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Clinical Study Protocol

Safety of Percutaneous Cryoablation in Patients with Painful Bone and Soft Tissue Tumors: A Single Center Prospective Study (SCIRO-1502)

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This single center prospective study is being conducted to evaluate the safety of the cryoablation for patients with pathologically diagnosed painful bone and soft tissue tumors. Enrollment of 10 patients is planned over the 3-year recruitment period. Patients have related local pain after receiving medications or external radiation therapies will be included in this study. Cryoablation will be percutaneously performed under imaging guidance, and a temperature sensor will be used during treatment as necessary. The primary endpoint is prevalence of severe adverse events within 4 weeks after therapy. The secondary endpoint is effectiveness 4 weeks after the procedure.

Key words: cryoablation, soft tissue and bone tumor, pain, safety

Patients with painful bone and soft tissue tumors, including both benign and malignant tumors, are usually treated with medication and/or external radiation therapy to control or alleviate their pain. However, some patients have uncontrollable pain or recurrence of pain after these treatments. The worsening of the quality of life (QOL) caused by painful bone and soft tissue tumors such as bone metastases is a serious social problem. Although surgical resection of the painful tumor is sometimes performed for these patients, tumor location, tumor size, patient comorbidities, and general conditions can limit those that can undergo surgery. Additionally, surgical interventions can potentially lead to post-surgical dysfunctions.

According to a meta-analyses examining the clinical outcomes of the external radiation therapy for patients with metastatic bone pain, complete or partial pain relief is obtained in 23-34% and 59-73% of patients, respectively [1-3]. In other words, metastatic bone pain in 30-40% of patients cannot be relieved using external radiation therapy. Although additional external radiation treatments may be considered for lesions that show resistance to initial external radiation therapy and medication, additional radiation is still controversial in Japan, and its indication is generally limited. No effective therapies have been proven as safe and effective after failure of such standard therapies in Japan.

Cryoablation is a local treatment that induces coagulating necrosis by using rapid freezing, slow

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thawing, and repetition of the freeze-thaw cycle [4]. Clinically, this therapy has already been used for various organ tumors, including those of the kidney [5, 6], liver [7], lung [8] and other organs. However, in Japan, cryoablation is only covered by national health insurance to treat small renal cancers. Many reports show favorable outcomes of cryoablation for patients with small renal cell carcinoma [5, 6]. Cryoablation can be performed safely and accurately under imaging guidance, such as computed tomography (CT) and magnetic resonance imaging (MRI). Additionally, it can be performed percutaneously with minimal invasiveness under local anesthesia and conscious sedation. Therefore, even if patients cannot undergo surgery because of severe comorbidities, they can often be candidates for this therapy.

Recently, percutaneous radiofrequency (RF) ablation was utilized as effective local therapy for bone metastases. Several investigators reported that patient pain was significantly improved after this therapy [9]. Both RF ablation and cryoablation are local thermal therapies that require probe insertion into the target area under image guidance. In RF ablation, the ablation zone is usually invisible on CT images while performing treatment. Conversely, in cryoablation, the ablation zone is visible as an "ice ball" during ablation. Intraprocedural CT images show the ice ball as a low attenuation area with sharply defined borders [10]. Intraprocedural MRI shows the ice ball as a markedly hypointense area relative to the renal parenchyma [10]. Therefore, cryoablation is advantageous in terms of safety and targeting accuracy. Additionally, measuring the temperature of adjacent critical organs and structures at risk of thermal injury can increase the safety of this therapy.

In general, conventional external radiation therapy requires approximately 2–3 weeks for completion of treatment, and patients experience pain relief gradually. If pain recurrence unfortunately occurs after radiation therapy, additional radiation treatments to the same area are not always performed because of the increased risk of radiation damage. Conversely, cryoablation can relieve pain immediately after the procedure [11] and can be performed repeatedly even if recurrence occurs. In this regard, we assumed that cryoablation has potential advantages over external radiation therapy. Therefore, we wanted to evaluate the safety of the cryoablation prospectively for patients with painful bone and soft tissue tumors.

We plan to conduct an exploratory clinical trial to evaluate the safety of percutaneous cryoablation treatment of painful soft tissue and bone tumors. Herein, we describe the detailed protocol of this prospective feasibility study.

Endpoints

Purpose. This study is being conducted to evaluate the safety of percutaneous cryoablation, in terms of severe adverse event (SAE) prevalence 4 weeks after treatment in patients with painful bone and soft tissue tumors at our institution.

Study design. This study is a single-center, single-arm, prospective, open-label feasibility study. No hypothesis testing is being performed for the primary endpoint.

This study protocol has been approved by the ethics committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences at Okayama University Hospital (approval number, RIN1511-004). This study has been registered with the University Hospital Medical Information Network (UMIN) in Japan (trial registration number: UMIN000019077).

Endpoints. The primary endpoint is SAE prevalence 4 weeks after undergoing cryoablation. A SAE is an adverse event (AE) that is a significant hazard or side effect that occurs during this period regardless of the investigator's opinion on the relationship between the occurrence and cryoablation. This includes, but may not be limited to, any event that is fatal, is life-threatening, requires or prolongs inpatient hospitalization, persists or significantly disables or incapacitates, or is considered an important medical event. Evaluations for AEs after the procedure are classified based on the Common Terminology Criteria for Adverse Events (CTCAE) ver.4.0.

