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Postoperative renormalization of C-reactive protein with adjuvant lienal polypeptide and its association with tumour recurrence in T1 clear cell renal cell carcinoma

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Abstract

Objectives: To evaluate the effect of pre- and postoperative C-reactive protein (CRP) levels on tumour recurrence following curative nephrectomy in patients with stage T1 clear cell renal cell carcinoma (CCRCC).

Methods: Patients with stage T1 CCRCC were recruited. CRP was quantified 3 days before and 4 weeks after surgery. Patients were followed-up for clinical outcome every 3 months. A subset of patients received lienal polypeptide as adjuvant treatment.

Results: Patients with elevated preoperative CRP levels ($\geq$8.2 mg/l; $n = 61$) had higher grade tumours, were more likely to require radical nephrectomy and were more likely to experience recurrence than those with normal CRP levels. Non-normalization of elevated preoperative CRP was associated with tumour recurrence, but elevated CRP was not an independent risk factor of tumour recurrence.

Conclusion: Postoperative renormalization of elevated CRP is associated with decreased risk of recurrence in CCRCC.

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Introduction

Kidney neoplasms represent around 3–5% of all cancers in developed countries, such as the USA.[1] Outcome varies according to tumour type, grade and stage, with recurrent and metastatic disease being predictive of poor survival.[2–4] It is difficult to predict which early stage (T1) tumours will recur after curative nephrectomy, however.

Studies have investigated the relationship between systemic inflammatory biomarkers and clinical outcome in malignancies such as renal cell carcinoma (RCC).[5] The acute phase reactant, C-reactive protein (CRP), is predictive of poor prognosis in RCC:[6] elevated preoperative CRP is associated with higher tumour stage and grade, and is predictive of worse survival in clear cell RCC (CCRCC).[7] Although the prognostic value of the preoperative CRP level has been investigated, it is not known whether postoperative renormalization of CRP is related to clinical outcome of CCRCC.

The aim of the present prospective study was to investigate whether postoperative renormalization of CRP (compared with preoperative levels) was associated with tumour recurrence following curative nephrectomy in patients with stage T1 CCRCC.

Patients and methods

Study population

The study recruited patients undergoing curative nephrectomy for T1 CCRCC at Huashan Hospital of Fudan University, Shanghai, China, between January 2011 and June 2014. Tumour staging was determined by pathological examination and with reference to the 2010 tumour-node-metastasis classification.[8] Exclusion criteria were: (i) suspected lymph node or distant metastasis, according to preoperative computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET); (ii) acute or chronic inflammatory or autoimmune conditions; (iii) long term chronic disease, inducing organ dysfunction.

The study was approved by the internal review board of Huashan Hospital of Fudan University, and complied with the Declaration of Helsinki. All patients provided written informed consent prior to collection of blood samples.

Treatment

Venous blood was collected from each patient 3 days before surgery using standard methods; CRP was quantified via nephelometry using an Abbott AxSYM automated analyser (Abbott Laboratories, Lake Bluff, IL, USA). Postoperative CRP levels were quantified at 4 weeks after surgery. The CRP cut-off value was set as <8.2 mg/l.

A sex-, tumour stage-, tumour grade- and surgical technique-matched subset of patients with elevated preoperative CRP received adjuvant therapy with 10 ml/day lienal polypeptide injection (Jilin Fsens Pharmaceutical Co. Ltd., Jilin, China) for 3 days after surgery. This subset included all patients with elevated CRP levels who were treated between August 2013 and June 2014. These patients were compared with patients with elevated CRP levels who did not receive adjuvant therapy, who were treated between January 2011 and June 2013.

Patients underwent radical or partial curative nephrectomy (dependent on tumour size) by laparoscopy or open surgery. All surgeries used a retroperitoneal approach.

Follow-up

Patients were followed-up every 3 months until June 2015. Follow-up examinations included ultrasonography of the surgical area and chest X-radiography, with CT every 6 months. Patients with suspected recurrence underwent PET for additional diagnosis. Localized recurrence and distant metastasis were defined as postoperative recurrence and failure of surgical treatment.

Statistical analyses

Data were presented as mean ± SD, or *n* (%) of patients. Between-group differences were analysed using χ^2-test, and Cox regression analysis was used to determine risk factors for recurrence. All tests were two-sided. Analyses were performed using using Stata® version 12.0 (StataCorp LP, College Station, TX, USA). *P*-values < 0.05 were considered statistically significant.

