Differential diagnosis between bacterial infection and neoplastic fever in patients with advanced urological cancer: The role of procalcitonin

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Short Communications

The role of procalcitonin in differentiation between bacterial infection and neoplastic fever in patients with advanced urological cancer

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Abstract

It is difficult to determine the cause of high fever in patients with advanced cancer, because these patients tend to have both neoplastic fever and bacterial infections with elevated white blood cell number and C-reactive protein level. Procalcitonin has been reported to be a valuable marker for prediction of bacterial infections in a wide range of clinical areas. However, there have been no studies regarding the usefulness of procalcitonin for differentiation between febrile episodes caused by bacterial infections and neoplastic fever in patients with advanced urological cancer. In the present study, to investigate the efficacy of procalcitonin for differentiation of bacterial infections, 37 febrile episodes were retrospectively analyzed. Although there were no differences in white blood cell number, C-reactive protein level, or body temperature between bacterial infections and non-bacterial infections, procalcitonin level was significantly higher in the former than the latter. Our findings show that measurement of procalcitonin may be valuable to determine the cause of febrile episodes in patients with advanced urological cancer and can help clinicians to make immediate decisions for treatment.

Key words

Advanced cancer, bacterial infections, neoplastic fever, procalcitonin, urological cancer

Introduction

Patients with advanced cancer, which is associated with a huge volume of primary tumor or disseminated metastases, are susceptible to bacterial infections (BI) due to their poor systemic condition, and such BI usually cause high fever exceeding 38.0°C. Although most BI may be diagnosed quickly and easily because physical findings, blood tests, and radiological examinations can detect the focus of BI, some patients show no evidence of infection other than high fever and may only show high white blood cell (WBC) counts and C-reactive protein (CRP) levels. On the other hand, non-BI (NBI), such as neoplastic fever (NF), can also cause high fever and result in high WBC counts and CRP levels similar to BI. The possibility of NF increases as the tumor volume or number of metastases increases. Therefore, it is sometimes very difficult to determine the cause of high fever in patients with advanced cancer, especially when there is no association with febrile neutropenia. When BI is diagnosed immediately during febrile episodes, antibiotics will be administered appropriately. However, if the time of diagnosis is delayed, the possibility of inappropriate use of antibiotics for NBI will increase. In such cases, the patients' relief from distress over high fever will also be delayed, and there is likely to be vast economic loss

due to the misuse of antibiotics. Procalcitonin (PCT) has been reported as a valuable serum marker for prediction of BI in a wide range of clinical areas. However, there have been no previous reports of the clinical usefulness of PCT for differentiation between febrile episodes caused by BI and NBI, mainly NF, in patients with advanced urological cancer. In the present study, we investigated the usefulness of PCT in patients with advanced urological cancer and our results indicated that PCT was beneficial over conventional uses of WBC and CRP.

Methods

Study population

All studies were performed retrospectively in Kanazawa University using charts of patients who were hospitalized in the Department of Urology from May 2009 to August 2010. Febrile episodes > 38.0°C in patients with advanced urological cancer were analyzed. The records of blood tests, including WBC, CRP, and PCT immediately after the onset of fever, were acquired for each febrile episode. Advanced urological cancer was defined as a large primary tumor (long diameter > 5 cm) or the presence of metastasis.

Definition of BI

BI was defined according to the following criteria: positive blood culture, symptoms and obvious findings of BI on physical examination, and rapid recovery of fever after antibiotic administration. Radiological findings and results of urine and sputum culture were also taken into account for diagnosis. Febrile episodes that did not meet the criteria of BI were defined as NBI, and if no cause of fever was found in NBI, the episode was classified as NF.

