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Clinical Trial Results

A Phase II Study of Tumor Ablation in Patients with Metastatic Sarcoma Stable on Chemotherapy

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01986829
- **Sponsor(s)**: Division of Oncology, Washington University School of Medicine
- **Principal Investigator**: Brian A. Van Tine
- **IRB Approved**: Yes

Lessons Learned

Ablation therapy appears to be a reasonably safe and effective approach to obtain a significant treatment-free interval for a subset of patients with limited sites of metastatic disease for which systemic control can be obtained with six cycles of chemotherapy.

Abstract

Background. Metastatic sarcoma often becomes resistant to treatment by chemotherapy. There is sometimes prolonged stable disease from active chemotherapy that provides a window of opportunity for an intervention to prolong disease-free survival.

Materials and Methods. We performed a phase II study in patients with metastatic sarcoma who had been stable on six cycles of chemotherapy who then received ablation therapy to their residual disease. Histologies captured in this study included leiomyosarcoma, malignant peripheral nerve sheath tumor, pleiomorphic rhabdomyosarcoma, and myxoid liposarcoma. Sites ablated included lung metastases and retroperitoneal metastatic deposits. In this study, up to three lesions were ablated in any given interventional radiology session. After ablation, patients were not treated with any further therapy but were followed by surveillance imaging to determine progression-free rate (PFR).

Results. Although terminated early because of slow accrual, this study demonstrated a 3-month PFR of 75% for this cohort of eight patients treated with ablation performed after completion of six cycles of chemotherapy with stable disease. Median progression-free survival (PFS) was 19.74 months, and the median overall survival (OS) was not reached.

Conclusion. Our data are the first prospective study to suggest that ablation therapy in selected patients who are stable on chemotherapy can provide a significant progression-free interval off therapy and warrants further study in a randomized trial. ***The Oncologist*** 2018;23:760–e76

Discussion

Sarcomas are rare cancers that encompass a group of an estimated 70 different histologic subtypes with varying biology [1]. Given the diversity of these tumors, a single drug therapy is not likely to be successful across all subtypes [2].

In this phase II trial of patients with metastatic soft tissue sarcoma, we demonstrate a 3-month PFR of 75% after ablation. Based on prior studies, this degree of response certainly supports the hypothesis that ablation after stability on chemotherapy can serve as a well-tolerated maintenance therapy and provide a significant PFS along with a chemotherapy-free interval for patients with metastatic soft tissue sarcoma [7, 8].

Unfortunately, this study was closed early because of low accrual at a single center. Nonetheless, most patients on trial did very well, and median overall survival had not been reached at the time of manuscript preparation (Figure 1). Furthermore, we report a median PFS of 19.7 months compared with the 13.4 months reported for pulmonary metastasectomy in sarcoma, suggesting that ablation therapy is a viable option to a surgical metastasectomy [3–5, 9, 10]. Additionally, ablation, which

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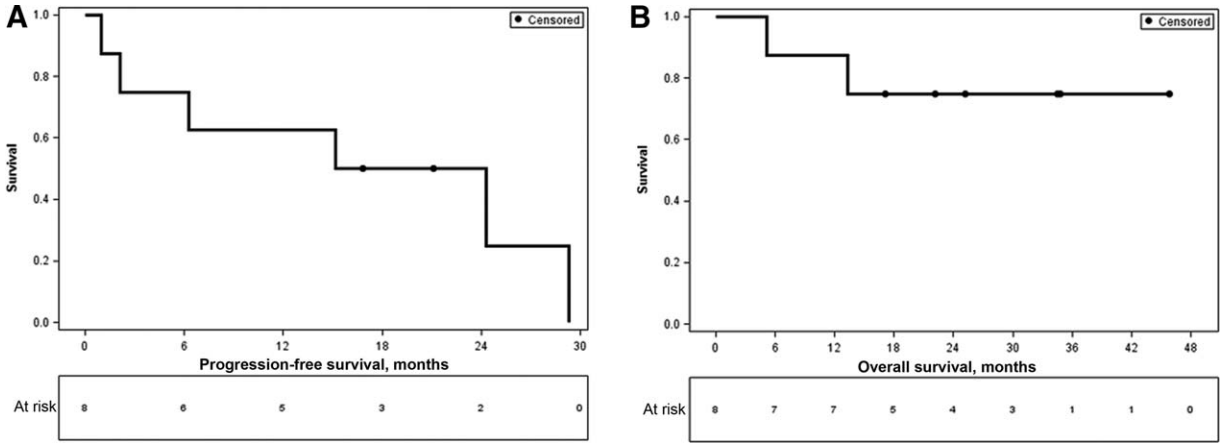

Figure 1. Kaplan-Meier curves for progression-free and overall survival. **(A):** Progression-free survival. **(B):** Overall survival.

has a quick recovery time, can be used on lesions such as bone metastases, liver metastases, and various visceral sites that may pose more of a challenge for surgical intervention, especially in cases in which more than one organ site is involved in the same patient [4].

