Clinical Study

Post-ablation Syndrome after Percutaneous Cryoablation of Small Renal Tumors: A Prospective Study of Incidence, Severity, Duration, and Effect on Lifestyle

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ABSTRACT

Purpose: To prospectively investigate the incidence, severity, duration, and effect on lifestyle of post-ablation syndrome (PAS) after percutaneous renal cryoablation.

Materials and Methods: We enrolled 39 patients (27 male and 12 female; mean age, 62 years) who underwent 40 CT-guided cryoablation sessions for pathologically proven renal cancer (mean size, 20 mm) between December 2015 and December 2017. Four symptoms attributable to PAS, i.e., fever, nausea, vomiting, malaise, and the synergistic effect of these symptoms on lifestyle by 21 days after ablation were evaluated using a questionnaire. Symptoms were graded according to the common toxicity criteria of adverse events.

Results: The incidences of fever, nausea, vomiting, and malaise were 100% (40/40), 20% (8/40), 20% (8/40), and 63% (25/40), respectively. Most (78/81, 96%) symptoms had begun by day 2. The highest grade of fever per session was 0 (defined as ≥37.0°C and <38.0°C) (n = 24), 1 (n = 15), or 2 (n = 1); that of nausea was 2 (n = 8); that of vomiting was 1 (n = 7) or 3 (n = 1); and that of malaise was 1 (n = 14) or 2 (n = 11). Most (76/81, 94%) symptoms had resolved by day 8. The average values for the maximum scores of interference with general activity and work were 3.6 and 1.1, respectively.

Conclusion: All symptoms were generally early-onset and self-limiting, with minimal impact on lifestyle and resolution by day 8. The clinical course and impact of PAS should be acknowledged by practitioners who manage patients undergoing renal cryoablation.

KEYWORDS

Post-ablation syndrome, Cryoablation, CT-guided, Renal cancer

INTRODUCTION

Percutaneous ablation is commonly used for the treatment of small renal tumors. According to the American Urological Association's guideline for the management of clinical T1 renal masses [1], ablation is recommended for patients with cT1a renal masses with major comorbidities. However, the ablation procedure may be associated with flu-like symptoms (e.g., fever, vomiting, nausea, and malaise), collectively known as post-ablation syndrome (PAS), regardless of the target organs. Previous studies have shown that after hepatic radiofrequency (RF) ablation, PAS occurred in 36% (14/39) of patients [2] and after hepatic microwave ablation, it developed in 60% (30/50) of patients [3]. Other studies showed that the incidence of PAS after hepatic or renal RF ablation was 89% (32/36) [4] and 32% (17/53) [5], respectively. Wah et al. [4] demonstrated that PAS resolved more quickly after renal RF ablation than after hepatic RF ablation.

To our knowledge, only one study focused on PAS after renal cryoablation, revealing an incidence of 63% (40/64) [6]. Deeper understanding of the clinical course and impact of PAS is still required for the management of patients undergoing renal cryoablation. We therefore aimed to evaluate the incidence, severity, duration, and lifestyle effect of PAS after percutaneous renal cryoablation.

MATERIALS AND METHODS

This prospective study was approved by the relevant institutional review board (approval number, *blinded for review*). Written informed consent was obtained from all patients.

Study Population

We included patients who 1) had pathologically proven primary or secondary renal cancer, 2) refused to undergo or were not candidates for nephrectomy, 3) were aged 20 years or older, and 4) agreed to participate in this study. In contrast, we excluded patients who 1) had fever, nausea, vomiting, and/or malaise before cryoablation, 2) regularly used steroids or non-steroid anti-inflammatory drugs, 3) had undergone transcatheter renal arterial embolization within 1 month before cryoablation, 4) were not permitted to discontinue anticancer drug use, or 5) were deemed ineligible for participation in this study (e.g., poor compliance).

