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Impact of serum sodium concentration on survival outcomes in patients with invasive bladder cancer without metastasis treated by cystectomy

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Abbreviations & Acronyms
BC = bladder cancer
BMI = body mass index
CI = confidence interval
CRP = C-reactive protein
CSS = cancer-specific survival
cT = clinical T
Hb = hemoglobin
HR = hazard ratio
LDH = lactate dehydrogenase
NAC = neoadjuvant chemotherapy
RC = radical cystectomy
TURBT = transurethral resection of bladder cancer

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Approximately 35% of local invasive BC patients who undergo RC develop distant metastasis and eventually die.[1,2] Thus, identification of poor prognostic factors is a major concern for clinicians. Recently, serum sodium concentration was reported to be associated with prognosis in localized cancers (N0M0), such as non-small cell lung cancer,[3] upper urinary tract cancer[4] and renal cell carcinoma,[5] even if it is within the normal range. However, there are no reports on BC. In the present study, we evaluated the prognostic significance of preoperative clinical, pathological and laboratory factors in local invasive BC after RC.

Between 2000 and 2015, 179 patients with locally invasive BC (pTany, pN0 cM0) who underwent RC with pelvic lymph node dissection in Osaka Rosai Hospital were retrospectively reviewed. Data collected on each patient included age, sex, BMI, cT stage, tumor nuclear grade, values of serum sodium, LDH and CRP, Hb concentrations, administration of NAC, and follow-up data. All patients underwent TURBT before cystectomy and were histologically diagnosed as having urothelial carcinoma. No patients received adjuvant chemotherapy. Survival data were available for all patients, and laboratory data were obtained at the first visit before TURBT. Statistical analyses were carried out using JMP 12 (SAS Institute, Cary, NC, USA).

Perioperative information is summarized in Table S1. The median follow-up duration was 50 months, and the 5-year CSS estimate was 72.8%. Overall, 59 (33.6%) patients experienced recurrence and 49 (27.3%) patients died of BC.

Kaplan–Meyer analysis and log–rank tests identified cT stage (P = 0.0050), tumor nuclear grade (P = 0.0357), CRP (P = 0.0004) and serum sodium concentration (P = 0.0355) as showing significant associations with CSS (Fig. S1a–d). The optimal cut-off values of CRP and serum sodium by receiver operating curve analysis were 0.4 mg/dL and 139 mEq/L, respectively. Thereafter, we divided the patients into two groups according to CRP >0.4 mg/dL (high-CRP, n = 53) and CRP ≤0.4 mg/dL (low-CRP, n = 126), and Na ≥140 mEq/L (high-Na, n = 127) and Na ≤139 mEq/L (low-Na, n = 52) for further study. We confirmed that CRP level and serum sodium concentration were most significantly related to CSS when comparing the two groups according to the optimal cut-off values (Fig. S1e,f).

Univariate and multivariate Cox proportional hazards analyses were used to evaluate the association of the 10 preoperative factors with CSS, both when divided into two groups (Table 1) and when considered as a continuous variable (Table S2). In univariate analysis, cT stage, tumor nuclear grade, CRP level and serum sodium concentration were significantly associated with CSS by both analyses. In the multivariate models, serum sodium concentration and CRP level correlated significantly with CSS by two-groups analysis (Table 1), and by continuous variable form, serum sodium concentration was also an independent risk factor for CSS (Table S2).

A prognostic model of risk classification was then constructed based on CRP level and serum sodium concentration as independent predictors of CSS (Table 1). Patients were divided into the low-risk, moderate-risk or high-risk group according to the number of positive independent prognostic factors: CRP ≥0.4 mg/dL and Na ≤139 mEq/L. Patients with low-CRP and high-Na were classified into the low-risk group (n = 94), patients with one prognostic factor into the moderate-risk group (n = 65), and patients with high-CRP and low-Na into the high-risk group (n = 20). Kaplan–Meyer analysis and log–rank tests showed the respective 5-year CSS estimates to be 88.6%, 60.6% and 37.5% for the low-risk, moderate-risk and high-risk groups (Fig. S2).

