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Incidence of hypercoagulable events following image-guided percutaneous cryoablation of renal tumors: a single center experience

Jason B. Hartman[1], **Nicholas Bhojwani**[2], **David J. Corn**[3], **Matthew M. Cooney**[4], **John Haaga**[5], **Lee Ponsky**[6], **Robert Abouassaly**[7], **Akshay Paspulati**[8], and **J. David Prologo**[9]

[1]Case Western Reserve University School of Medicine, 2109 Adelbert Rd, Cleveland, OH 44106

[2]Department of Radiology, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106

[3]Department of Radiology, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106

[4]Department of Hematology/Oncology, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106

[5]Department of Radiology, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106

[6]Department of Urology, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106

[7]Department of Urology, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106

[8]Case Western Reserve University, 10900 Euclid Ave, Cleveland, OH 44106

[9]The Centers for Dialysis Care, 18720 Chagrin Boulevard, Shaker Heights, Ohio 4412

Abstract

Purpose—To retrospectively identify hypercoagulable events that occurred over time in patients who underwent image guided percutaneous renal cryoablation, and compare the incidence to a cohort of patients who underwent surgical partial nephrectomy (PN) during the same time period.

Methods—An electronic medical record database was queried for patients who underwent percutaneous image guided renal mass cryoablation or PN between September 2006 and June 2012. Records were examined for thrombotic events during the year following the procedure in

Corresponding Author: Jason Hartman, Case Western Reserve University School of Medicine, 2109 Adelbert Rd, Cleveland, OH 44106, 1-(925) 451-2596, jason.hartman@case.edu.

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each group. Incidence rates, Kaplan-Meier estimates, and patient demographic variables were compared using the stratified log-rank test and the t-test for independent samples.

Results—One hundred fourteen cryoablation cases were included. The cumulative incidence of thrombotic events after 1-year was 4.39%. The incidence per 100 person-years was 4.84. One hundred five PN cases were included. The cumulative incidence of thrombotic events after 1-year was 1.0%. The incidence per 100 person-years was 1.14. The person-time incidence rate difference for these two groups did not reach statistical significance (p = 0.0894).

Conclusion—The incidence of thrombotic events in patients who underwent percutaneous renal cryoablation in this study was not significantly different than a comparable cohort who underwent surgical PN during the same time period.

Introduction

The mechanism of cryoablation induced cell death differs from radiofrequency ablation in that the latter maintains cell surface integrity (1, 2). Cryoablation damages the cell membrane directly through formation of ice crystals, indirectly through formation of free radicals during reperfusion, and finally through ischemia following thrombosis of the microcirculation (3, 4). This process, termed “disruptive necrosis,” results in release of intracellular contents to the systemic circulation that initiate inflammatory and coagulopathic responses (1–8).

Alterations in serum chemistries, coagulation profiles, cell counts, and specific inflammatory markers following hepatic cryoablation have been extensively defined, and linked to a clinical syndrome termed “cryoshock” (5, 9, 10). Cryoshock has also been reported following cryoablation for renal cell cancer, as have coagulation related clinical events (11–13). Preclinical studies have linked cryoablation to dysregulated activation of the coagulation cascade and pro-inflammatory responses (1–3, 6, 11).

The purpose of this study was to retrospectively identify hypercoagulable events that occurred over time in patients who underwent image guided percutaneous renal cryoablation, and compare the incidence to a cohort of patients who underwent surgical partial nephrectomy (PN) during the same time period.

Materials/Methods

Local institutional review board approval was obtained and the study was compliant with the Health Insurance Portability and Accountability Act. An electronic medical record database was queried for patients who underwent percutaneous image guided renal mass cryoablation or partial nephrectomy between September 2006 and June 2012.

One hundred twenty eight consecutive patients who underwent cryoablation for suspected renal cell carcinoma (RCC) were reviewed. Fourteen of these were excluded because, 1) no post-ablation records were available (n=11) or, 2) the procedures were aborted due to technical problems (n=3). The remaining sample consisted of 114 patients. Each case was referred by a urologist and selected for therapy by fellowship trained interventional radiologists or interventional abdominal imagers. There were 4 different operators over 6

years. All procedures were performed with CT guidance (Brilliance 16 CT, Phillips Healthcare, Cleveland, Ohio). Seventy two of 114 procedures were performed with general anesthesia, 41 with conscious sedation, and in 1 case it was not charted. Between 1 and 6 cryoablation probes were inserted based on manufacturer's predicted ablation zones for each lesion. Tumors were classified as either central (if they were in contact with renal sinus fat), exophytic (if more than 50% of their circumference was outside the renal capsule), or intraparenchymal (if less than 50% was outside the renal capsule) (14). One hundred five patients underwent PN for renal masses during the same time period. Comparative demographic data for both groups are delineated in Table 1.