The secondary endpoints are (1) effectiveness, as measured by relief of the pre-treatment symptoms and changes between pre- and postoperative radiological images of the target lesions, (2) procedure- or device-related AEs, and (3) device malfunction. Each secondary endpoint will be evaluated 4 weeks after the procedure.

Local pain related to the target lesion will be evaluated by using the visual analogue scale.

Subsequently, the prevalences of symptom-free, improved, stable, or progressing disease, which will be evaluated using pretreatment scores, will be calculated. To evaluate vascularity and target lesion size, contrast-enhanced CT or MRI images will be obtained before and 4 weeks after the procedure.

Procedure-related AEs are defined as any new, undesirable medical occurrences or worsening of a pre-existing condition that occur in a subject and are considered to be associated with the procedure. Device-related AEs are defined as any new, undesirable medical occurrences or changes considered to be associated with cryoablation products.

Eligibility Criteria

Inclusion criteria. 1) The patient has painful bone and soft tissue tumors that are resistant to medication. 2) The target lesion is histopathologically diagnosed. 3) The target lesion can be evaluated with imaging, *i.e.*, CT and/or MRI, before and after cryoablation. 4) The patient is expected to survive more than 1 month after registration for this study. 5) Written informed consent for percutaneous cryoablation is obtained from the patient. 6) The patient is equal to or more than 20 years old. 7) The patient is not a candidate for or refuses to undergo surgical resection for the target lesion.

Exclusion criteria. 1) Cryoprobe insertion cannot be performed safely because of vital organs and/or vessels on the insertion route. 2) The patient has heart failure (New York Heart Association Functional Classification $\geq$ Ⅲ) and/or active infection, with the exception of viral hepatitis. 3) The patient has a body temperature of 38℃ or more. 4) The target lesion cannot be evaluated with imaging, *i.e.*, CT and/or MRI. 5) The patient is confirmed or suspected of being pregnant. 6) The patient is at risk of worsening pathological fracture due to cryoablation. 7) The patient is at risk of worsening QOL due to cryoablation. 8) Main organ functions are abnormal based on the blood and biochemical tests as follows: i) white blood cell count $<2{,}500/\mu L$; ii) platelet count $<50{,}000/\mu L$; iii) hemoglobin $<6.0\,g/dL$; iv) creatinine $>2.0\,mg/dL$; or v) total bilirubin $>3.0\,mg/dL$. 9) The patient is regarded as inappropriate for this study by physicians.

Treatment Methods

Cryoablation procedure. In this study, cryoablation for bone and soft tissue tumors will be performed under ultrasound, CT, or MRI guidance. Under local anesthesia, one or more cryoprobes (IceRod or IceSeed, Galil Medical, Yokneam, Israel) will be introduced into the target lesions percutaneously. Each cryoprobe will be connected to an argon-based cryoablation system (CryoHit, Galil Medical). The standard ablation protocol includes a double freeze cycle in 2 cycles of maximum 15-min freezes separated by 2 min of thawing. As the ablated zone is visible as an ice ball, the ablation procedure generally aims to cover the target lesion and 6-mm ablative margins, creating the ice ball. However, to ensure safety, the aforementioned ablation protocol may be altered. For lesions located adjacent to the skin or visible nerves, for example, freezing duration is decreased in order to limit ice ball size and avoid injury to the skin or nerves. After ablation, cryoprobes are withdrawn, and CT or MRI images of the ablated target lesion are obtained to evaluate procedure- or device-related AEs (e.g., hematoma or adjacent organ injury). Characteristics of target lesions, ablation protocols for each patient, and AEs after the procedure will be recorded on case report forms.

Temperature measurement. In this study, the operator will insert the temperature sensor (Fluoroptic Temperature Probe; LumaSense Technologies, CA, USA) near adjacent critical organs and structures during the procedure to determine potential risk of thermal injury caused by cryoablation on pre-ablative images. First, an 18-gauge coaxial needle (Surflo; Terumo, Tokyo, Japan) or a 20-gauge coaxial catheter for percutaneous transhepatic biliary drainage (Happycath; Medikit, Tokyo, Japan) will be inserted near the surface of the adjacent organs/structures under CT guidance. The internal needle will be withdrawn, and subsequently, the temperature sensor will be advanced into the outer catheter to the surface of the adjacent organs/structures. During cryoablation, the temperature will be continuously measured and recorded. If the operator determines that there may be a high risk of thermal injury for adjacent organs/structures, the cryoablation procedure will temporarily be discontinued, and the position of cryoprobes will be changed as needed.

Statistical Consideration

Statistical analysis. Clinical data obtained in this study will be summarized using descriptive statistics. The results of all endpoint analyses are reported as the proportion of cases and the 95% confidence interval, which is presented as Agresti and Coull upper and lower limits.

Interim analysis and monitoring. An interim analysis is not planned during the study period. The data and safety monitoring committee (DSMC) independently reviews the report of SAEs, if present, and decides to terminate studies early. In-house monitoring will be performed to ensure patient eligibility, protocol compliance, data submission, and proper reporting of AEs related to the cryoablation. The monitoring reports will be submitted to and reviewed by the independent DSMC.

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