The size of the study population was not determined based on statistical evidence because of the exploratory nature of the study. Between December 2015 and December 2017, 126 patients underwent a total of 153 percutaneous renal cryoablation sessions. Among those, 87 patients (113 sessions) were excluded based on the above-mentioned criteria (**Fig 1**). Ultimately, the study population comprised 39 patients who underwent 40 sessions.

Definition of PAS and Study Endpoint

PAS was defined as the occurrence of at least one symptom among fever, nausea, vomiting, and malaise within 21 days after cryoablation. The endpoints of our study were the incidence, severity, duration, and effect on lifestyle of PAS after renal cryoablation. Factors associated with each symptom were also evaluated.

Cryoablation Procedure

Percutaneous renal cryoablation was always performed in an inpatient setting. Intraprocedural pain was treated with local anesthesia along with conscious sedation using an intravenous drip infusion of fentanyl and hydroxyzine in 38 sessions and using general anesthesia in two sessions.

First, CT was performed to plan the procedure. The number of cryoprobes (IceRod or IceSeed, Galil Medical, Yokneam, Israel) used was mainly based on tumor size. Approximately two cryoprobes were used for tumors <1.5 cm, while three or more cryoprobes were used for tumors ≥1.5 cm. The cryoprobe was inserted into the tumor with intermittent use of CT fluoroscopy. The cryoprobe was connected to an argon-based cryoablation system (Cryohit, Galil Medical). The ablation protocol typically included two freezing cycles separated by at least 2-min intervals; each cycle lasted 10–15 min. Adjunctive protective measures including artificial pneumothorax, hydrodissection, and retrograde pyeloperfusion were employed as necessary to prevent injury to surrounding organs.

The ablation zone, shown as a low attenuation area ("ice-ball") [7], was evaluated on CT images at the end of each cycle. In accordance with Georgiades et al. [8], the procedure aimed at inclusion of the tumor within the ice-ball with ablative margins of a minimum of 6 mm. If the margins were deemed insufficient at the end of the second cycle, the cryoprobe was re-inserted into the region of insufficiency for additional freezing. After confirmation that the ice-ball included the tumor and sufficient margins, all cryoprobes were removed. A final CT scan was then performed to evaluate complications, which were graded according to the Society of Interventional Radiology Classification System [9].

The patients were discharged after any substantial symptoms had subsided. As necessary, fever, nausea/vomiting, and postoperative pain were treated with oral antipyretic, antiemetic, and analgesic medications, respectively. However, prophylactic medication was not allowed.

Examination Protocol

The pre-ablation examination included a complete blood count, biochemical tests, and abdominal CT. CT was performed before contrast administration and in the arterial phase (36 s after initiation of contrast administration of 600 mg I/kg in 30 s), nephrogenic phase (63 s), and excretory phase (240 s). On days 1 and 3, the complete blood count and biochemical tests were repeated. On day 3, CT was performed with the same protocol as that used before cryoablation. Unenhanced MRI was alternatively performed in one case of impaired renal function after cryoablation. The MRI protocol included axial and coronal T1-, T2-, fat-suppressed T2-weighted, and axial diffusion-weighted images.

Assessment of PAS

Fever was defined as a temperature ≥37.0°C. For evaluation of fever, patients were instructed to measure axillary temperature at rest at least once each in the morning and afternoon until day 3. From days 4 to 7, temperature was measured at least once a day, in the morning or in the afternoon. After day 8, temperature was measured only when the patients felt warm or feverish. When temperature was measured multiple times in the same day, the maximum value was used as the datum for that day.

The symptoms and their synergistic effect on lifestyle were assessed with interviews using a standardized questionnaire on days 1, 2, 4, 7, 14, and 21. Bedside or telephone interviews were conducted for inpatients or outpatients, respectively. To avoid obsequiousness bias, all interviews were performed by medical clerks or residents who were not involved in the cryoablation procedures. Symptoms were graded according to the common toxicity criteria of adverse events (CTCAE) v. 4.0. [10] (**Table 1**). Because fever <38.0°C is not graded in the CTCAE, we defined fever ≥37.0°C and <38.0°C as grade 0.