In conclusion, we have shown a 75% PFR with a median PFS of 19.74 months for patients stable on chemotherapy who then underwent ablation of residual sites of disease, strongly supporting ablation as a potential form of maintenance therapy for soft tissue sarcomas (Figure 1).

Trial Information	
Disease	Sarcomas – Adult
Stage of Disease/Treatment	Metastatic/Advanced
Prior Therapy	No designated number of regimens
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Progression-free rate (PFR)
Secondary Endpoint	Overall survival
Secondary Endpoint	Quality of life
Additional Details of Endpoints or Study Design	

Patients

This study was performed under an active Human Studies Protocols approved by the Institutional Review Boards at Washington University in St. Louis (201309108) in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This trial was registered on ClinicalTrials.gov (NCT01986829). Patients with histologically or cytologically confirmed high-grade metastatic sarcoma that had been stable on 6–12 cycles of one chemotherapeutic regimen (cytotoxic or biologic) were recruited from the Washington University Sarcoma Clinic. Patients had to be at least 18 years of age. Other patient entry criteria included measurable disease defined as lesions that could be accurately measured in at least one dimension (longest diameter to be recorded) as $>$10 mm with CT, positron emission tomography/CT, or magnetic resonance imaging; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, and normal bone marrow and organ function. The patients could have no more than 10 treatable lesions, as evaluated by an experienced interventional radiologist for eligibility and technical accessibility. The lesions had to be amenable to a safe, ultrasound/computed tomographic guided percutaneous approach, as assessed by one of the three interventional radiologists involved in the study. The targeted metastases had to be sufficiently separateable from the central nervous system, major peripheral motor nerves, bowel, and bladder. Key exclusion criteria were: (a) history of another malignancy within 5 years, (b) known brain metastasis, (c) patients receiving other investigational agents, (d) intercurrent illness that would limit compliance with the study, (e) pregnancy, and (f) patients wishing to receive chemotherapy after ablation.

Study Design and Procedures

Patients whose disease was stable on six cycles of standard-of-care chemotherapy and who met the above inclusion criteria were offered the option of enrolling in this trial.

Eligible patients could have had their lesions ablated using cryoablation, radiofrequency ablation, or microwave ablation. These techniques are thought to be equivalent. The choice of the procedure was based on the expertise of the interventional oncologic radiologist and the site of metastasis. Cryoablation was used on all eight patients in the current study.

Cryoablation of the soft tissue and parenchymal metastases were performed under CT guidance with cryoprobes from Endocare Inc. (Irvine, CA) or Galil Medical (Arden Hills, MN). For cryoablation, a single freeze-thaw-freeze cycle was performed for each lesion. The freezing portions of the cycle varied depending on size of the ice ball and adequacy of coverage and proximity to adjacent critical structures. Nonenhanced computed tomography was performed every 3 to 5 minutes, with soft tissue windows throughout the freezing cycle to monitor growth of the ice ball. After completion of the final freeze cycle of the cryoablation procedure, the cryoprobes were actively heated with helium until temperature was above 20°C, and then the probe(s) was (were) withdrawn.

Ablations were performed according to the manufacturer's recommendations in the package insert. After completion of ablation, tract ablation occasionally was performed as the probe was withdrawn. Procedures were performed on an outpatient basis, but patients were

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admitted for observation after the procedure as deemed appropriate by the treating interventional radiologist. Patients were generally under moderate conscious sedation with continuous nurse monitoring of pulse oximetry, blood pressure, cardiac rhythm and rate, and respirations. One percent lidocaine alone or a 1:1 mixture of 1% lidocaine and 0.25% bupivicaine or 0.5% ropivicaine was used for local anesthesia.