Primary outcome variables were the incidence and time of diagnosis of thrombotic events within the first year post procedure (image guided cryoablation or surgical partial nephrectomy). Patients' medical records were examined for thrombotic events including deep venous thrombosis (DVT), pulmonary embolism (PE), or embolic stroke during the year following their procedure. Incidence rates were calculated as cumulative incidence and as person-time (events per 100 patient-years). Data was collected in accordance with JVIR reporting standards for percutaneous thermal ablation of renal cell carcinomas (15).

The Kaplan-Meier estimator was used to evaluate differences in patient and disease characteristics such as gender, age, and presence or absence of metastasis. Kaplan-Meier estimates were compared using the stratified log-rank test. Analysis time began at the date of procedure and ended at the 1-year follow-up date for event-free patients; for all other patients time ended the date a VTE occurred or was right-censored at the latest follow-up hospital record, post procedure. Serum chemistry data, tumor sizes, and person-time incidence were compared using a t-test for independent samples. Data quality was checked using descriptive and frequency analyses; all proportionality assumptions were met. All statistical analyses were two-tailed using an alpha of 0.05 and were performed using Stata 12 (StataCorp, College Station, TX).

Results

Twenty four patients underwent cryoablation with 1 probe, 36 with 2 probes, 24 with 3 probes, 11 with 4 probes, 3 with 5 probes, and 1 with 6 probes. Three patients underwent cryoablation with 1.7 mm probes, 29 with 17 gauge probes, and 33 with 2.4 mm probes; probe size was not recorded in the other 49 cases. Fifty-five tumors were exophytic, 35 were intraparenchymal, and 24 were central. The average time of procedure for cryoablations was 133 ± 34.9 minutes, and did not correlate with subsequent thrombotic events.

Of the cryoablation cases reviewed, 5 patients were found to have venous thromboembolic disease (VTE). These adverse events were noted 5 days (1^{st} order branch PE), 6 days (posterior tibial vein DVT), 16 days (bilateral PEs), 158 days (multiple segmental PEs), and 364 days (1^{st} order branch PE) after successful cryoablation. The cumulative incidence after 1-year post cryoablation was 4.39%. The incidence per 100 person-years was 4.84. In comparison, of the PN cases reviewed, 1 patient was found to have VTE 3 days after the procedure (cephalic vein thrombosis). The cumulative incidence of VTE 1-year post procedure was 1.0%. The incidence per 100 person-years was 1.14. Despite the empirical

inequality of the VTE incidence rates between patients that underwent cryoablation versus those who underwent PN, the differences were not statistically significant ($p = 0.0894$).

The Kaplan-Meier estimates for those who underwent cryoablation were proportional to those who underwent PN. The log-rank test detected no significant effect due to undergoing cryoablation versus PN on the incidence of VTE during the first year post-procedure ($p = 0.1444$). Stratified on disease severity (metastasis), there was no significant difference in Kaplan-Meier estimates both within (cryoablation: $p = 0.7281$; PN: $p = 0.9104$) and between each treatment group ($p = 0.1727$). Comparisons of tumor size and serum laboratory values showed significant differences in tumor size ($p = 0.0001$), platelets ($p = 0.0001$), and white blood cells ($p = 0.0001$) (Table 2).

Discussion

Although hypercoabulable conditions have been noted post procedure in the setting of renal cell carcinoma ablations, (11, 12, 16, 17) no study has examined the incidence over time of these events in patients who underwent cryoablation for renal masses. We hypothesized that there may be a higher rate of thrombotic events in cryoablation patients compared to controls over time based on 1) data describing alterations in systemic inflammation and thrombosis after cryoabaltion (described below), 2) our subjective experience with renal cryoablation, 3) a suspicion that these events were excluded by traditional time limited periprocedural complication reporting, (18, 19) and 4) the notion that because thrombotic phenomena related to cryoablation may be separated in time from the physical procedure and occur in patients with underlying malignancy, they may be misinterpreted independent events.