The effect of PAS on lifestyle was evaluated using a scale ranging from 0 (no interference) to 10 (complete interference) measuring interference with general activity and work during each period (i.e., days 0–1, 1–2, 2–4, 4–7, 7–14, and 14–21). During hospitalization, interference with work was not evaluated.

Evaluation of Factors Associated with PAS

We investigated the associations between PAS and multiple variables, including patient-, tumor-, and procedure-related factors. Patient variables were age, sex, and body mass index. The tumor variables included volume, location, and tumor type. Tumor volume was calculated on preprocedural CT images, by contouring tumors on consecutive axial CT images of 5 mm thickness with SYNAPSE VINCENT® (Fuji Film, Tokyo, Japan). Tumor location was classified into central, parenchymal, exophytic, or mixed according to the system proposed by Gervais et al. [11].

The procedure variables included total ablated tissue volume, ablated marginal parenchymal volume, increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) values after ablation, and the use of hydrodissection. Total ablated tissue volume was calculated on day 3 by contouring the no contrast-enhanced area of the treated kidney in the excretory phase on 5-mm-thick axial CT images or the hypointense area on 4-mm-thick axial T2-weighted images. The ablated marginal parenchymal volume was then calculated by subtracting the tumor volume from the total ablated tissue volume. Increases in AST, ALT, and LDH values after ablation were calculated by subtracting the pre-ablation from the post-ablation values; the evaluation took place on both days 1 and 3, and the largest of the two values for each patient was adopted as that patient's post-ablation value.

Statistical Analysis

Cryoablation sessions were divided into two groups according to the grade of fever (grade 0 vs. ≥1) or the presence of other symptoms (no vs. yes). The above-mentioned variables were compared between the two groups using univariate analyses with two-sided Student's *t* test or Mann-Whitney U test (as appropriate following normality tests) for numerical variables, and the χ^2 test or Fisher's exact test for categorical variables. A *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed with the Statistical Package for the Social Sciences version 25 software (IBM, Armonk, NY, USA).

RESULTS

Patients, Lesions, and Procedures

Characteristics of the patients, tumors, and procedures are shown in **Table 2**. The study population comprised 39 patients (27 male and 12 female), with a mean age of 62 years. One patient with multiple tumors underwent two sessions, and thus, 39 patients underwent a total of 40 sessions. The mean maximum tumor diameter and tumor volume were 20 mm and 3.6 mL, respectively. Most tumors (29/40, 73%) were clear cell carcinomas and showed exophytic location (30/40, 75%).

Hydrodissection, artificial pneumothorax, and retrograde pyeloperfusion were used in 24, 1, and 2 sessions, respectively. Three cryoprobes were used in most sessions (32/40, 80%). The mean total freezing time was 34 min, and the mean ablated total tissue volume was 28.6 mL, while the mean ablated marginal parenchymal volume was 25.0 mL. No major complications occurred.

PAS

The incidence, grade, onset, and duration of PAS are summarized in **Table 3**.

The 39 patients experienced a total of 81 symptoms after 40 sessions. The incidences of fever, nausea, vomiting, and malaise per session were 100% (40/40), 20% (8/40), 20% (8/40), and 63% (25/40), respectively, yielding an incidence of PAS of 100% (40/40). Fever alone occurred after 12 sessions, while a combination of fever with any of the other symptoms occurred after 28 sessions. All four symptoms occurred after four sessions.

