Incidence of Hypercoagulable Events after Image-Guided Percutaneous Cryoablation of Renal Tumors: A Single-Center Experience

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ABSTRACT

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

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

Results: The study comprised 114 cryoablation cases. The cumulative incidence of thrombotic events after 1 year was 4.39%. The incidence per 100 person-years was 4.84. There were 105 PN cases. 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 ($P = .0894$).

Conclusions: 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.

ABBREVIATIONS

PE = pulmonary embolism, PN = partial nephrectomy, RCC = renal cell carcinoma, VTE = venous thromboembolism

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 after hepatic cryoablation have been extensively defined and linked to a clinical syndrome termed “cryoshock” (5,9,10). Cryoshock has also been reported after 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 proinflammatory responses (1–3,6,11).

The purpose of this study was to identify retrospectively hypercoagulable events that occurred over time in patients who underwent image-guided percutaneous renal cryoablation and compare the incidence with a cohort who underwent surgical partial nephrectomy (PN) during the same time period.
MATERIALS AND 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 PN between September 2006 and June 2012. We reviewed 128 consecutive patients who underwent cryoablation for suspected renal cell carcinoma (RCC). Of these patients, 14 were excluded because (a) no records after ablation were available (n = 11) or (b) the procedures were aborted because of 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 four different operators over 6 years. All procedures were performed with computed tomography guidance (Brilliance 16 CT; Philips Healthcare, Cleveland, Ohio). Of 114 procedures, 72 were performed with general anesthesia, and 41 were performed with conscious sedation; in 1 case, type of anesthesia was not charted. One to six cryoablation probes were inserted based on manufacturer’s predicted ablation zones for each lesion. Tumors were classified as central (if they were in contact with renal sinus fat), exophytic (if >50% of their circumference was outside the renal capsule), or intraparenchymal (if <50% was outside the renal capsule) (14). During the same time period, 105 patients underwent PN for renal masses. 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 after the procedure (image-guided cryoablation or surgical PN). Patients’ medical records were examined for thrombotic events, including deep venous thrombosis, pulmonary embolism (PE), or embolic stroke, during the year after the procedure. Incidence rates were calculated as cumulative incidence and as person-time (events per 100 patient-years). Data were collected in accordance with Society of Interventional Radiology (SIR) reporting standards for percutaneous thermal ablation of RCCs (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 the procedure and ended at the 1-year follow-up date for event-free patients; for all other patients, time ended the date a venous thromboembolism (VTE) occurred, or data were right-censored at the latest follow-up hospital record after 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 α of .05 and were performed using Stata 12 (StataCorp, College Station, Texas).

RESULTS

In 24 patients, cryoablation was performed with one probe; in 36, with two probes; in 24, with three probes;
in 11, with four probes; in 3, with five probes; and 1, with six probes. In 3 patients, 1.7-mm probes were used; in 29, 17-gauge probes; and in 33, 2.4-mm probes. Probe size was not recorded in the other 49 cases. Of tumors, 55 were exophytic, 35 were intraparenchymal, and 24 were central. The average procedure time for cryoablations was 133 minutes ± 34.9 and did not correlate with subsequent thrombotic events.

Five patients who underwent cryoablation were found to have VTE. These adverse events were noted 5 days (first-order branch PE), 6 days (posterior tibial vein deep venous thrombosis), 16 days (bilateral PEs), 158 days (multiple segmental PEs), and 364 days (first-order branch PE) after successful cryoablation. The cumulative incidence of VTE 1 year after cryoablation was 4.39%. The incidence per 100 person-years was 4.84. In comparison, of the PN cases reviewed, one patient was found to have VTE 3 days after the procedure (cephalic vein thrombosis). The cumulative incidence of VTE 1 year after the procedure was 1.0%. The incidence per 100 person-years was 1.14. Despite the empiric inequality of the VTE incidence rates between patients who underwent cryoablation versus patients who underwent PN, the differences were not statistically significant ($P = .0894$).

The Kaplan-Meier estimates for patients who underwent cryoablation were proportional to the estimates for patients who underwent PN. The log-rank test detected no significant effect because of undergoing cryoablation versus PN on the incidence of VTE during the first year after the procedure ($P = .1444$). Stratified on disease severity (metastasis), there was no significant difference in Kaplan-Meier estimates both within (cryoablation, $P = .7281$; PN, $P = .9104$) and between each treatment group ($P = .1727$). Comparisons of tumor size and serum laboratory values showed significant differences in tumor size ($P = .0001$), platelets ($P = .0001$), and white blood cells ($P = .0001$) (Table 2).

**DISCUSSION**

Although hypercoagulable conditions have been noted after procedures in the setting of RCC 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 patients undergoing cryoablation compared with controls over time based on (a) data describing alterations in systemic inflammation and thrombosis after cryoablation (described subsequently); (b) our subjective experience with renal cryoablation; (c) a suspicion that these events 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 after cryoablation have been described. Hepatic cryoablation in animal models resulted in (i) systemic increase of cytokines and proinflammatory proteins, including interleukin-6, tumor necrosis factor-α, C-reactive protein, macrophage inhibitory factor, and serum amyloid A (secreted during inflammation); (ii) distant tissue manifestations of inflammation; and (iii) local and distant activation of nuclear factor κB, a transcriptional complex that regulates cytokine production and is linked to development of adult respiratory distress syndrome (2-4,20). Clinical sequelae of this phenomenon have been described after ablation of hepatic neoplasms, the most severe of which manifests as multiorgan failure, disseminated intravascular coagulation, and adult respiratory distress syndrome and is termed “cryoshock” (9). Also, it has been suggested that the presence of these antigens in the systemic circulation after cryoablation may induce at least a temporal tumoral immunity response (8,21,22), a phenomenon that may play a role in the increased survival of patients who undergo metastatic ablations (1,22).

Jansen et al (6) reported that serum thrombomodulin (a vasoconstrictor with prothrombotic properties) levels increased 9-fold with simultaneous procoagulant activation and fibrinolysis suppression after hepatic cryoablation in sheep. After 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 VTE in patients who underwent percutaneous image-guided cryoablation for

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<tr>
<th>Table 2. Patient Disease and Serum Chemistry Data Statistical Results</th>
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<td><strong>Tumor size (cm)</strong></td>
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<td><strong>White blood cell count (× 10^9/L)</strong></td>
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Note. Values are mean ± SD.
RCC in this study was significantly higher than published rates (23–25). The incidence of VTE in the year following image-guided percutaneous renal cryoablation in this study was greater than the incidence in a comparable cohort who underwent surgical PN as well, but this did not reach statistical significance.

This study has several limitations. The number of thrombotic events in either cohort may be underrepresented because patients may have developed thrombosis after the procedure during the time period included for this study but presented elsewhere; may have 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 as a result of thrombotic events; or may have died a short time after therapy, preventing sufficient evaluation time. The study is limited further by the assumption that other factors predisposing patients to VTE (e.g., immobilization, oral contraceptives, factor V Leiden, lupus anticoagulant, family history, sepsis, obesity) do not vary between cohorts and by the paucity of data available regarding the characteristics of patients included in independent published rates of thrombosis in patients with RCC. Finally, all of the patients undergoing PN were prescribed sequential pneumatic compression devices during postoperative recovery—a potential explanation for the absolute difference in incidence of thrombotic events.

In conclusion, the incidence of thrombotic events in patients who underwent percutaneous renal cryoablation in this study, although higher than published results of patients with RCC 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.

REFERENCES


