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Clinical Study Protocol

Single Center Prospective Phase II Trial of CT-guided Radiofrequency Ablation for Pulmonary Metastases from Colorectal Cancer (SCIRO-1401)

Jun Sakurai[a]*, Yusuke Matsui[b], Takao Hiraki[b], Toshihiro Iguchi[b], Hiroyasu Fujiwara[b], Hideo Gobara[b], Toshiharu Mitsuhashi[a], Takeshi Nagasaka[c], and Susumu Kanazawa[b]

[a]Center for Innovative Clinical Medicine, [b]Department of Radiology, and [c]Department of Gastroenterological Surgery Transplant and Surgical Oncology, Okayama University Hospital, Okayama 700–8558, Japan

The present single center prospective phase II clinical trial is designed to evaluate the efficacy and safety of percutaneous radiofrequency (RF) ablation for colorectal lung metastases. Patients who have colorectal lung metastases without extrapulmonary metastases are included in this study. The primary endpoint is 3-year overall survival (OS) after RF ablation. The secondary endpoints are the prevalence of adverse events within 4 weeks, local tumor progression rate, 1- and 5-year OS, cause-specific survival, and relapse-free survival. The recruitment of patients commenced in July 2014, and the enrolment of 45 patients is intended over the 3 years of study period.

Key words: radiofrequency ablation, colorectal cancer, lung metastasis

Colorectal cancer (CRC) is one of the most common cancers globally [1]. Approximately 608,000 deaths (8% of all cancer deaths) associated with CRC are estimated rendering it the fourth most common cause of death from cancer. As previously described, metastatic disease develops in 50% of patients with CRC [2]. Pulmonary metastasis develops in 5 to 15% of CRC patients, and surgical resection of the metastatic tumor has been accepted as a potentially curative intervention for such patients [3–7]. While video-assisted thoracic surgery as a less invasive intervention is becoming widespread, poor pulmonary function or extrapulmonary comorbidities may hinder the surgical intervention. In addition, according to the large-scale retrospective surveillance of curative resection for the treatment of CRC in Japan, pulmonary metastasectomy has been employed for the treatment of 38% of patients [8].

Recently, several retrospective studies have indicated the safety, feasibility, and promising anticancer effect of radiofrequency (RF) ablation as an alternative option for patients with unresectable pulmonary metastases post-surgery [9–11]. However, the aforementioned studies were designed as retrospective observational studies, and an assessment of the hypothesis with regard to the outcomes of patients treated with RF ablation for colorectal lung metastases has not been performed. In view of the notion that RF ablation is less invasive than surgical resection, and thus may be a promising alternative, the prospective evaluation of its effectiveness is warranted.

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*Corresponding author. Phone:+81-86-235-6510; Fax:+81-86-235-6505
E-mail:sakurai-jun@okayama-u.ac.jp (J. Sakurai)

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Based on the previous retrospective studies, we hypothesized that the outcomes of treatment with RF ablation are comparable to those of the surgical metastasectomy.

Based upon this hypothesis, we intend to conduct the present study in order to evaluate the efficacy and safety of RF ablation therapy for the treatment of colorectal lung metastases. Herein, we present a detailed protocol for this prospective phase II clinical trial.

Endpoints

Purpose. The primary objective of this study is to evaluate the effectiveness of lung RF ablation, as indicated by the 3-year overall survival (OS), in patients with pulmonary metastases from CRC at our institution.

Study Design. The present study is a single-center, single-arm, prospective, open-label phase II clinical trial. The study protocol has been approved by Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, Ethics Committe (m29005). In addition, this study is registered at the University Hospital Medical Information Network (UMIN), Japan (Trial registration number: 000014391).

Endpoints. The primary endpoint is the 3-year OS. OS time is defined as the time from registration date to death from any cause, and will be censored at the last follow-up date if the patient is alive. Furthermore, 3-year OS is evaluated for the patients who meet eligibility criteria and are performed lung RF ablation in compliance with the protocol.

The secondary endpoints are as follows; (1) the prevalence and severity of adverse events (AEs) within 4 weeks of the procedure, (2) the local tumor progression rate, (3) 1- and 5-year OS, (4) cause-specific survival (CSS), and (5) recurrent-free survival (RFS).