Statistical analysis

Statistical analyses were performed using commercially available software (Prism). Comparisons between two groups were performed by unpaired two-sided *t* test and chi-square test for trends. Comparisons among multiple groups were performed by chi-square test and one-way ANOVA. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Patient characteristics

Of 28 patients enrolled in the present study, 37 febrile episodes could be analyzed. In the overall patient population, the median age was 71 years (range, 14 – 84) and the numbers of cases of prostate cancer, urothelial carcinoma, renal cell carcinoma, germ cell tumor, and other type of malignant tumor were 11, 12, 6, 6, and 2, respectively. Nineteen had already undergone primary tumor resection and had metastatic lesions, and 18 still had the primary tumor. The median maximum axillary body temperature (BT), median WBC, and CRP were 38.5°C (range, 38.0°C – 40.7), 7.77×10^3/μl (range, 2.04 – 31.07), and 10.3 mg/dl (range, 0.4 – 33.3), respectively. PCT were divided into 4 categories from – (< 0.5 ng/ml) to +++ (10.0 ng/ml), and the numbers of –, +, ++, and +++ were 20, 8, 3, and 6, respectively (**Table 1**).

Causes of febrile episodes

Seventeen of 37 febrile episodes were regarded as BI, and the remaining 20 febrile episodes were regarded as NBI. Single blood culture was done in each of 29 febrile episodes and 4 were

positive. Of 17 BI, 6 were diagnosed as acute pyelonephritis, 3 were diagnosed as pneumonia, and the remaining 8 could not be diagnosed as a specific focal infection. Of 20 NBI, 3 were caused by reaction to injection of anti-tumor drugs, and 1 was caused by rheumatoid arthritis, accordingly, 16 were diagnosed as NF.

Differences in background factors between BI and NBI

First, the differences in WBC, CRP, and BT between BI and NBI were compared because these factors are generally regarded as signs that can reflect the severity of BI. As shown in **Fig. 1**, although there were no significant differences in WBC, CRP, or BT between BI and NBI, there was a significant difference between age in BI and NBI ($P = 0.0048$). Next, to determine whether the type of primary cancer has any relation to the cause of febrile episode, 4 primary cancer sites were compared. The results indicated significant differences between these primary cancer sites (**Fig. 2** *upper*, $P = 0.0005$). However, there were also significant differences in age among these 4 groups (**Fig. 2** *lower*, $P < 0.0001$). Finally, the difference in PCT between BI and NBI was analyzed. Negative PCT was found 15 of 20 NBI and 5 of 17 BI. The results indicated that BI had significantly higher PCT compared with NBI (**Fig. 3**, *upper*, $P = 0.0024$). There were no

differences in age distributions between the 4 groups classified according to PCT level (**Fig. 3**, *lower*).

Discussion

PCT is produced by thyroid C-cells and is detected in blood when severe inflammation occurs. Normally, the PCT level in serum is below the limits of detection because all PCT is converted into calcitonin. [1, 2] Therefore, PCT has been suggested to be a reliable marker for the severity of sepsis or bacteremia. [3, 4] In the adult hemato-oncological field, the role of PCT has been reported in studies. [5-7] The largest study assessed the PCT of 236 febrile episodes in 166 hemato-oncological patients treated with aggressive chemotherapy, and showed that PCT increased in infections, but not in fever of unknown origin. [8] With regard to solid tumors, the role of PCT in febrile neutropenic patients has also been studied and it was reported that PCT was valuable as a diagnostic and prognostic tool in patients with febrile neutropenia. [1, 7, 9] There have been only 2 previous reports focusing not on febrile neutropenia in patients with solid tumor, but on febrile episodes without neutropenia. One study did not show the usefulness of PCT to discriminate between infections and other causes of febrile episodes. [10] Another study concluded that PCT was a good indicator of bacteremia. [11] However, these studies included few cases of urological malignancy as well as other studies focusing on the role of PCT in patients with

malignancy. Our results showed that age may contribute to an increase in the possibility of infection during febrile episodes in patients with advanced urological cancer. Our analysis suggested that cancer type also affects the increase in possibility of infection. However, age may be a confounding factor for this result (**Fig. 2**). On the other hand, PCT could predict infection although CRP and WBC could not predict infection in patients with advanced urological cancer. Although there were false positive and negative episodes in this study, [12] this result indicated that PCT is useful to discriminate between BI and NBI, mainly NF. This study had some limitations. It was a retrospective study with small sample size. This may have prevented determination of the precise statistical significance of differences between groups with bias. Definition of BI might be incomplete because the single blood culture lacked in power to detect bacteremia. Larger prospective studies with proper definition of BI are needed to confirm our findings. In conclusion, this is the first study to show the usefulness of PCT in patients with advanced urological cancer, and PCT may be a rapid and affordable marker for differentiation between BI and NF in such patients.

