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Original article

Fas expression in nephrectomized, non-cancerous specimens predicts post-nephrectomy chronic kidney disease progression in patients with renal and upper urinary tract malignancies

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Abstract

Objectives: Despite the surgical curability of renal cell carcinoma (RCC) and upper urinary tract urothelial carcinoma (UUT-UC), post-nephrectomy chronic kidney disease (CKD) continues to be a cause of concern. We investigated the correlation between the expression of apoptotic regulatory molecules in the nephrectomized, noncancerous cortex, as well as CKD progression and CKD-related mortality.

Materials and methods: Fas and Bcl-2 mRNA and protein expression in surgically resected specimens from 100 patients with RCC and UUT-UC were determined. The estimated glomerular filtration rates (eGFR) were determined sequentially before surgery and up to 5 years after surgery. The relationships between CKD progression, the expression of these molecules in the renal cortex, and the clinical characteristics were analyzed.

Results: The mean 1-year postoperative percent eGFR decrease was 30.2 (Standard deviation [SD]: 15.2). The 1-year postoperative percent eGFR decrease greater than the approximate value of mean ± SD (45) was categorized as severe renal functional deterioration (SRFD). Glomerular Fas protein expression and a Fas/β-actin mRNA ratio >0.3 were independent predictors for SRFD. Significantly increased mortality rates due to cardiovascular events were indicated by glomerular Fas protein expression, Fas mRNA levels >0.3, and SRFD. No significant change in Bcl-2 levels was observed.

Conclusions: This study is the first report to demonstrate the significance of Fas expression in the nephrectomized normal cortex as a predictor of post-nephrectomy CKD progression. The results from nephrectomized kidney showed that the natural course of renal function in the remaining kidney may be affected not only by Fas-induced glomerular cell apoptosis but also by the total amount of Fas mRNA in cortical cells. © 2013 Elsevier Inc. All rights reserved.

Keywords: Fas; Nephrectomy; Nephroureterectomy; Chronic kidney disease

1. Introduction

Concerns after nephrectomy or nephroureterectomy for patients with renal cell carcinoma (RCC) or upper urinary tract urothelial carcinoma (UUT-UC) involve not only oncologic outcome but also chronic kidney disease (CKD) progression because of the large amount of nephron tissue loss. Adverse renal outcomes in subjects undergoing nephrectomy for RCC were determined by large population-based analysis [1]. For UUT-UC patients, the deterioration of renal function after nephroureterectomy ultimately led to an adverse chemotherapeutic treatment strategy [2]. Such obstacles have also been investigated in living recipients of kidney transplantation. Post-donor nephrectomy CKD has become a medical problem in recent years, and risk factors associated with the deterioration of renal function after donor nephrectomy have been investigated [3–5].

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Table 1
Patient and tumor characteristics in RCC

Characteristics	Values or number of cases
Mean age at surgery (years); range	66.7; 52–77
Sex male/female	55/25
Tumor site; left/right	42/38
Clinical result;	
Died due to cancer/cardiovascular events/others	32/9/8
Metastasis at first visit	9
Recurrence	25
Stage	
pT1a	19
pT1b	20
pT2	15
pT3a	17
pT3b	7
pT4	2
Grade	
1/2/3–4	24/27/29
Cell type	
Clear	41
Granular	12
Chromophobe	17
Spindle	1
Cyst-associated	1
Papillary	8

RCC = renal cell carcinoma.

The research history with respect to renal cell apoptosis is relatively short. Although apoptosis was originally described by Kerr and Wyllie in 1972 [6], it was not described in the kidney until 1987, when it was identified in the pathogenesis of renal tubulointerstitial damage after unilateral hydronephrosis [7]. A common feature of chronic renal diseases of varying etiologies is the loss of intrinsic renal cells through apoptosis, which is associated with a decrease in renal function. Increased apoptosis has been demonstrated to contribute to various types of chronic renal disease, including diabetic nephropathy [8], glomerulosclerosis [9], IgA nephropathy [10], lupus nephritis [11], and renal injury [12].

However, no studies have examined the association between the expression of apoptotic regulatory molecules in normal renal tissues and CKD progression after nephrectomy or nephroureterectomy to date. We investigated the correlation between the expression of Fas and Bcl-2, which are major apoptotic regulators in nephrectomized, noncancerous cortex, as well as clinical and demographic factors and CKD progression. Moreover, the potent factors influencing CKD-related mortality were investigated using long-term follow-up data.

2. Materials and methods

2.1. Patients and data collection

A total of 113 patients underwent nephrectomy or nephroureterectomy between 1997 and 2003 at our institution. We excluded the contribution of the tumor to the renal insufficiency of the disease-side kidney and total renal insufficiency as much as possible by carefully selecting cases. Our study selected cases in which both kidney functions were practically identical on radiographic findings. Cases with variable contrast materials accumulation in the normal parenchyma in the early, late, and excretion phase on preoperative CT scans were excluded. Cases with infiltrating tumor invasions in renal parenchyma were also excluded. Only mild hydronephrosis (Ellenbogen, [13]) patients in UUT-UC in whom the CT scan results met the aforementioned criteria were included. However, any hydronephrosis cases in RCC were not included. UUT-UC cases which received pre- or post-operative chemotherapy were also excluded because a cisplatin-based regimen could have deteriorated renal function. Finally, 100 patients (80 with RCC and 20 with UUT-UC) were eligible for the study. The patients' backgrounds are summarized in Tables 1 and 2 according to the International Union against Cancer Standards (6th edition). The estimated glomerular filtration rates (eGFR) were determined using the Modification of Diet in Renal Disease study equations, and data were collected sequentially before surgery and 3 months after surgery, and 1, 3, and 5 years after surgery. Survival data focusing on mortality because of cardiovascular events were collected from more than 5 years' worth of follow-up data.

2.2. Surgical tissue sample collection for analysis of Fas and Bcl-2 expression

Fractions of the tumor and noncancerous cortical tissue samples from surgical specimens were collected after obtaining informed consent from patients, and the study was approved by an appropriately constituted ethics committee

Table 2
Patient and tumor characteristics in UUT-UC

Characteristics	Values or number of cases
Mean age at surgery (years); range	69.6; 55–84
Sex male/female	14/6
Tumor site left/right	11/9
Clinical result	
Died due to cancer/cardiovascular events/others	4/2/4
Metastasis at first visit	1
Recurrence	3
Stage	
pT1a	2
pT1	5
pT2	6
pT3	7
Grade	
1/2/3–4	3/12/5
Cell type	
UC	19
Sarcomatoid UC	1

UUT-UC = upper urinary tract urothelial carcinoma.

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