Periprocedural factors associated with overall patient survival following percutaneous image-guided liver tumor cryoablation

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ABSTRACT
Purpose: To assess the impact of periprocedural factors, including adverse events, on overall patient survival following image-guided liver tumor cryoablation procedures.
Methods: In this retrospective single-institution study, 143 patients (73 male, 70 female, ages 29–88) underwent 169 image-guided liver tumor cryoablation procedures between October 1998 and August 2014. Patient, tumor and procedural variables were recorded. The primary outcome was overall survival post-procedure (Kaplan–Meier analysis). Secondary outcomes were the impact of 15 variables on patient survival, which were assessed with multivariate cox regression and log-rank tests.
Results: Mean tumor diameter was 2.5 ± 1.2 cm. 26 of 143 (18.2%) patients had primary hepatic malignancies; 117 of 143 (81.8%) had liver metastases. Survival analysis revealed survivor functions at 3, 5, 7, 10 and 12 years post-ablation of 0.54, 0.37, 0.30, 0.17 and 0.06, with mean survival time of 40.8 ± 4.9 months. Tumor size >4 cm (p = .018), pre-procedural platelet count <100 × 10³/μL (p = .023), and prior local radiation therapy (p = .014) were associated with worse overall patient survival. Grade 3 or higher adverse events were not associated with reduced survival (p = .49).
Conclusions: All variables associated with overall survival were patient-related and none were associated with the cryoablation procedure. Pre-procedural thrombocytopenia, larger tumor size and history of prior local radiation therapy were independent risk factors for reduced overall survival in patients undergoing hepatic cryoablation. Adverse events related to hepatic cryoablation were not associated with decreased survival.

Introduction
Primary and metastatic liver tumors are a common cause of mortality [1]. Globally, the incidence of primary liver malignancies, including hepatocellular carcinoma and cholangiocarcinoma, has been increasing annually with over 854,000 cases and 810,000 deaths annually [2]. In the United States, primary hepatobiliary cancers are the fourth most common type of gastrointestinal cancer [3] with metastatic disease to the liver occurring frequently, most commonly from primary tumors of colorectal, pancreas, stomach, lung and breast origin [4–8]. As a result, treatment of primary and metastatic liver tumors remains a major clinical problem.

Local therapies can provide a significant survival advantage in patients with hepatic tumors [9]. Common local treatment options for hepatic tumors include surgery, stereotactic radiation, catheter-directed therapy and thermal ablation [10–12]. Image-guided percutaneous ablation has been a rapidly growing option especially for patients who are not surgical candidates [13]. Ablation can also be used to bridge patients to liver transplantation. Ablation options include microwave ablation (MWA), radiofrequency ablation (RFA) and cryoablation. While the safety and efficacy of heat-based MWA and RFA are well established [13–15], there is less data on hepatic tumor cryoablation. Potential advantages of cryoablation include decreased post-procedural pain and precise intraprocedural monitoring of the ice ball with CT or MRI enabling ablation closer to critical structures [16–19]. Other methods for intraprocedural temperature monitoring in cryoablation include monitoring of luminal temperatures of surrounding structures and short tau inversion-recovery ultrashort eco-time magnetic resonance imaging sequence [20,21].

Prior reports have demonstrated that image-guided percutaneous cryoablation of hepatic tumors can be effective and safe [22,23]. The endpoints of one study included initial technical success, technique efficacy at 3 months post-procedure, local tumor progression based on all available follow-up, and grade 3 or higher adverse event rate [22]. However, factors impacting overall survival were not addressed in the study. The purpose of this article was to expand on this previous report and assess the impact of...
periprocedural factors, including adverse events, on overall patient survival following image-guided liver tumor cryoablation.

**Material and methods**

**Patient selection**

This retrospective cross-sectional study was approved by the Institutional Review Board and the need for informed consent was waived. A query of the divisional interventional radiology tumor ablation database found 186 patients (>18 years) who underwent 236 image-guided hepatic cryoablation procedures to treat 299 malignant tumors between October 1998 and August 2014. The end-of-study date was selected to allow for long-term survival analysis. Three patients with four tumors not treated with curative intent due to extrahepatic metastasis and were excluded. Forty patients with 65 treated tumors had less than three months’ imaging follow-up at our institution and were excluded (Figure 1). However, one patient with less than three months follow-up experienced a grade 5 adverse event and was included to prevent underestimating adverse event-related mortality. The final study cohort consisted of 143 patients (73 male, 70 female, mean age 61, range 29–88) who underwent 169 procedures to treat 230 tumors (Table 1). All tumors were treated with curative intent. Twenty-six of 143 (18.2%) patients had primary hepatic malignancies, 33 of 143 (23.1%) patients had colorectal metastases to the liver, and 84 of 143 (58.7%) patients had other metastases to the liver. Technical success, defined as complete coverage of the tumor by the ablation zone on post-procedure imaging, was noted in 217 of 230 tumors (94.3%). This patient cohort has been previously reported in a study that examined technical success, technique efficacy, local tumor progression and adverse event rate [22]. The same endpoints will not be addressed in this study.

