Percutaneous ultrasound-guided radiofrequency ablation for patients with liver metastasis from pancreatic adenocarcinoma

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ABSTRACT

Objective: To analyze the survival outcomes and prognostic factors of radiofrequency ablation (RFA) for pancreatic adenocarcinoma liver metastasis (PALM).

Methods: Between January 2010 and July 2021, 20 patients (13 males) with an average age of 58.9 ± 11.7 years who underwent RFA for PALM were included. The mean maximum diameter of PALMs was 2.6 ± 1.1 cm (1.0–6.0 cm). Survival curves were built using the Kaplan-Meier method and compared by the log-rank test. Multivariable analyses were performed by using the Cox proportional hazards model.

Results: Twenty patients with 29 PALMs underwent 23 RFA sessions. Technical efficacy was achieved in 28 PALMs (28/29, 96.6%). The mean overall survival (OS) after RFA was 14.6 months and the 1-, 2- year survival rates were 39.5%, 18.1%, respectively. With multivariate analysis, abnormal serum levels of CA199 (p = 0.023) and extrahepatic metastasis before RFA (p = 0.038) were identified as independent prognostic factors for OS in patients with PALM. Additionally, the mean progression-free survival (PFS) after RFA was 11.5 months and 1-, 2- year survival rates were 26.0%, 17.3%, respectively. With multivariate analysis, abnormal serum levels of CA199 (p = 0.016) and extrahepatic metastasis before RFA (p = 0.043) were also identified as independent prognostic factors for PFS in patients with PALM.

Conclusion: RFA is a safe and effective treatment for patients with PALM, especially in patients with normal serum level of CA199 or the patients without extrahepatic metastases before RFA.

Introduction

Pancreatic cancer, which has high morbidity, difficult diagnosis, and poor treatment results, is one of the most aggressive and rapidly progressing human tumors [1,2]. The main tumor type of pancreatic cancer is adenocarcinoma, which accounts for approximately 90% of cases [3,4]. The prognosis of pancreatic ductal adenocarcinoma remains very poor with a median overall survival of 3–5 months [5]. Because little evidence can be detected in the early stage of pancreatic cancer, it is often diagnosed when local advanced pancreatic neoplasia has occurred [2].

Typically, pancreatic cancer invades and metastasizes early, spreading first to regional lymph nodes, then to the liver, and less commonly to the lung [6]. Patients with hepatic metastases have a worse prognosis with a shorter survival time of 3 months [7]. The introduction of new chemotherapeutic agents such as gemcitabine has extended the median survival time of patients with advanced pancreatic ductal adenocarcinoma [8]. However, the median survival time of patients who present with liver metastasis at initial diagnosis or during follow-up after pancreatic resection is less than 12 months, with chemotherapy or chemoradiotherapy showing limited benefit [8,9]. In addition, the role of radiation therapy and/or transcatheter arterial chemoembolization (TACE) in the treatment of patients with advanced pancreatic cancer also remains unclear [9]. A previous study showed that surgical resection of hepatic metastases from pancreatic ductal adenocarcinoma was associated with a significantly improved overall 1-year and 3-year survival (p < 0.001). Additionally, a recent case report showed that selected cases benefit from successful multimodal treatment, including resection combined with local ablative techniques and systemic chemotherapy [10]. Therefore, the options for managing pancreatic cancer liver metastasis are in desperate need of further investigation.

Radiofrequency ablation (RFA) has been proven to be a feasible alternative to surgery due to its convenient availability and wide applicability to both primary and secondary hepatic malignancies [11], especially in tumors ≤3 cm. In general, there are three imaging modalities for the guidance of RFA, including CT, MRI and ultrasound. CT provides high-quality images, which can accurately indicate the target tumor position and map the ablated zone. CT-guided RFA
has been performed on liver tumors for many years [12]. The detection rate of small HCCs by MRI is higher than that of ultrasound and CT, particularly in patients with cirrhosis [13]. In our center, ultrasound was the main modality used in the guidance of RFA of liver tumors because of its easy operation and real-time monitoring.

Abundant literature has reported that US-guided RFA is a safe option in treating metastatic liver lesions originating from the digestive tract, especially in colorectal cancer [14,15]. However, its safety and efficacy and whether it would benefit overall survival and control local progression in patients with PALM need to be further researched [16]. Hence, our study was conducted to evaluate the long-term outcomes and analyze the prognostic factors of US-guided RFA treatment for patients with PALM.

Materials and methods

Patients

This study was approved by the institutional review board of the Peking University Cancer Hospital (2007AA02Z4B88). Signed informed consent for RFA procedures and the use of data for research purposes were required from patients before their treatment.