Each symptom mostly (78/81, 96%) began on days 0–2 and rarely (3/81, 4%) on day 3 or later. Fever, nausea, vomiting, and malaise lasted for an average of 4, 3, 1, and 6 days, respectively. The incidence of each symptom over time is shown in **Figure 2**. Most (76/81, 94%) symptoms had resolved by day 8, although there were 2 (5%) cases of fever, 1 (3%) of nausea, and 2 (5%) of malaise on day 8. Regarding severity, the highest grade per session was 0 or 1 in most cases of fever (39/40, 98%), 2 in all 8 cases of nausea, 1 in most cases of vomiting (7/8, 88%), and 1 or 2 in all 25 cases of malaise. Regarding the effect on lifestyle, the average scores for the maximum effect on general activity and work were 3.6 and 1.1, respectively. Oral antipyretic, antiemetic, and analgesic medication was administered after 12, 7, and 13 sessions, respectively.

Factors Associated with PAS

The results of the analyses for the association between PAS and individual variables are shown in **Table 4**. Ablated marginal parenchymal volume and the increases in AST, ALT, and LDH values after ablation were all larger in the group with grades 1 and 2 fever and the groups with other symptoms than in the group with grade 0 fever and the groups without other symptoms. In particular, increases in AST, ALT, and LDH were significantly larger in the group with nausea ($P = 0.027$, 0.011, and 0.015, respectively). The incidences of nausea and vomiting were significantly higher in

female patients (P <0.001 and 0.005, respectively).

DISCUSSION

The present study showed that the overall incidence of PAS after renal cryoablation was 100% (40/40). Fever as a PAS symptom occurred in all cases. The second most frequent symptom was malaise (63%), followed by nausea and vomiting (20%). In contrast, Zhong et al. showed that the overall incidence of PAS after renal cryoablation was 63% (40/64) and that of fever was 11% (7/64) [6]. These authors used a thermometer to measure temperature in the morning when patients first woke up, and as needed for the 10 days after cryoablation. It is well known that body temperature shows circadian variation and is lowest early in the morning and highest in the evening [12,13]. Hence, the higher incidence of fever in our study may be mainly attributable to the methodological differences pertaining to the times of day and frequencies of temperature measurement.

Our study showed that PAS after renal cryoablation was generally early-onset and self-limiting with minimal effects on lifestyle and had mostly resolved by day 8. Recognition of the onset, severity, and duration of PAS may be helpful in distinguishing PAS from complications that show similar symptoms, such as urinary tract infection [14,15] and perirenal abscess [16,17], thereby facilitating prompt treatment of such complications.

PAS is generally believed to result from an inflammatory response to the necrotic tissue, with associated cytokine production. In fact, PAS incidence after hepatic RF ablation was positively associated with tumor volume, total ablated tissue volume, ablated nontumorous tissue volume, and post-ablation AST levels [2]. PAS after hepatic

microwave ablation was positively associated with post-ablation AST levels [3]. The present study also showed that increases in AST, ALT, and LDH after ablation were significantly associated with the occurrence of nausea. Further, nausea and vomiting occurred significantly more frequently in female patients, who are more likely to have nausea and vomiting associated with surgery [18–20] and chemotherapy [21–23].

The present study has some limitations. The sample size was small because numerous cases were excluded based on our relatively strict criteria. At the same time, however, the homogeneity of the sample constitutes a strength of this study. The incidence of nausea and vomiting due to PAS might have been overestimated, because the fentanyl we used for sedation may cause such symptoms [24–25]. Further, other potential confounders for symptom development may have been present such as the general anesthesia that was administered to two patients, oral medication for symptoms after cryoablation, minor transient infection such as urinary tract infection associated with retrograde pyeloperfusion, and stress associated with hospitalization and participation in this study. Additionally, the two sessions in the same patient were registered as independent sessions, although multiple measurements in each patient are correlated to some extent, and the type of anesthesia administered was heterogeneous. Finally, the association between ablated retroperitoneal fat volume and PAS was not evaluated because fat necrosis could not be clearly visualized on CT or MRI images.