**Cryoablation procedures**

All cryoablations were performed by one of three radiologists with between 1 and 16 years of experience with cryoablation over the course of the study. Procedures were performed with Visual Ice, Galil Medical Inc (Arden Hills, MN) and 17- or 14-gauge applicators. The mean applicator gauge and density (defined as number of applicators/maximum tumor diameter in cm) were 15.8 ± 2.2 and 1.7 ± 1.1. Applicators were insulated in almost all procedures (92%). The standard cryoablation procedure protocol used two 15-min freeze cycles separated by a 10-min thaw. An anesthesiologist assisted all ablation procedures, using either general anesthesia (n = 111) or monitored anesthesia (n = 32). Seventy-three patients underwent ablations performed under CT-guidance, 63 under MRI-guidance and 7 under PET/CT-guidance. CT-guided procedures used one of three scanners: CT scanner portion of Biograph mCT PET/CT scanner (Siemens, Erlangen, Germany), Somatom Sensation (Siemens, Erlangen, Germany), or Definition AS (Siemens, Erlangen, Germany). MRI-guided procedures used a 70 cm, wide bore Magnetom Verio 3 Tesla MR scanner platform (Siemens, Erlangen, Germany). PET/CT-guided procedures used a Biograph mCT (Siemens, Erlangen, Germany) with CT-fluoroscopy capability and 21 cm z-axis field of view (PET) for guidance.

**Study outcomes**

The primary outcome of this study was overall patient survival, calculated as the length of time a patient lived after

**Table 1. Patient, tumor and procedural variables assessed for potential impact on overall survival.**

| Variable analyzed, by patient (n = 143) | Mean ± SD or number (%) |
|---------------------------------------|-------------------------|
| Gender                                |                         |
| Male                                  | 73 (51.0)               |
| Female                                | 70 (49.0)               |
| Age (years)                           | 60.8 ± 12.9             |
| Prior local radiation to the liver    |                         |
| Yes                                   | 16 (11.2)               |
| No                                    | 127 (88.8)              |
| Prior liver tumor resection           |                         |
| Yes                                   | 31 (21.7)               |
| No                                    | 121 (84.6)              |
| Tumor diameter ≥4 cm                  |                         |
| Yes                                   | 22 (15.4)               |
| No                                    | 121 (84.6)              |
| Number of tumors ablated              | 1.6 ± 0.9               |
| Tumor pathology                       |                         |
| Primary hepatic malignancy            | 26 (18.2)               |
| Colorectal metastasis                 | 33 (23.1)               |
| Other metastasis                      | 84 (58.7)               |
| Pre-procedural platelet count <100 × 10^{3}/µL |                 |
| Yes                                   | 56 (39.2)               |
| No                                    | 87 (60.8)               |
| Pre-procedural creatinine (mg/dL)      | 1.0 ± 0.5               |
| Post-procedural serum myoglobin (mg/mL)| 374.4 ± 574.6           |
| Anesthesia type                       |                         |
| General anesthesia                    | 111 (77.6)              |
| Monitored anesthesia care             | 32 (22.4)               |
| Applicator density (applicator #/max tumor diameter in cm) | 1.7 ± 1.1 |
| Applicator gauge                      | 15.8 ± 2.2              |
| Applicator insulation                 |                         |
| Yes                                   | 11 (7.7)                |
| No                                    | 132 (92.3)              |
| Procedural adverse events             |                         |
| Grade 0                               | 113 (79.0)              |
| Grade 1–2                             | 12 (8.4)                |
| Grade 3                               | 11 (7.7)                |
| Grade 4                               | 6 (4.2)                 |
| Grade 5                               | 1 (0.7)                 |