Between January 2010 and July 2021, 20 patients (13 males) with 29 PALMs underwent ultrasound-guided percutaneous radiofrequency ablation (RFA) in our center. The inclusion criteria for RFA were as follows: (1) liver metastases visible by ultrasound (US) or contrast-enhanced ultrasound (CEUS); (2) largest tumor size ≤6 cm in diameter for solitary PALM and tumor numbers ≤5 for multiple PALMs; (3) no evidence of invasion to nearby organs; (4) no metastases to distant organs or stable control of extrahepatic metastases within 6 months; (5) absence of portal vein or inferior vena cava tumor thrombus; and (6) no obvious coagulation dysfunction. The patient selection flow chart was shown in Figure 1. The decision to perform RFA was made by consensus from an interdisciplinary conference consisting of surgeons, oncologists, radiologists, radiation therapists, and pathologists before treatment. Doctors recommend RFA if liver metastasis is limited and extrahepatic metastasis is controlled.

Pre-RFA examination

All patients underwent a baseline evaluation including US/CEUS, computed tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen and pelvis prior to RFA. In addition, CT/MRI with a chest or head scan and radionuclide bone imaging was performed if the patient developed extrahepatic metastases. Serum laboratory tests (including a complete blood count, coagulation test, liver and kidney function tests, etc.) and serum tumor markers were measured two weeks before RFA. A liver biopsy was performed when necessary to confirm PALM. Difficult locations were defined as adjacent to large vessels, extrahepatic organs or the liver capsule. The RFA scheme and needle placement were designed based on imaging parameters, including tumor size, shape, number, border and location.

Equipment for RFA

In our study, two types of RFA systems were used: Valleylab (Tyco Health care, United States) and Celon Lab Power (Olympus, Germany). The 2-cm or 3-cm tip of a 17-gauge electrically insulated electrode (RFA 2020/2030 electrode, Valleylab, Tyco Health care) was used. The Celon Lab Power system is able to connect one to three 15-cm to 20-cm-long
electrodes with 3- to 4-cm exposed tips and provides a maximum output of 250 W. The ultrasound guidance and blood flow observation used in our study were Prosound x-10 (ALOKA, Japan) and Vivid E9 4 D (GE Healthcare, Chicago, IL) cardiovascular ultrasound systems. SonoVue (Bracco, Milan, Italy) was used as the US contrast agent.

**RFA procedure**

The RFA treatment procedure was performed by a radiologist team with more than ten years of experience in the interventional US (Wei Yang, Wei Wu, Kun Yan, Minhua Chen). All patients underwent RFA under conscious sedation given intravenously. Local infiltration of anesthesia was provided by an anesthesiologist using 2.5–5.0 mg of midazolam (Roche; Basel, Switzerland) and 50–100 μg fentanyl (Fentaini; Renfu, Yichang, China). RFA devices can create an ablation zone with a maximum diameter of up to 5 cm in the liver. Overlapping ablations were performed if tumors were larger than 3 cm. An ablative margin was defined as the range beyond the borders of the tumor that should be ablated simultaneously to guarantee complete tumor destruction, commonly 0.5–1.0 cm [17]. For tumors in difficult locations, the ablative margin was less than 0.5 cm. Therefore, some individualized protocols, including artificial pleural or abdomen effusion, were established to reduce thermal injury as previously described [18]. The heart rates, blood pressure, and respiration saturation were continuously monitored during the RFA procedure. The average time consumption of the RFA procedure (from the time the electrode was inserted to the first lesion to the time the last lesion was destroyed) was 25.5 ± 10.0 min. After treatment, tract ablation was performed when withdrawing the electrode. After RFA, CEUS was immediately performed to evaluate the ablation zone.

**Results**

**Patients characteristics**

The basic characteristics of all enrolled patients were listed in Table 1. The average age was 58.9 ± 11.7 years old (34–79 years old). The average diameter of PALMs was 2.6 ± 1.1 cm (1.0–6.0 cm). There were 6 patients with solitary liver metastases (6/20, 30.0%) and 14 patients with multiple liver metastases (14/20, 70.0%). The interval between the pancreatic adenocarcinoma diagnosis and the liver metastasis diagnosis ranged from 0 to 24 months (mean 11.3 ± 7.9 months). One patient had synchronous PALM, and 19 patients had metachronous PALMs. Extrahepatic metastases before RFA 0.091