The prevalence of AEs at 4-weeks is to be defined as the proportion of patients display AEs within 4 of undergoing. Severe adverse event (SAE) is defined as an AE that poses a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the RF ablation system product. It includes, but is not limited to, any event that is fatal, life-threatening, requires or prolongs inpatient hospitalization, causes a persistent or significant disability or incapacity, or is considered an important medical event. The severity of the AEs is classified based on the Common Terminology Criteria for Adverse Events version. 4.0.

The local tumor progression is defined as the circumferential enlargement of the target lesion, the appearance of irregular, scattered, nodular, or eccentric foci, which is measurable by contrast-enhanced CT (3, 6, 9, 12 and every 6 months after the RF ablation). The local tumor progression rate is defined as a proportion of the local tumor recurrence for all the target lesions.

The CSS time is defined as the number of days from the registration date to death related to CRC progression. The RFS time is defined as the time from the registration date to the earliest date between that of the diagnosis of local tumor progression or the death of the patient from any cause. Each CSS and RFS time will be censored at the last follow-up date if the patient is alive.

Primary hypothesis and statistical sample size calculation. This study has been designed to compare the OS after the use of RF ablation for the treatment of pulmonary metastases to a target performance goal. The estimated 3-year OS after RF ablation for pulmonary metastases is approximately 50% (46–57%) based on the previous retrospective studies [11–16], which is comparable to that of patients treated with pulmonary metastasectomy (60%) [3–7], and is considered the performance goal of this phase II trial. Thus, the null and alternative hypotheses are given below:

H_0: $P_T \leq 50\%$

H_1: $P_T > 50\%$

where P_T is the anticipated 3-year OS after RF ablation. The use of RF ablation for the treatment of pulmonary metastases will be considered effective if the results of the present study verify that the lower limit of the one-sided 95% confidence interval for PT is above 50%. We did not have relevant data regarding the additional expected effect of RF ablation for colorectal lung metastases, so instead simply assumed that a 20% or more decrease in 3-year OS, i.e., 3-year OS threshold of 30%, would be clinically meaningless. Against this background, 39 patients in total would provide a statistical power of 80% to test the primary hypothesis at the one-sided significance

level of 0.05. Thus, the planned sample size is 45 patients, including the subjects who are excluded from the analyses because of protocol violation or patient withdrawal from the study prior to evaluation of primary endpoint.

Investigation of change in pulmonary function and predictive biomarkers. To investigate the change in pulmonary function after the administration of RF ablation, vital capacity and forced expiratory volume in one second (FEV_1) at 4 weeks will be measured for all the patients. In addition, the predictive biomarkers, including gene mutation and microRNAs for the survival after RFA will be investigated in detail. Such biomarkers may be useful to determine suitable candidates for RF ablation preoperatively.

Eligibility Criteria

Inclusion criteria. 1) Patients with CRC in whom the primary lesion is controlled and the pulmonary metastasis is diagnosed clinically and radiologically without any viable extrapulmonary metastases. 2) All pulmonary target lesions are considered to be treatable with RF ablation. 3) The number of target lesions are less than 6 in total, and the long axis diameter of each lesion is less than 3.0 cm. 4) Major organ function is normal based on the blood, biochemical, and pulmonary function tests as follows:
a, White blood-cell count $\geq$ 3,000/μL; b, Platelet count $\geq$ 50,000/μL; c, Hemoglobin $\geq$ 7.5 g/dL; d, Serum total bilirubin $\leq$ 2.0 mg/dL; e, Serum creatinine $\leq$ 2.0 mg/dL; f, PT-INR $\geq$ 1.5; g, $FEV_1 \geq$ 1.0L.

Exclusion criteria. 1) Absence of safe needle insertion pathway. 2) RF ablation is considered to be hazardous because of critical organs in proximity to the target lesion. 3) The patient has more than one of the severe comorbidities as follows:
a. Severe heart failure (New York Heart Association [NYHA] Classification III or IV); b. Progressive inflammation or infectious disease except viral hepatitis. 4) The presence of other uncontrollable malignant tumors. 5) Peritoneal dissemination and/or malignant ascites. 6) The patient has a fever higher than 38℃ before the RF ablation. 7) Severe impairment of contralateral pulmonary function. 8) Presence of pulmonary hypertension. 9) Presence of interstitial pneumonia. 10) Usage of antiplatelet agent, anticoagulant, or thrombolytic agent that cannot be ceased temporarily during the perioperative period. 11) The patient is or may have a potential to be pregnant. 12) The patient is regarded as inappropriate for being enrolled into the study by physicians.