Chemotherapy was stopped at initiation of ablation therapy, and ablation therapy was completed within 3 weeks of enrollment. Patients were followed with CT scans every 9 weeks for the first year, every 12 weeks for the second year, and then every 6 months until a new biopsy-proven lesion or a previously ablated lesion grew by 20% in size. Additionally, patients completed a quality of life assessment the 7-item functional assessment of cancer therapy-general (FACT-G7) prior to ablation, 1 month after ablation, and at progression.

Study Outcome and Statistical Analysis

The primary outcome was to determine the PFR at 3 months. Three-month PFR was defined as the percentage of patients with no progression (local recurrence of an ablated lesion or the appearance of a new lesion) at 3 months after ablation. Secondary outcomes included overall survival and quality-of-life measures.

Our power analysis was based on the following hypotheses. The null hypothesis assumed that the 3-month progression-free survival (PFS) for treatment with ablation therapy would be overall 20% for patients with metastatic sarcoma. We hypothesized in the alternative hypothesis that the 3-month PFS would be at least 40% with ablation therapy. This was based on data from a clinical trials database used to provide reference values for conducting phase II studies in sarcoma with PFR as the principal endpoint [14]. An enrollment of 36 patients was intended to achieve at least 80% power to reject the null hypothesis based on a two-sided one-sample proportion test at a significance level of 0.05. This trial was closed early, however, because of slow accrual.

Descriptive statistics were used to describe the characteristics and adverse events of the patients. OS was defined as the time from prior to chemotherapy to death from any cause, and PFS was defined as the time prior to ablation to documented disease progression or death. The Kaplan-Meier product limit method was applied to estimate the empirical survival probabilities for OS and PFS. Median survival times were estimated. The Wilcoxon signed-rank test was used to determine whether there was an improvement in quality of life after ablation versus baseline. All p values were two-sided, and significance was claimed at the 5% level. All statistical analyses were performed using the statistical software SAS (version 9.4, SAS Institute, Cary, NC).

Investigator's Analysis	Activity suggested and should be further pursued

Patient Characteristics

Number of Patients, Male	4
Number of Patients, Female	4
Stage	Metastatic
Age	Median (range): 60 years
Number of Prior Systemic Therapies	Median (range): 1
Performance Status: ECOG	0 — 8 1 — 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	
leiomyosarcoma	
malignant peripheral nerve sheath tumor	
pleiomorphic rhabdomyosarcoma	
myxoid liposarcoma	

Primary Assessment Method for Phase II Control

Title	Total Patient Population
Number of Patients Screened	9
Number of Patients Enrolled	8
Number of Patients Evaluable for Toxicity	8
Number of Patients Evaluated for Efficacy	8
Evaluation Method	RECIST, version 1.1
Response Assessment CR	$n = 6$ (75%)
(Median) Duration Assessments PFS	19.74 months

Adverse Events

All Dose Levels, Cycle 1							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Pneumothorax	0%	0%	0%	12.5%	12.5%	0%	25%

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Adverse Events Legend

Two patients experienced adverse events, which are summarized in the above table. One patient developed a pneumothorax and a small pleural effusion that resolved. The second patient developed a hemopneumothorax and died 1 month after the procedure. The second patient who experienced an adverse event had required two ablation procedures because she had lesions in both lungs. Although this patient had stable disease at the end of six cycles of chemotherapy, she was found to have progressive disease (rapid increase in size of one of the nodules to be ablated) at the time of the second ablation procedure and afterwards continued to experience rapid progression of her disease.

Abbreviation: NC/NA, no change from baseline, no adverse event.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Did not fully accrue
Investigator's Assessment	Activity suggested and should be further pursued

Sarcomas encompass a group of an estimated 70 different histologic subtypes with varying biology [1]. There are approximately 15,000 new cases of sarcoma per year in the United States, accounting for about 1% of adult malignancies [2]. Prognosis is poor for patients with metastatic disease, with a median overall survival of only 12–14 months. Given the biological diversity of these tumors, a single drug therapy is not likely to be successful across all subtypes [3]. As such, novel and multidisciplinary approaches will be imperative to improve survival.

Cytotoxic chemotherapy is the mainstay of therapy for metastatic sarcoma. This alone, however, is very unlikely to result in a durable remission or cure. The combination of chemotherapy with resection of pulmonary metastases has been shown to increase the 3-year overall survival in metastatic osteosarcoma from approximately 5% to 65% [4]. Similar data exist for soft tissue sarcomas as well [5, 6]. Unfortunately, not all metastases are amenable to resection.