Results

The study included 233 patients between January 2011 and June 2013 (124 male/109 female; mean age 57.54 ± 27.32 years; age range 38–82 years). The median duration of follow-up was 38 months (range 25 – 54 months). Recurrence occurred in 18/233 patients (7.7%). Demographic and clinical characteristics of the study population as a whole, and stratified according to preoperative CRP level (elevated [≥8.2 mg/l] vs normal), are shown in Table 1. Patients with elevated preoperative CRP were significantly older ($P = 0.026$), more likely to be male ($P = 0.004$), had higher grade tumours ($P = 0.006$), were more likely to require radical nephrectomy ($P = 0.042$) and were significantly more likely to experience recurrence, compared with those with normal CRP levels (<8.2 mg/l; $P = 0.017$, Table 1).

Recurrence was significantly associated with elevated preoperative CRP ($P = 0.017$) and tumour grade ($P = 0.015$; Table 2). Multivariate regression analysis found that tumour grade only was an independent risk factor for recurrence (odds ratio 2.862, 95% confidence intervals 0.701, 4.599; Table 3).

Data regarding postoperative CRP levels in patients with elevated preoperative CRP ($n = 61$) are shown in Table 4. Patients whose CRP levels did not normalize after surgery were significantly more likely to experience recurrence than those whose postoperative CRP returned to normal levels ($P = 0.038$). There were no between-group differences in sex, tumour stage or grade, or surgical technique (Table 4). Multivariate regression analysis found no independent predictors of recurrence in this patient group (data not shown).

A subset of 40 patients with elevated preoperative CRP, treated between August 2013 and June 2014, received postoperative lienal polypeptide therapy; results were compared with those who did not receive treatment (treated between January 2011 and June 2013; $n = 61$). Significantly more patients who received lienal polypeptide had normalized postoperative CRP levels compared with those who did not (30 of 40 patients [75.0%] vs 33 of 61 patients [54.1%]; $P = 0.034$).

Discussion

Despite of timely and effective treatment of localized RCC, some patients with T1 tumours develop recurrent and metastatic disease, which substantially affects 5-year survival rates.[9] Inflammation is known to have a role in tumour development,[10] and the value of CRP as a prognostic biomarker in RCC has been established.[7]

Preoperative elevated CRP levels were sometimes, but not always, normalized following curative nephrotomy in the present study. It is unclear what effect, if any, this modification in CRP has on clinical outcome of RCC. A study determined that elevated postoperative CRP was associated

Table 1. Demographic and clinical characteristics of patients included in a study to investigate whether postoperative renormalization of C-reactive protein (CRP), compared with preoperative levels, is associated with tumour recurrence following curative nephrectomy for stage T1 clear cell renal cell carcinoma, stratified according to preoperative CRP level[8]

Characteristic	Total patient cohort $n = 233$	Preoperative CRP level[a]		Statistical significance[b]
		Elevated group $n = 61$	Normal group $n = 172$	
Age, years		64.21 ± 22.55	55.18 ± 28.51	$P = 0.026$
Sex				
Male	124 (53.2)	42 (68.9)	82 (47.7)	$P = 0.004$
Female	109 (46.8)	19 (31.1)	90 (52.3)	
Unilateral tumour				
Left	128 (54.9)	35 (57.4)	93 (54.1)	NS
Right	105 (45.1)	26 (42.6)	79 (45.9)	
Tumour stage				
1a	145 (62.2)	35 (57.4)	110 (64.0)	NS
1b	88 (37.8)	26 (42.6)	62 (36.0)	
Fuhrmann grade				
I/II	152 (65.2)	31 (50.8)	121 (70.3)	$P = 0.006$
III/IV	81 (34.8)	30 (49.2)	51 (29.7)	
Surgery				
Radical	51 (21.9)	19 (31.1)	32 (18.6)	$P = 0.042$
Partial	182 (78.1)	42 (68.9)	140 (81.4)	
Technique				
Laparoscopy	161 (69.1)	41 (67.2)	120 (69.8)	NS
Open surgery	72 (30.9)	20 (32.8)	52 (30.2)	
Tumour recurrence				$P = 0.017$
Positive	18 (7.7)	9 (14.8)	9 (5.2)	
Negative	215 (92.3)	52 (85.2)	163 (94.8)	

Data presented as *n* (%) of patients.
NS, not statistically significant ($P \geq 0.05$).
[a]Elevated CRP ≥ 8.2 mg/l.
[b]χ^2-test.