Conflict of interest

None declared.

References

1. Jimeno A, Garcia-Velasco A, del Val O, Gonzalez-Billalabeitia E, Hernando S, Hernandez R*, et al.* Assessment of procalcitonin as a diagnostic and prognostic marker in patients with solid tumors and febrile neutropenia. Cancer 2004;100:2462-9.

2. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. Physiol Res 2000;49 Suppl 1:S57-61.

3. Luyt CE, Guerin V, Combes A, Trouillet JL, Ayed SB, Bernard M*, et al.* Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. Am J Respir Crit Care Med 2005;171:48-53.

4. Tsalik EL, Jaggers LB, Glickman SW, Langley RJ, van Velkinburgh JC, Park LP*, et al.* Discriminative value of inflammatory biomarkers for suspected sepsis. J Emerg Med 2012;43:97-106.

5. al-Nawas B, Shah PM. Procalcitonin in patients with and without immunosuppression and sepsis. Infection 1996;24:434-6.

6. Engel A, Steinbach G, Kern P, Kern WV. Diagnostic value of procalcitonin serum levels in

neutropenic patients with fever: comparison with interleukin-8. Scand J Infect Dis 1999;31:185-9.

7. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection 2008;36:396-407.

8. Sandri MT, Passerini R, Leon ME, Peccatori FA, Zorzino L, Salvatici M*, et al.* Procalcitonin as a useful marker of infection in hemato-oncological patients with fever. Anticancer Res 2008;28:3061-5.

9. Kim DY, Lee YS, Ahn S, Chun YH, Lim KS. The usefulness of procalcitonin and C-reactive protein as early diagnostic markers of bacteremia in cancer patients with febrile neutropenia. Cancer Res Treat 2011;43:176-80.

10. Penel N, Fournier C, Clisant S, N'Guyen M. Causes of fever and value of C-reactive protein and procalcitonin in differentiating infections from paraneoplastic fever. Support Care Cancer 2004;12:593-8.

11. Kallio R, Surcel HM, Bloigu A, Syrjala H. C-reactive protein, procalcitonin and interleukin-8 in the primary diagnosis of infections in cancer patients. Eur J Cancer 2000;36:889-94.

12. Christ-Crain M, Muller B. Procalcitonin in bacterial infections--hype, hope, more or less? Swiss Med Wkly 2005;135:451-60.

Figure legends

Fig. 1 – Comparison of WBC, CRP, BT, and age between NBI (*n* = 20) and BI (*n* = 17). Unpaired two-sided *t* test was used. *Bars*, Means ± SEM.

