysis. The association between galectin-9 expression and clinicopathological characteristics, and clinical outcome including recurrence-free survival (RFS) and cancer-specific survival (CSS) were also evaluated. Moreover, we evaluated the predictive potential of galectin-9 expression in patients with UCB after adjuvant chemotherapy.

2. Patients and methods

2.1. Patients

The Clinical Research Ethics Committee of Zhongshan Hospital approved this study. The database included patients with bladder cancer who underwent radical cystectomy between 2002 and January 2014 at Zhongshan Hospital (Fudan University, Shanghai, China). Standard lymph node dissections were performed as a part of radical cystectomy. Nodal tissues up to the common iliac bifurcation, lateral to the genitofemoral nerves, were removed, including the bilateral internal iliac, obturator fossa, and external iliac nodes. The inclusive criteria are as follows: (A) pathologic type is urothelial carcinoma; (B) no distant metastasis before surgery; and (C) no radiotherapy or systemic chemotherapy before surgery. Pathologic data were collected according to the 2004 World Health Organisation classification by a genitourinary pathologist. Tumor and nodal stages were assessed according to the 2009 TNM classification. Owing to the long time span (from 2002–2014), the indications for adjuvant chemotherapy were changed. Based on hospital archives, until the end of 2013, indications for adjuvant chemotherapy were pT2+ patients, either with lymphovascular invasion (LVI) or high grades or pN+ disease. From 2014 to the end of our study period, the indications changed to pT3+ patients or with pN+ disease or both. Eligible patients were offered cisplatin-based combination chemotherapy and received at least 1 therapeutic cycle. Physical examination, urine cytology, chest imaging, and abdominal ultrasound or computed tomography scan were performed postoperatively every 3 to 4 months in the first year, semiannually in the second year, and annually thereafter.

2.2. Tissue microarray and immunohistochemistry

All tissue microarrays were scored for galectin-9 expression by a single pathologist in a blinded fashion. H-score, a semiquantitative immunoreactivity score, was applied by multiplying the staining intensities (0: negative, 1: weak staining, 2: moderate staining, and 3: strong staining) and distribution areas (0–100) for each sample. The score ranged from 0 to 300.