with metastasis and death after curative nephrectomy for CCRCC, but preoperative CRP levels were not evaluated.[11] A further study of 40 patients with metastatic RCC undergoing cytoreductive nephrectomy found that patients whose CRP levels did not normalize had worse prognosis than other patients, and that non-normalized CRP was an independent factor predicting poorer survival.[12] Patients with higher tumour grades (III/IV) were more likely to have elevated preoperative CRP in the present study, compared with those with tumour grades I/II. In addition, both elevated preoperative CRP and tumour grade were associated with tumour recurrence after curative surgery in the present study. In addition, in those patients with elevated preoperative CRP, non-normalized postoperative CRP was associated with tumour recurrence.

In general, patients with T1 RCC have an optimistic prognosis and require no adjuvant therapy. Treatment with the

Table 2. Demographic and clinical characteristics of patients with stage T1 clear cell renal cell carcinoma, stratified according to tumour recurrence following curative nephrectomy[8]

Characteristic	Total patient cohort $n = 233$	Recurrence group $n = 18$	Statistical significance[a]
Sex			
Male	124 (53.2)	10 (55.6)	NS
Female	109 (46.8)	8 (44.4	
Preoperative CRP			
Elevated (≥8.2 mg/l)	61 (26.2)	9 (50.0)	$P = 0.017$
Normal	172 (73.8)	9 (50.0)	
Tumour stage			
1a	145 (62.2)	8 (44.4)	NS
1b	88 (37.8)	10 (55.6)	
Fuhrmann grade			
I/II	152 (65.2)	7 (38.9)	$P = 0.015$
III/IV	81 (34.8)	11 (61.1)	

Data presented as *n* (%) of patients.
NS, not statistically significant ($P \geq 0.05$); CRP, C-reactive protein.
[a] χ^2-test.

Table 3. Multivariate Cox regression analysis of factors associated with tumour recurrence following curative nephrectomy, in patients with stage T1 clear cell renal cell carcinoma ($n = 233$)[8]

Parameter	Odds ratio	95% confidence intervals
Preoperative CRP, elevated (≥ 8.2 mg/l) vs normal	0.847	−0.095, 1.744
Sex, male/female	0.211	−0.216, 0.849
Tumour stage, 1a/1b	1.046	−0.277, 2.311
Fuhrmann grade, I/II vs III/IV	2.862	0.701, 4.599

CRP, C-reactive protein.

immunomodifier lienal polypeptide in the present study resulted in significantly more patients with normalization of CRP compared with those who did not receive adjuvant therapy. Detailed analysis of the mechanism of action and effect on prognosis of such treatment requires further study.

Our study has several limitations. CRP is an acute phase reactant and can be affected by many factors. CRP was only quantified once before and once after surgery, and these data may not fully reflect the clinical status of the patient. The inclusion of only patients with T1 CCRCC limits the generalizability of our findings. In addition, a longer duration of follow-up would be useful in determining the full impact of CRP normalization via adjuvant therapy. Further studies with larger patient cohorts and increased duration of follow-up are required to validate our findings.

In conclusion, postoperative renormalization of elevated CRP is associated with decreased risk of recurrence in CCRCC. It is unclear whether adjuvant therapy significantly improves postoperative outcome.

Table 4. Demographic and clinical characteristics of patients with stage T1 clear cell renal cell carcinoma, stratified according to renormalization of C-reactive protein (CRP) following curative nephrectomy[8]

Characteristic	Postoperative CRP		
	Normalized group $n = 33$	Unchanged group $n = 28$	Statistical significance[a]
Sex			
Male	22 (66.7)	20 (71.4)	NS
Female	11 (33.3)	8 (28.6)	
Tumour stage			
1a	20 (60.6)	15 (53.6)	NS
1b	13 (39.4)	13 (46.4)	
Fuhrmann grade			
I/II	19 (57.6)	12 (42.9)	NS
III/IV	14 (42.4)	16 (57.1)	
Technique			
Laparoscopy	22 (66.7)	19 (67.9)	NS
Open surgery	11 (33.3)	9 (32.1)	
Tumour recurrence			
Positive	2 (6.1)	7 (25.0)	$P = 0.038$
Negative	31 (93.9)	21 (75.0)	

Data presented as *n* (%) of patients.
NS, not statistically significant ($P \geq 0.05$).
[a]χ^2-test

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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