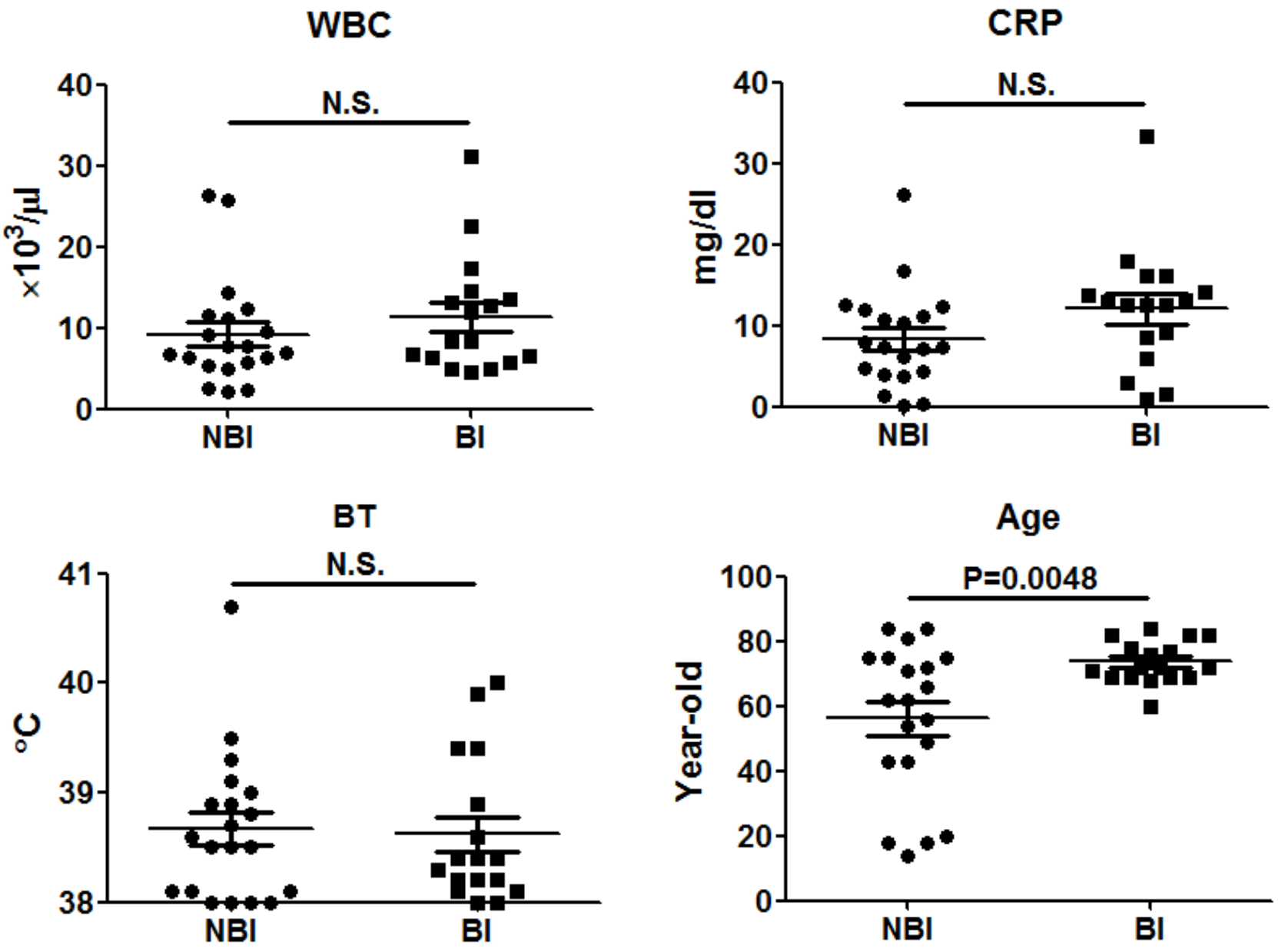
Fig. 2 – (*Upper panel*) The percentages of NBI and BI in 4 types of urological cancer. Chi-square test was used. (*Lower panel*) The distributions of age in 4 types of urological cancer. One-way ANOVA was used. *Bars*, Means ± SEM. PCa = prostate cancer, UC = urothelial carcinoma, RCC = renal cell carcinoma, GCT = germ cell tumor, Oth = other neoplasms.

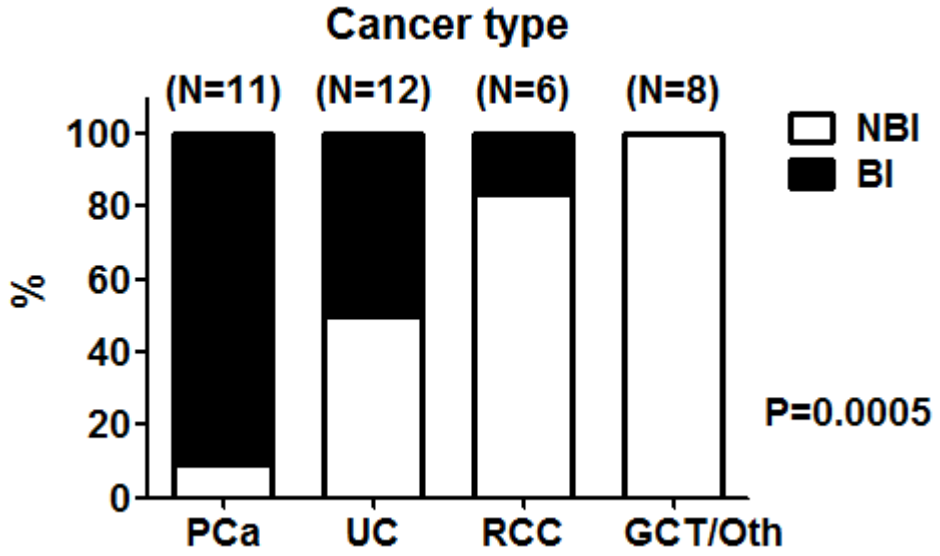
Fig. 3 – (*Upper panel*) The percentages of each PCT level in NBI and BI. Chi-square test for trends was used. (*Lower panel*) The distributions of age in each PCT level. One-way ANOVA was used. *Bars*, Means ± SEM.