In summary, all symptoms attributable to PAS were generally early-onset and self-limiting, with minimal impact on lifestyle and resolution by day 8. The clinical course and impact of PAS should be acknowledged by practitioners who manage patients undergoing renal cryoablation.

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Conflict of interest

The authors have no conflicts of interest to disclose related to this article.

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Figure Captions

Figure 1.

Flow chart of study candidates to select the study population

Figure 2.

Incidences of each symptom attributable to post-ablation symptom over time

Table 1. Grade classification of each symptom due to post-ablation syndrome according to common toxicity criteria of adverse events v. 4.0.

Symptom	Grade 1	2	3	4	5
Fever	38.0–39.0°C	>39.0–40.0°C	>40.0°C for ≤24 h	>40.0°C for >24 h	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	NA	NA
Vomiting	1–2 episodes (separated by 5 min) in 24 h	3–5 episodes (separated by 5 min) in 24 h	≥6 episodes (separated by 5 min) in 24 h; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	NA	NA	NA

ADL = activities of daily life, NA = not applicable, TPN = total parenteral nutrition

Table 2. Characteristics of patients, lesions, and procedures.

Variable		Value
Patient characteristics (*n* = 39)		
Age (y)	Mean ± SD (range)	62.2 ± 13.4 (21–87)
Gender	Male/Female	27/12
Body mass index	Mean ± SD (range)	24.2 ± 4.4 (15.7–35.0)
Lesion characteristics (*n* = 40)		
Cancer type	Primary (Clear cell/Chromophobe/Papillary/Undetermined)/Secondary	39 (29/4/2/4)/1
Tumor Location	Exophytic/Parenchymal/Central/Mixed	30/6/1/3
Maximum tumor diameter (mm)	Mean ± SD (range)	19.9 ± 5.6 (7.0–29.0)
Tumor volume (mL)	Mean ± SD (range)	3.6 ± 2.6 (0.2–11.1)
Procedure characteristics (*n* = 40)		
Number of cryoprobes used	2/3/4	7/32/1
Ablated total tissue volume (mL)	Mean ± SD (range)	28.6 ± 11.8 (8.6–55.8)
Ablated marginal parenchyma volume (mL)	Mean ± SD (range)	25.0 ± 10.3 (8.4–45.3)
Hydrodissection	Yes/No	24/16
Artificial pneumothorax	Yes/No	1/39

Pyeloperfusion	Yes/No	2/38
Total freezing time (min)	Mean ± SD (range)	34.4 ± 9.9 (20–60)

SD = standard deviation

Table 3. Each symptom of post-ablation syndrome after 40 sessions.

Symptom	Number of sessions (%)									Duration of symptom, mean (range) of days
	Overall	According to highest grade				Onset of symptom				
		Grade				Post-ablation day				
		0	1	2	3	0	1	2	3 or later	
Fever	40 (100)	24	15	1	0	34	4	2	0	4.1 (1–13)
Nausea	8 (20)	NA	0	8	0	6	0	1	1	3.1 (1–12)
Vomiting	8 (20)	NA	7	0	1	7	0	0	1	1.1 (1–2)
Malaise	25 (63)	NA	14	11	NA	19	2	3	1	5.5 (1–18)