Treatment Methods

Radiofrequency ablation procedure. Written informed consent for RF ablation is obtained from the patient. The RF ablation procedure will be performed percutaneously under the guidance of CT fluoroscopy. Intraprocedural pain will be treated by using a combination of local anesthesia and intravenous administration of fentanyl or local plus epidural anesthesia. Under local anesthesia, a 17-gauge multitined expandable electrode with arrays (LeVeen, Boston Scientific, MA, USA) or a single internally-cooled electrode (Cool-tip RF needle, Medtronic, MN, USA) will be introduced into the target lesions percutaneously. Each electrode is connected to RF generator (RF 3000; Boston Scientific, or Cool-tip RF generator; Medtronic).

In the case of the Boston Scientific device, the RF energy is applied by increasing the RF power in incremental steps until a noticeable increase is observed in the impedance or automatic shut-off occurred at 15 min; this is repeated once at each site. Further to this, repositioning of the electrode for multiple overlapping ablations is performed. When using the Medtronic device, radiofrequency energy is applied with an impedance control algorithm for 12 minutes during internal cooling of the electrode. Thereafter, the temperature is measured at the electrode tip; if it does not reach 60℃, another energy application is performed at the same site (see Appendix).

Immediately after the procedure, a CT scan of the entire thorax will be performed to evaluate the presence of AEs and ground-glass attenuation (GGA), which indicates the ablation zone, surrounding the target lesions. Further to this, an upright posteroanterior chest radiograph will be obtained 4 hours after the procedure and repeated the following morning to evaluate the presence of any early AEs. The characteristics of the target lesion, the ablation protocol for each patient, and the AEs after the procedure will be recorded on the case report form.

Statistical Consideration

Interim analysis and monitoring. Neither an interim analysis nor in-house monitoring is planned to be performed during the study period. The Data and Safety Monitoring Committee independently reviews the reports of SAEs, and if present, may decide on the early termination of this study.

Statistical analysis. Clinical data obtained in this study will be summarized by descriptive statistics. OS, CSS, and RFS will be estimated using the Kaplan-Meier method. If the lower limit of the 95% confidence interval for 3-year OS is greater than 50%, the null hypothesis for effectiveness will be rejected in favor of the alternative hypothesis.