Specific systemic mediators of adverse events following cryoablation have been described. Hepatic cryoablation in animal models resulted in 1) systemic increase of cytokines and pro-inflammatory proteins, including interleukin-6, tumor necrosis factor-α, C-reactive protein, macrophage inhibitory factor, and serum amyloid A (secreted during inflammation), 2) distant tissue manifestations of inflammation, and 3) local and distant activation of NF-κB, a transcriptional complex that regulates cytokine production and is linked to development of adult respiratory distress syndrome (ARDS) (2–4, 20). Clinical sequelae of this phenomenon have been described following ablation of hepatic neoplasms, the most severe of which manifests as multiorgan failure, disseminated intravascular coagulation, and ARDS – and is termed “cryoshock” (9). Also, it has been suggested that the presence of these antigens in the systemic circulation following cryoablation may induce at least a temporal tumoral immunity response, (8, 21, 22) a phenomenon which may play a role in the increased survival of patients who undergo metastatic ablations (1, 22).

Jansen, et al reported that serum thromboxane (a vasoconstrictor with prothrombotic properties) levels increased nine-fold with a simultaneous pro-coagulant activation and fibrinolysis suppression following hepatic cryoablation in sheep (6). Following the procedure, animals developed increased levels of thrombin and thrombin antithrombin complexes with suppression of plasminogen activity, portal levels of plasminogen activator levels, and fibrin degradation products. The response mirrors the procoagulant response

initiated during inflammation, but is inadequately balanced because of suppressed fibrinolysis - which resulted in widespread intravascular fibrin deposition.

The observed incidence of venous thromboembolic disease in patients that underwent percutaneous image guided cryoablation for renal cell carcinoma in this study was significantly higher than published rates (23–25). The incidence of VTE in the year following an image guided percutaneous renal cryoablation in this study was greater than the incidence in a comparable cohort who underwent surgical PN as well, but did not reach statistical significance.

This report has several limitations. It is possible that the number of thrombotic events in either cohort may be under represented, as patients may have developed thrombosis following the procedure during the time period included for this study, but presented elsewhere, transferred care to another institution for any number of reasons, were not seen in our system for lengthy periods of time, had acute or chronic (primary) clinical care elsewhere, may have died from thrombotic events, or may have expired a short time after therapy, preventing sufficient evaluation time. It is further limited by the assumption that other factors predisposing patients to VTE (immobilization, oral contraceptives, factor V Leiden, lupus anticoagulant, family history, sepsis, obesity, etc.) do not vary between cohorts, and by the paucity of data available regarding the patient characteristics of those included in independent published rates of thrombosis in RCC patients. Finally, all of the PN patients were prescribed sequential pneumatic compression devices during postoperative recovery – a potential explanation for the absolute difference in incidence of thrombotic events.

The incidence of thrombotic events in patients who underwent percutaneous renal cryoablation in this study, although higher than published results of RCC patients as a whole, was not significantly different than a comparable cohort who underwent surgical PN during the same time period. Larger, prospective studies tracking similar events may be helpful to validate these results.

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Table 1

Patient demographics

	Cryoablation	Partial Nephrectomy
Number of Patients	114	105
Age	68 ± 12 years, range 31–88	55 ± 13 years, range 19–81
% M, F	62,38	56,44
Tumor size	2.5 ± 1.1 cm, range 0.5 – 6	3.9 ± 2.3 cm, range 1 – 14
Tumor Type		
Clear Cell	44	68
Papillary	19	11
Oncocytic	18	8
Angiomyolipoma	2	3
Epithelial	8	5
Metastatic melanoma	1	0
Cystic neoplasm	3	4
Chromophobe	3	1
Non-diagnostic	8	0
No malignancy	8	5
Venous Thromboembolic Disease		
Cumulative Incidence	4.39%	1.00%
Incidence (per 100 person-years)	4.84	1.14

Table 2

Table of patient disease and serum chemistry data statistical results.

	Cryoablation	Partial Nephrectomy	*p*-value
Tumor Size	2.58 ± 1.08 cm	3.88 ± 2.34 cm	0.0001
Hemoglobin	12.31 ± 1.90 g/dL	11.90 ± 1.49 g/dL	0.0897
Platelets	188.15 ± 61.72 × 10^9/L	233.34 ± 64.13 × 10^9/L	0.0001
White Blood Cell	9.79 ± 3.60 × 10^9/L	11.98 ± 3.77 × 10^9/L	0.0001