> Figure 1. Flow chart of inclusion and exclusion criteria for the final study cohort.
the date of the cryoablation procedure. Secondary outcomes were impact of 15 variables on overall patient survival (Table 1): two patient demographic variables – age and gender; five clinical characteristics – prior local radiation therapy to the liver, prior liver tumor resection, tumor diameter $\geq 4$ cm, number of tumors ablated and tumor pathology (primary hepatic malignancy, colorectal metastasis and other metastasis); four procedural variables – anesthesia type, applicator density, applicator insulation and applicator gauge; three lab values – pre-procedural platelet count less than 100 $\times 10^3/\mu$L, pre-procedural creatinine, post-procedural myoglobin; and grade 3 or higher adverse events based on National Cancer Institute’s Common Terminology Criteria for Adverse Events version 5 (CTCAE) [24].

**Statistical analysis**

Overall patient survival was assessed using Kaplan–Meier analysis. Survival analyses were conducted by patient. To investigate the association between patient survival time and the collected variables, a cox regression model was constructed. Kaplan–Meier curves and log-rank tests were used for univariate analysis to assess the association between any categorical variables and survival time. Cox proportional regression analysis was used for multivariate analysis to assess the association of all 15 factors with the outcome being assessed. $p$ Values $<.05$ were considered statistically significant and all tests were two-tailed. All statistical analysis was performed using STATA version 14 software (STATA Inc., College Station, TX).

**Results**

**Patient population**

The mean tumor size was $2.5 \pm 1.2$ cm (range: 0.6–7.8 cm) and the mean number of tumors ablated per patient was 1.6 $\pm$ 0.9 (range: 1–6). Twenty-two of 143 (15.4%) patients had tumors $\geq 4$ cm. Sixteen of 143 (11.2%) patients had prior local radiation to the liver and 31 of 143 (21.7%) patients had prior liver tumor resection. Patient characteristics are summarized in Table 1.

**Overall survival analysis**

The mean overall survival was 40.8 $\pm$ 4.9 months (Figure 2). The survivor functions, defined as the fraction of patients still alive, at 3, 5, 7, 10 and 12 years post-ablation were 0.54, 0.37, 0.30, 0.17 and 0.06.

**Factors associated with patient survival**

Of all 15 variables assessed, the Kaplan–Meier analysis identified 2 of the 15 variables to be associated with decreased survival functions – tumor size $\geq 4$ cm ($p = .018$) and pre-procedural platelet count $< 100 \times 10^3/\mu$L ($p = .023$) (Figure 3). Multivariate cox regression survival analysis identified prior radiation as associated with decreased long-term survival (hazard ratio [HR] $= 2.25$, $p = .014$) while prior liver tumor resection was associated with increased survival (HR $= 0.38$, $p = .005$). No other variables (age, gender, tumor pathology, number of tumors ablated, pre-procedural creatinine, post-procedural myoglobin, anesthesia type, applicator density, applicator gauge and applicator insulation) were associated with decreased or increased long-term overall patient survival (Table 2). Local tumor progression was also not associated with survival ($p = .36$).

**Adverse events**

Eighteen of 143 (12.6%) patients experienced grade 3 or higher adverse events. However, grade 3 or higher adverse events were not associated with reduced survival (HR $= 0.77$, $p = .49$) as found on multivariate cox regression survival analysis (Table 2). Patients were grade 3 and 4 adverse events all experienced full recovery. The most common grade 3 or 4 adverse events were related to post-procedural thrombocytopenia. For example, one patient who experienced hepatic hemorrhage with post-procedural thrombocytopenia (platelet $= 88,000 \times 10^3/\mu$L) and anemia (hematocrit $= 37\%$) was transfused with 4 units of packed red blood cells. The patient fully recovered with no lasting adverse sequelae or local recurrence based on imaging 11 years later (Figure 4). The single grade 5, procedure-related adverse event was an 88-year-old male with preexisting congestive heart failure and metastatic colorectal cancer who developed oliguric renal failure and myoglobinuria following hepatic cryoablation of a 7.8 cm metastasis (the largest ablated tumor in our cohort). The patient died 3 days later from aspiration and pulmonary edema.

**Discussion**

This study assessed the impact of clinical characteristics, procedural factors, lab values and adverse events on long-term overall survival of patients undergoing hepatic cryoablation.
A previous study of this patient cohort focused on therapeutic efficacy. For all tumors studied, the technical success rate was 94.6% and the technique efficacy rate was 89.5% [22]. Local tumor progression was calculated to be 23.3% based on all available follow-up. Grade 3–5 adverse events occurred in 10.6% of cases. For tumors, less than 4 cm in size, technique efficacy, local tumor progression and grade 3 or higher adverse event rates were 93.4, 18.0 and 8.7% [22].