An alternative procedural approach to treating metastatic cancer includes ablation therapy. There are several types of ablation procedures, including radiofrequency ablation, cryoablation, irreversible electroporation, and microwave ablation [7–11]. Each technique has its merits and disadvantages, but their results are thought to be equivalent, and the choice of which type of ablation to use is typically based on the site of metastasis and operator preference.

There are retrospective data suggesting that radiofrequency ablation is safe in patients with sarcoma with lung metastases with a 3-year overall survival of 65%, similar to what is quoted in surgical studies [12]. Given these data, we performed this single-arm prospective phase II trial of ablation therapy in patients with metastatic sarcoma who had fewer than 10 lesions and whose disease was stable on chemotherapy. These patients were stable on 6–12 cycles of cytotoxic chemotherapy, as this is the natural stopping point for doxorubicin-based chemotherapy, which is the standard treatment in soft tissue sarcoma [13]. Ablation therapy then served as a form of maintenance therapy.

In this early terminated phase II trial of patients with metastatic soft tissue sarcoma, we demonstrated a 3-month progression-free rate (PFR) of 75% with a median PFS of 19.74 months after ablation. Based on prior studies, this magnitude of response certainly supports the hypothesis that ablation after stability on chemotherapy can serve as a well-tolerated maintenance therapy and provide a significant PFS along with a chemotherapy-free holiday for patients with metastatic soft tissue sarcoma [14, 15]. Furthermore, median overall survival has not been met to date, and several patients are still being monitored off any therapy after ablation (Figure 1). The antitumor mechanisms may be twofold. First, there may be direct antitumor effects associated with the ablation process. Additionally, there are data from other studies suggesting immune modulation after ablation therapy as evidenced by increases in levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), as well as tumor-antigen-specific T cells in the bloodstream after ablation [16, 17].

Unfortunately, this study was closed early because of low accrual at a single center. There were two major reasons for this. The first was that there was a limited population of patients with metastatic sarcoma who were able to maintain stable disease for six cycles of chemotherapy, indicating that this will not be an option for all patients. Second, given that metastatic sarcomas are not curable, most academic centers offer clinical trials for patients with metastatic disease, and most clinical trials maintain patients on therapy until progression. As such, after discussing all options, many patients chose to enroll in another clinical trial rather than pursue a standard-of-care regimen with the hope that they would obtain stable disease for six cycles in order to be eligible to consent for this ablation study. Nonetheless, most patients on trial did very well, and median overall survival had not been reached at the time of manuscript preparation. Furthermore, we report a median PFS of 19.7 months compared with the 13.4 months reported for pulmonary metastectomy in sarcoma, suggesting that ablation therapy is a viable option to a surgical metastectomy [4–6, 18, 19]. Additionally, ablation, which has a quick recovery time, is able to be used on lesions, such as bone metastases, liver metastases, and various visceral sites, that may pose more of a challenge for surgical intervention, especially in cases in which more than one organ site is involved in the same patient [5].

We reported two adverse events in this study. One patient developed a pneumothorax and pleural effusion that required hospitalization. That patient was treated with a chest tube and antibiotics, recovered, and had a 6-month PFS after recovery. The second patient required two ablation procedures, which were spaced by 2 weeks. In that 2-week period, the patient demonstrated significant progression despite having stable scans at the end of chemotherapy. She subsequently developed

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a hemopneumothorax after a second ablation procedure. During hospitalization, she developed rapidly progressive disease and passed away 1 month after ablation. None of the other patients experienced any adverse events. Overall, ablation is a safe and well-tolerated procedure for sarcomas [12, 20, 21].

Although no statistically significant changes were reported in quality-of-life measures, several observations were made. Most patients reported increased pain on the survey performed after the ablation procedure. That symptom resolved in all patients assessed at their next follow-up appointment in clinic and was thought to be because of the discomfort associated with the procedure, not a change in the pain related to their malignancy. Most patients reported a decrease in nausea, improvement in energy, decreased worry, and overall improvement in quality of life (Figure 2).

In conclusion, we report the results of a phase II trial for patients with metastatic sarcoma stable on six cycles of chemotherapy who then underwent ablation of the residual metastatic sites. This is the first prospective examination of ablation therapy in metastatic sarcoma. Furthermore, we have shown a 75% PFR with a median PFS of 19.74 months, strongly supporting this as a beneficial form of maintenance therapy.