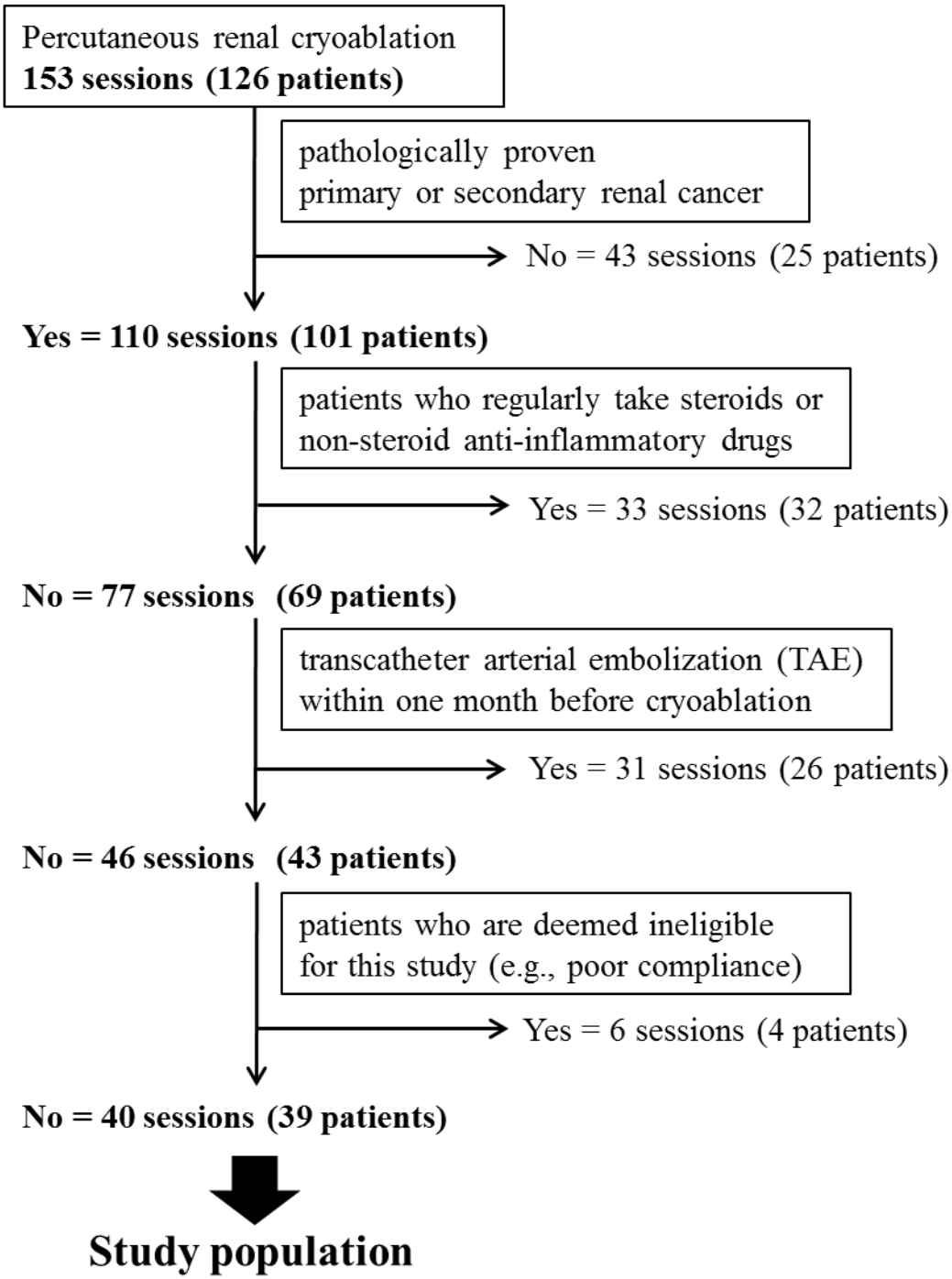
NA = not applicable

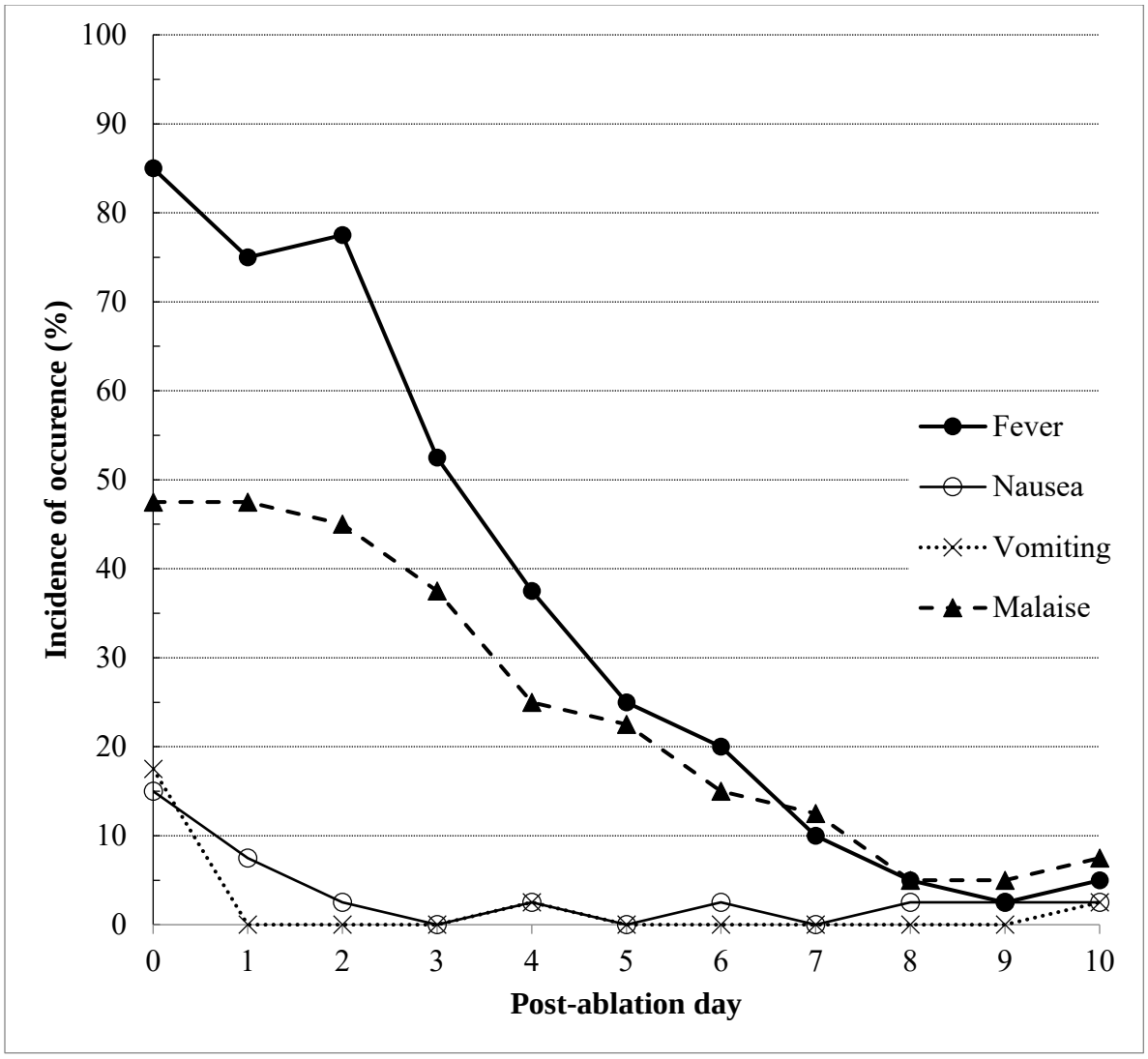
Table 4. Results of univariate analyses of factors for each symptom of post-ablation syndrome.