Technical success and technique efficacy for cryoablation were comparable to those reported for RFA for the treatment of hepatocellular carcinoma and hepatic metastases [14,19,25]. Most adverse events were mild or centered on routine management of expected post-procedure thrombocytopenia with platelet transfusions. Smaller tumors (<4 cm) were more likely to be treated successfully and without major adverse event. Despite the advantages of percutaneous liver cryoablation, adoption has been limited by concerns over bleeding, liver fracture and cryoshock, particularly based on early open cryosurgical experience [26].

Therefore, the goal of this study was to expand on the previous report by analyzing the impact of periprocedural factors including adverse events on overall patient survival. The average survival time after cryoablation was 40.8 months with survivor functions at 3, 5, 10 and 12 years of 0.54, 0.37, 0.17 and 0.06. Patients with ablated tumors ≥ 4 cm, pre-procedural platelet count < 100 k, prior local radiation therapy, and those that had not undergone prior tumor resection experienced decreased overall survival in our study. There was also no association between local tumor progression and survival although the analysis did not include a matched control group not undergoing ablation.

The survival rates are comparable to what has been reported for RFA and cryoablation of liver tumors [27–31]. One study of patients undergoing RFA for colorectal metastases to the liver found survival functions at 3 and 5 years to be 0.50 and 0.29 [27]. In another study, survival functions at 5 and 10 years of patients undergoing RFA for hepatocellular carcinoma were reported to be 0.39 and 0.23 and, for colorectal metastases, 0.28 and 0.15 [28]. The mean survival for RFA of complex unresectable liver tumors was 33.2 months in another study [29], which was slightly lower than the mean survival of 40.8 months for patients in this study.
study. Two previous studies on percutaneous cryoablation of patients with treatment naïve hepatocellular carcinoma found 5-year survival functions of 0.60 and 0.50 [30,31].

Patients with larger tumors, prior local radiation therapy and unresectable tumors would be expected to have more aggressive or advanced disease with greater tumor burden that may be associated with worse prognosis regardless of treatment strategy. Since liver resection is often the first-line local treatment option for curative intent, patients without prior liver resection may have included a significant number of patients with greater operative risk and poorer overall prognosis; this may explain the better survival in patients with prior resection. Our results are consistent with prior studies of patients undergoing RFA for unresectable, and recurrent liver tumors that resulted in shorter survival times [27,29,32–34].

Lower preprocedural platelet count may be an indicator of a compromised baseline health condition or drug side-effect, which could potentially lead to worse prognosis with or without ablation. For RFA of hepatocellular carcinoma, pre-procedure thrombocytopenia has been associated with liver function deterioration and reduced survival [35,36].

While larger tumor size and preexisting thrombocytopenia have been associated with an increased incidence of adverse events following hepatic cryoablation, the impact of these adverse events on overall survival has not been specifically addressed. The occurrence of grade 3 or 4 procedural adverse events was not associated with reduced overall patient survival in this study; these patients with cryoablation-related adverse events recovered fully. Post-procedural thrombocytopenia was the most common adverse event and was effectively managed with platelet transfusions as needed. Hepatic cryoablation can be expected to induce thrombocytopenia in proportion to the amount of normal hepatic tissue ablated; therefore, our clinical practice includes routine peri-procedural monitoring and management of the platelet level [37].

Limitations of this study include a retrospective design and moderate-sized patient cohort. Future study with a larger cohort size could be considered to validate these findings. Additionally, all-cause mortality was the primary endpoint. Stratification of mortality causes is challenging in a retrospective study but could be performed prospectively to further understanding of patient mortality after liver cryoablations.

In summary, all variables associated with overall survival were patient-related and none were associated with the cryoablation procedure. Pre-procedural thrombocytopenia, larger tumor size and history of prior local radiation therapy were independent risk factors for reduced overall survival in patients undergoing hepatic cryoablation. Adverse events related to hepatic cryoablation were not associated with decreased survival. Therefore, hepatic cryoablation appears to be an acceptably safe treatment option in patients with limited hepatic tumors.

Ethics approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approved IRB protocol number: 2001P000028.

Informed consent
For this type of study formal consent is not required.

Disclosure statement
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Code available upon request.

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