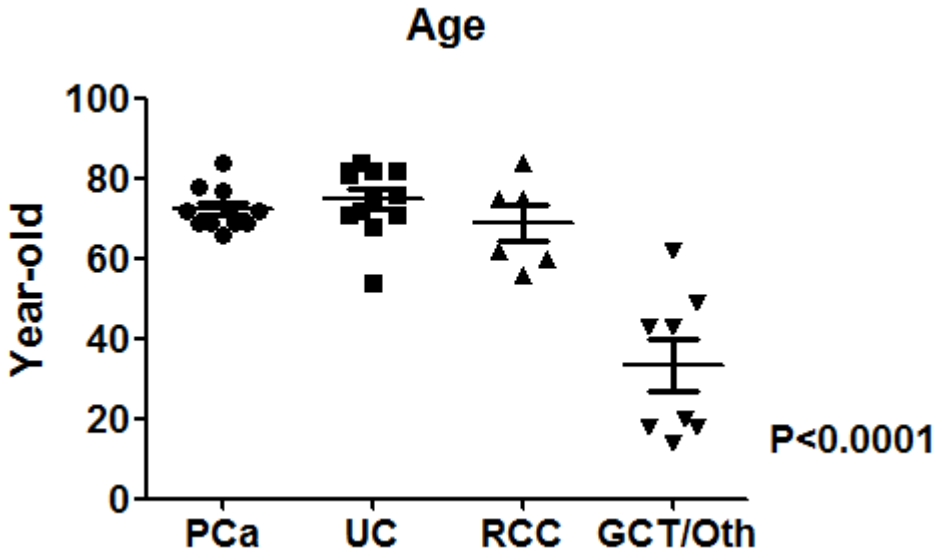
Table 1

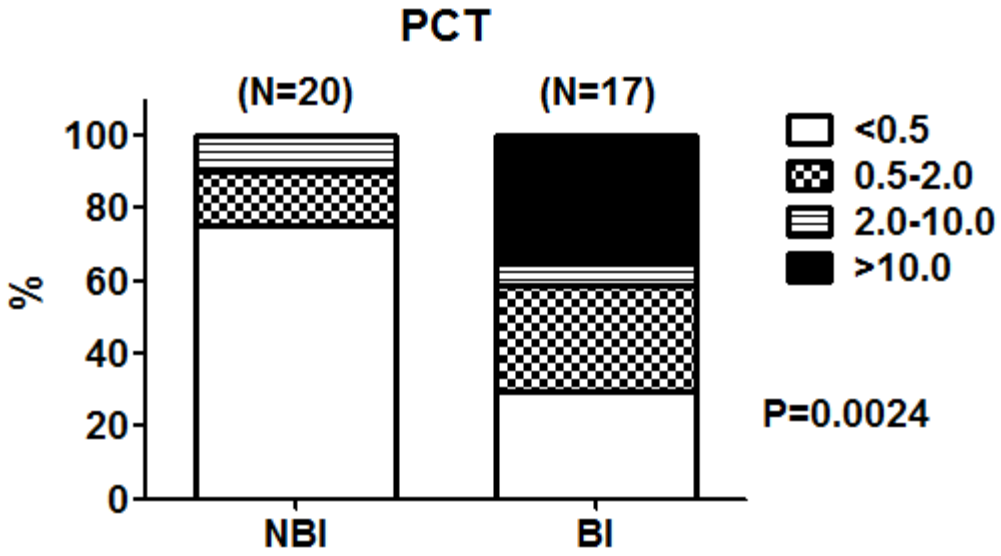
Patient characteristics (37 episodes in 28 patients)			
Age			71* (14 – 84)
Gender	Male		31
	Female		6
PS	0		2
	1		11
	2		4
	3		4
	4		16
Cancer type	PCa		11
	UC		12
		Bladder	8
		Ureter	2
		Renal pelvis	2
	RCC		6
	GCT		6
	Other		2
Primary tumor	size (cm)**		8.6* (5.0 – 17.6)
	resected		19
BT (°C)			38.5* (38.0 – 40.7)
WBC ($\times 10^3/\mu l$)			7.77* (2.04 – 31.07)
CRP (mg/dl)			10.3* (0.4 – 33.3)
PCT (ng/ml)	-	(< 0.5)	20
	+	(0.5 – 2.0)	8
	++	(2.0 – 10.0)	3
	+++	(> 10.0)	6