Acknowledgments

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

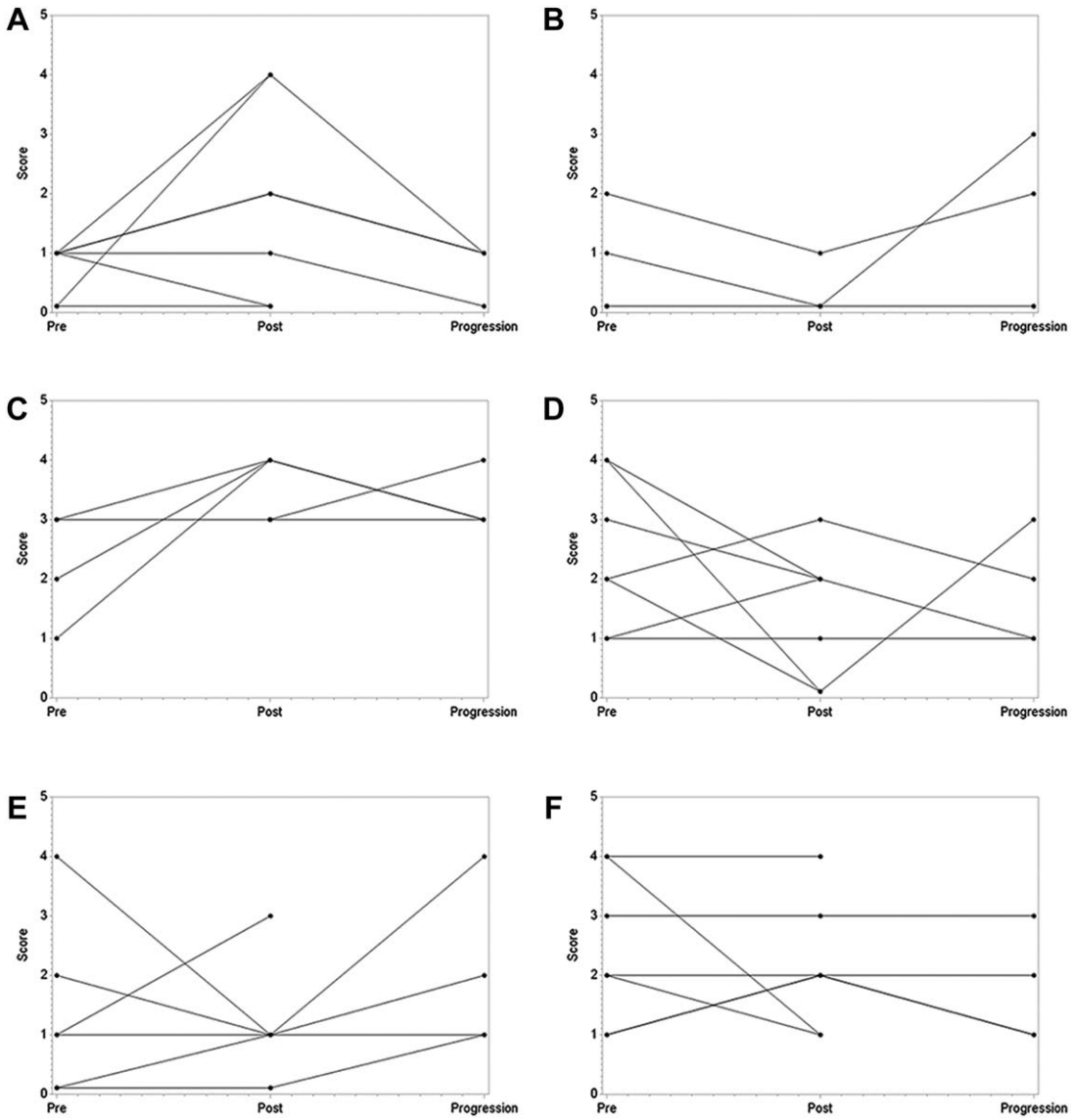

Figure 2. Quality of life (QOL) measurements before ablation, after ablation, and at progression. **(A):** Pain. **(B):** Nausea. **(C):** QOL. **(D):** Lack of energy. **(E):** Worry. **(F):** Sleeping well.

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