		Fever			Nausea			Vomiting			Malaise		
		Grade 0	Grades 1 and 2	*P* value	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
		n = 24	*n* = 16		*n* = 32	*n* = 8		*n* = 32	*n* = 8		*n* = 15	*n* = 25	
Patient-related factors													
Age (y)	Mean ± SD	64.3 ± 10.6	58.8 ± 16.4	0.21	63.0 ± 12.1	58.5 ± 17.7	0.78	61.9 ± 11.4	63.0 ± 20.1	0.83	66.0 ± 12.7	59.8 ± 13.3	0.15
Gender (Male/Female)	Number of sessions	18/6	10/6	0.49	27/5	1/7	<0.001*	26/6	2/6	0.005*	11/4	17/8	1.00
Body mass index (kg/m^2)	Mean ± SD	23.7 ± 4.1	24.9 ± 4.7	0.40	24.5 ± 4.0	22.7 ± 5.4	0.31	24.7 ± 4.3	21.9 ± 4.0	0.095	23.7 ± 4.5	24.4 ± 4.3	0.63
Tumor-related factors													
Tumor volume (mL)	Mean ± SD	3.71 ± 2.83	3.49 ± 2.19	0.92	3.82 ± 2.52	2.83 ± 2.76	0.28	3.98 ± 2.58	2.20 ± 2.05	0.051	4.11 ± 2.35	3.33 ± 2.68	0.31
Tumor type (clear cell /others)	Number of sessions	17/7	12/4	1.00	23/9	6/2	1.00	23/9	6/2	1.00	11/4	18/7	1.00
Tumor location (exophytic/others)	Number of sessions	20/4	10/6	0.16	26/6	4/4	0.09	26/6	4/4	0.09	13/2	17/8	0.27
Procedure-related factors													
Ablated total tissue volume (mL)	Mean ± SD	27.3 ± 12.4	30.6 ± 10.8	0.39	27.5 ± 11.1	33 ± 14.2	0.24	28.9 ± 12.2	27.5 ± 10.6	0.78	27.5 ± 10.3	29.3 ± 12.7	0.64
Ablated marginal parenchymal volume (mL)	Mean ± SD	23.6 ± 10.7	27.1 ± 9.6	0.30	23.7 ± 9.5	30.2 ± 12.4	0.11	24.9 ± 10.5	25.3 ± 10.2	0.92	23.4 ± 9.6	26.0 ± 10.8	0.44
Increased value of AST after ablation (U/L)	Mean ± SD	57.3 ± 42.9	64.8 ± 37.1	0.32	53.3 ± 34.6	88.3 ± 51.6	0.027*	54.6 ± 35.8	83.1 ± 51.5	0.088	59.4 ± 51.1	60.8 ± 33.5	0.31

Increased value of ALT after ablation (U/L)	Mean ± SD	35.2 ± 31.1	43.6 ± 25.4	0.19	32.6 ± 25.6	62.3 ± 31.0	0.011 *	36.0 ± 28.0	48.6 ± 32.2	0.26	35.7 ± 35.6	40.2 ± 24.7	0.23
Increased value of LDH after ablation (U/L)	Mean ± SD	495 ± 284	565 ± 238	0.42	473 ± 223	723 ± 340	0.015 *	501 ± 238	611 ± 360	0.45	477 ± 316	551 ± 232	0.20
Hydrodissection (yes /no)	Number of sessions	16/8	8/8	0.29	20/12	4/4	0.69	20/12	4/4	0.69	10/5	14/11	0.51

ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase, SD = standard deviation,*statistically significant difference


Percutaneous renal cryoablation
153 sessions (126 patients)
pathologically proven
primary or secondary renal cancer
No = 43 sessions (25 patients)
Yes = 110 sessions (101 patients)
patients who regularly take steroids or
non-steroid anti-inflammatory drugs
Yes = 33 sessions (32 patients)
No = 77 sessions (69 patients)
transcatheter arterial embolization (TAE)
within one month before cryoablation
Yes = 31 sessions (26 patients)
No = 46 sessions (43 patients)
patients who are deemed ineligible
for this study (e.g., poor compliance)
Yes = 6 sessions (4 patients)
No = 40 sessions (39 patients)
Study population


100
90
80
70
60
50
40
30
20
10
0
Incidence of occurence (%)
0
1
2
3
4
5
6
7
8
9
10
Post-ablation day
Fever
Nausea
Vomiting
Malaise