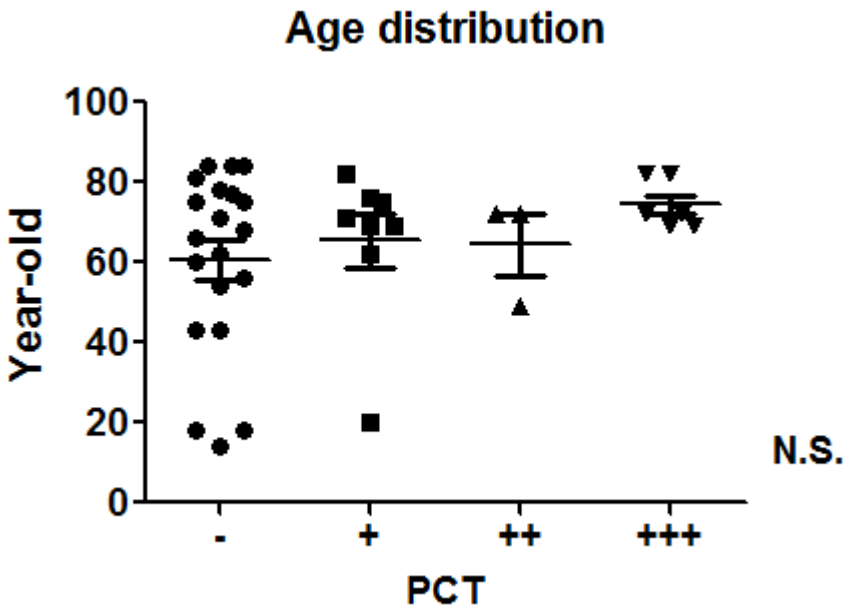
PS = performance status, PCa = prostate cancer, UC = urothelial carcinoma, RCC = renal cell carcinoma, GCT = germ cell tumor, BT = body temperature, WBC = white blood cell, CRP = c-reactive protein, PCT = procalcitonin. * median, ** not resected


WBC
N.S.
40
30
20
10
0
×10³/μl
NBI
BI
CRP
N.S.
40
30
20
10
0
mg/dl
NBI
BI
BT
N.S.
41
40
39
38
°C
NBI
BI
Age
P=0.0048
100
80
60
40
20
0
Year-old
NBI
BI


Cancer type
(N=11)
(N=12)
(N=6)
(N=8)
NBI
BI
%
100
80
60
40
20
0
PCa
UC
RCC
GCT/Oth
P=0.0005


Age
Year-old
100
80
60
40
20
0
PCa
UC
RCC
GCT/Oth
P<0.0001


PCT
(N=20)
(N=17)
100
80
60
40
20
0
%
NBI
BI
<0.5
0.5-2.0
2.0-10.0
>10.0
P=0.0024


Age distribution
100
80
60
40
20
0
Year-old
-
+
++
+++
PCT
N.S.