Some meta-analyses showed that preoperative laboratory data, such as CRP and Hb, were predictive factors for prognosis after RC.[6,7] However, there is no report on serum sodium concentration. This is the first report to show preoperative Na ≤139 mEq/L to be related to poor prognosis after RC. Recently, high immune response was reported to lead to the development of hyponatremia because of pro-inflammatory cytokines.[8] Therefore, we speculated that low-Na might affect the cancer-related immune response. Our patients who presented

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Table 1 Univariate and multivariate Cox regression analysis of 10 preoperative parameters associated with cancer-specific survival according to the optimal cut-off value

		Univariate analysis		Multivariate analysis	
	n	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)					
<69	90	Reference	0.6259		
≥69	89	1.15 (0.65–2.03)			
Sex					
Male	133	Reference	0.5779		
Female	46	0.83 (0.40–1.57)			
BMI (kg/m^2)					
<24.0	105	Reference	0.5960		
≥24.0	35	0.81 (0.35–1.69)			
cT stage					
≤cT2	101	Reference	0.0056	Reference	0.1133
≥cT3	78	2.22 (1.26-4.02)		1.62 (0.89–3.02)	
Grade					
G2	36	Reference	0.0224	Reference	0.1107
G3	132	2.59 (1.13–7.50)		2.06 (0.87–6.07)	
Na					
≤139 mEq/L	52	Reference	0.0280	Reference	0.0442
≥140 mEq/L	127	0.51 (0.29–0.93)		0.54 (0.30–0.98)	
LDH					
Normal	150	Reference	0.2585		
High	29	1.52 (0.72–2.93)			
CRP					
≤0.4 mg/dL	126	Reference	0.0002	Reference	0.0010
>0.4 mg/dL	53	3.01 (1.71–5.30)		2.68 (1.50–4.84)	
Hb					
Normal	102	Reference	0.3724		
Anemia	77	1.29 (0.73–2.27)			
NAC					
Yes	85	Reference	0.4217		
No	94	1.26 (0.72–2.25)			

Total *n* = 179. Optimal cut-off value Na 139 mEq/L and CRP 0.4 mg/dL.

with both Na ≤139 mEq/L and CRP >0.4 mg/dL had a poor prognosis, and therefore might have benefited from adjuvant chemotherapy or extended lymph node dissection. However, because the present retrospective study included only a small number of cases from a single institution, the results still need to be validated in other cohorts.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. The association of preoperative parameters with CSS. (a) The cT stage, (b) tumor nuclear grade and (c) CRP showed a significant association with CSS. (d) Serum sodium

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concentration showed a significant relationship to CSS when divided into two groups according to the median value. When divided into two groups according to the optimal cut-off value, (e) CRP level and (f) serum sodium concentration showed a most significant relationship to CSS (Kaplan–Meier log–rank test).

Figure S2. CSS for risk classification (Kaplan–Meier log–rank test).
Table S1. Patients characteristics (n = 179).
Table S2. Univariate and multivariate Cox regression analysis of 10 preoperative parameters associated with CSS with continuous variable form (n = 179).

Editorial Comment

Editorial Comment from Dr Hashimoto to Impact of serum sodium concentration on survival outcomes in patients with invasive bladder cancer without metastasis treated by cystectomy

In clinical practice, oncologists may often encounter patients with metastatic advanced cancer who have experienced electrolyte abnormalities, including hyponatremia. Indeed, previous reports have suggested that approximately 14% of cases of hyponatremia in medical inpatients are due to tumor-related conditions.[1] However, it is rare to focus on serum sodium levels in patients with localized cancer. Nakata *et al.* reported that preoperative serum sodium levels ≤139 mEq/L were related to a poor prognosis in patients with invasive bladder cancer without metastasis after radical cystectomy.[2] Considering that previous reports have suggested that serum sodium abnormalities are associated with oncological outcomes, it is fully conceivable that serum sodium levels are affected by bladder cancer. Kobayashi *et al.* considered that low serum sodium levels could be reflected in cancer-related inflammation.[3] Hyponatremia has recently been recognized as a complication of several inflammatory diseases and as being related to inflammatory cytokines, such as interleukin-6.[4] In this regard, the report by Nakata *et al.* will be very interesting for urological oncologists.

However, a few obstacles might hinder oncologists from utilizing this result in clinical practice. Abnormalities in serum sodium usually progress in the presence of excessive water relative to existing sodium stores in the body. Some cytokines could change the homeostasis, and serum sodium could then be influenced by that condition. However, serum sodium levels would fluctuate within several days even in the same patient, because they will be affected by drugs administered for other diseases, blood pressure, renal function, salt intake and water intake. Furthermore, diurnal variation might be found in serum sodium levels. It has also been shown that hyponatremia occurs at a similar frequency in patients with cancer as that in general medical patients.[5] Therefore, it is possible to consider that serum sodium simply reflects a secondary change in patients' comorbidities that are not related to cancer. In consideration of this situation, there might be many problems in evaluating serum sodium levels in patients with invasive bladder cancer without metastasis. One of the most difficult problems is establishing a cut-off value. The cut-off value of serum sodium in the study by Nakata *et al.* was within the normal range. As aforementioned, the assessment of serum sodium levels within the normal range will be difficult. In addition, the measurement method, time of measurement, complications and medicines should be considered when evaluating serum sodium levels. I hope that further verification will be carried out in the future to overcome these problems.

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Conflict of interest

None declared.

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