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References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer (2010) 127: 2893–2917.
2. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA and Tschetter LK: Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol (1989) 7: 1407–1418.
3. Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H and Putnam JB Jr; International Registry of Lung Metastases: Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg (1997) 113: 37–49.
4. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB and Gervaz P: Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol (2013) 20: 572–579.
5. Blackmon SH, Stephens EH, Correa AM, Hofstetter W, Kim MP, Mehran RJ, Rice DC, Roth JA, Swisher SG, Walsh GL and Vaporciyan AA: Predictors of recurrent pulmonary metastases and survival after pulmonary metastasectomy for colorectal cancer. Ann Thorac Surg (2012) 94: 1802–1809.
6. Hirosawa T, Itabashi M, Ohnuki T, Yamaguchi N, Sugihara K and Kameoka S; Japanese Society for Cancer of the Colon and Rectum (JSCCR) Study Group for Pulmonary Metastases from Colorectal Cancer: Prognostic factors in patients undergoing complete resection of pulmonary metastases of colorectal cancer: a multi-institutional cumulative follow-up study. Surg Today (2013) 43: 494–499.
7. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H, Matsuguma H, Ikeda N, Yoshino I, Ozeki Y, Takagi K, Goya T, Kawamura M, Hamada C and Kobayashi K; Metastatic Lung Tumor Study Group of Japan: Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. Ann Surg (2013) 257: 1059–1064.
8. Kobayashi H, Mochizuki H, Sugihara K, Morita T, Kotake K, Teramoto T, Kameoka S, Saito Y, Takahashi K, Hase K, Oya M, Maeda K, Hirai T, Kameyama M, Shirouzu K and Muto T: Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: a multicenter study. Surgery (2007) 141: 67–75.
9. Hiraki T, Gobara H, Iguchi T, Fujiwara H, Matsui Y and Kanazawa S: Radiofrequency ablation as treatment for pulmonary metastasis of colorectal cancer. World J Gastroenterol (2014) 20: 988–996.
10. Matsui Y, Hiraki T, Gobara H, Iguchi T, Fujiwara H, Nagasaka T, Toyooka S and Kanazawa S: Long-term survival following percutaneous radiofrequency ablation of colorectal lung metastases. J Vasc Interv Radiol (2015) 26: 303–310.
11. Yamakado K, Hase S, Matsuoka T, Tanigawa N, Nakatsuka A, Takaki H, Takao M, Inoue Y, Kanazawa S, Inoue Y, Sawada S, Kusunoki M and Takeda K: Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. J Vasc Interv Radiol (2007) 18: 393–398.
12. Yan TD, King J, Sjarif A, Glenn D, Steinke K, Al-Kindy A and Morris DL: Treatment failure after percutaneous radiofrequency ablation for nonsurgical candidates with pulmonary metastases from colorectal carcinoma. Ann Surg Oncol (2007) 14: 1718–1726.
13. Hiraki T, Gobara H, Iishi T, Sano Y, Iguchi T, Fujiwara H, Tajiri N, Sakurai J, Date H, Mimura H and Kanazawa S: Percutaneous radiofrequency ablation for pulmonary metastases from colorectal cancer: midterm results in 27 patients. J Vasc Interv Radiol (2007) 18: 1264–1269.
14. Yamakado K, Inoue Y, Takao M, Takaki H, Nakatsuka A, Uraki J, Kashima M, Kusunoki M, Shimpo H and Takeda K: Long-term results of radiofrequency ablation in colorectal lung metastases: single center experience. Oncol Rep (2009) 22: 885–891.
15. Petre EN, Jia X, Thornton RH, Sofocleous CT, Alago W, Kemeny NE and Solomon SB: Treatment of pulmonary colorectal metastases by radiofrequency ablation. Clin Colorectal Cancer (2013) 12: 37–44.
16. Gillams A, Khan Z, Osborn P and Lees W: Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. Cardiovasc Intervent Radiol. (2013) 36: 724–730.

Appendix. Algorithm of Radiofrequency Ablation for Pulmonary Metastases from Colorectal Cancer

1. Selection of the RF needle. The length of the non-insulated active-tip or the diameter of expandable tines should be at least 10 mm longer than the long-axis diameter of the tumor. However, a needle with a shorter, non-insulated active-tip or expandable tines can be used when there is a high risk of injury to the thoracic wall, mediastinum, or large vessels.

2. Application algorithm

(1) LeVeen system. RF energy is applied with an impedance control algorithm. In general, RF application will be performed twice per needle position. The RF power is increased with time according to the algorithm shown in Table 1. The RF energy for 1 RF application is up to 190 W. The maximum duration for 1 RF application is 15 min.

Table 1 RF application algorithm for LeVeen system

Expandable tines	2 cm	3 cm	3.5 cm	4 cm
Initial RF power	10 W	20 W	30 W	40 W
Rate of increase	5 W/min	5 W/min	10 W/min	10 W/min

When the automatic shut-off ("roll-off") is observed, the second RF power is set to half of the first maximum RF power.

If the automatic shut-off is not observed, repeat RF application with the last maximum RF power is performed 30 sec after the end of the first application.

(2) Cool-tip system. RF energy is applied with an impedance control algorithm for 12 min per needle position during internal cooling of the electrode. The RF power is increased with time according to the algorithm shown in Table 2. The RF energy for 1 RF application is up to 140 W.

Table 2 RF application algorithm for Cool-tip system

	2 cm active tip	3 cm active tip
Initial RF power	30 or 40 W	40 or 50 or 60 W
Rate of increase	10 W/min	10 W/min

When the automatic shut-off ("break down") is observed, the RF application is restarted and continued until a total application time of 12 min. The second RF power is then set to half of that of the first maximum RF power.

If the automatic shut-off is not observed, or the temperature of the active tip is less than 60℃ after RF application for 12 min, additional RF application may be performed with the documentation of the cause of the additional RF application in the case report form.

3. Overlapping procedure. Overlapping ablation can be performed to achieve the entire coverage of the tumor with an ablative margin $>$ 5 mm.