| Variables                         | Number of patients (%) | 1-year     | 2-year     | 3-year     | p value |
|-----------------------------------|------------------------|------------|------------|------------|---------|
| Age                               |                        |            |            |            | 0.315   |
| ≤60 years old                     | 11 (55.0)              | 45.5       | 34.1       | 0          |         |
| >60 years old                     | 9 (45.0)               | 33.3       | 0          | 0          |         |
| Gender                            |                        |            |            |            | 0.414   |
| Male                              | 13 (65.0)              | 56.4       | 35.3       | 0          |         |
| Female                            | 7 (35.0)               | 14.3       | 14.3       | 0          |         |
| Resection for pancreatic tumor    |                        |            |            |            | 0.240   |
| Yes                               | 14 (70.0)              | 23.4       | 23.4       | 0          |         |
| No                                | 6 (30.0)               | 80.0       | 20.0       | 0          |         |
| Chemotherapy                      |                        |            |            |            | 0.911   |
| Yes                               | 17 (85.0)              | 40.7       | 12.7       | 0          |         |
| No                                | 3 (15.0)               | 33.3       | 0          | 0          |         |
| Tumor size                        |                        |            |            |            | 0.841   |
| <3 cm                             | 14 (70.0)              | 42.2       | 11.3       | 0          |         |
| ≥3 cm                             | 6 (30.0)               | 33.3       | 33.3       | 0          |         |
| Tumor number                      |                        |            |            |            | 0.594   |
| Single                            | 6 (30.0)               | 60.0       | 20.0       | 0          |         |
| Multiple                          | 14 (70.0)              | 31.4       | 21.0       | 0          |         |
| Interval between PA and LM         |                        |            |            |            | 0.514   |
| ≤12 months                        | 9 (45.0)               | 25.4       | 12.7       | 0          |         |
| >12 months                        | 11 (55.0)              | 50.5       | 18.9       | 0          |         |
| Extrahepatic metastases before RFA|                        |            |            |            | 0.091   |
| Yes                               | 5 (25.0)               | 20.0       | 15.0       | 0          |         |
| None                              | 15 (75.0)              | 46.4       | 29.0       | 0          |         |
| Serum CA 199                      |                        |            |            |            | 0.037   |
| Normal level                      | 6 (30.0)               | 60.0       | 60.0       | 0          |         |
| Abnormal level                    | 14 (70.0)              | 31.4       | 0          | 0          |         |
| Location of tumor                 |                        |            |            |            | 0.538   |
| Difficult locations               | 17 (85.0)              | 34.1       | 25.6       | 0          |         |
| None                              | 3 (15.0)               | 33.3       | 33.3       | 0          |         |

Note: Difficult locations*: locations adjacent to large vessels, extrahepatic organs or the liver capsule; RFA: radiofrequency ablation; PA: pancreatic adenocarcinoma; LM: liver metastasis; m: months.

**Statistical analysis**

Ten potential prognostic factors for OS and PFS were analyzed in this study, including age, gender, tumor size, tumor number, tumor location, extrahepatic metastases before RFA, resection for primary tumor before RFA, chemotherapy, interval (from the time pancreatic cancer was diagnosed until the liver metastases were diagnosed), and CA199. The Kaplan-Meier method was used to evaluate survival rates. In addition, a log-rank test was used in the univariate analysis. Cox proportional hazards model was used for the multivariate analysis. SPSS 23.0 software (SPSS, Chicago, IL) was used to perform statistical analyses, and p < 0.05 was considered statistically significant.
metastases were found in 5 patients (5/20, 25%) before RFA treatment. Among them, two patients developed extrahepatic metastases in the lung. Other extrahepatic metastases were superior mesenteric vein tumor thrombus and peritoneum (1 patient), multiple peritoneal metastasis (1 patient) and bone (1 patient). In our study, fourteen patients (70%) underwent resection of primary pancreatic tumor and seventeen patients (85%) received chemotherapy with FOLFIRINOX or gemcitabine/albumin-bound nab-paclitaxel as the first-line regimen before RFA.

**Early response**

A total of 23 RFA sessions (1–2 sessions) were performed and 29 PALMs were treated in 20 patients. Seventeen patients underwent one session of RFA, 3 patients underwent two sessions. The technical efficacy was 96.6% (28/29) according to enhanced CT/MRI one-month after RFA. A residual tumor (1/29, 3.4%) was found by MRI one month after RFA. This patient had extrahepatic metastasis and then underwent maintenance therapy with traditional Chinese medicine.

**Local tumor progression and new tumor development**

During the follow-up period, three patients with pancreatic adenocarcinoma (15.0%, 3/20) developed local tumor progression (LTP) at 6–24 months after RFA (Table 2). Among these three lesions, one tumor was found at the margin of the ablated zone and this patient underwent TACE treatment later. The other two patients underwent a second RFA combined with radiotherapy and chemotherapy. New tumor development was observed in 10 patients (50.0%, 10/20) including intrahepatic metastases (70%, 7/10) and extrahepatic metastases (30%, 3/10). Intrahepatic metastases developed at 1–52 months after RFA treatment. These three extrahepatic metastases developed in the lung (2 patients) and abdominal lymph nodes (1 patient) at 4, 6, and 34 months after RFA treatment, respectively.

**Survival outcomes and prognostic analysis**

At the last follow-up, five patients were still alive, while the other 15 patients died of disease progression. The mean overall survival of patients with PALM who underwent RFA was 14.6 months (1–33 months) and the 1-, 2-year survival rates were 39.5%, 18.1%, respectively. Based on the multivariate analysis, CA199 (p = 0.023) and extrahepatic metastases before RFA (p = 0.038) were independent prognostic factors for OS (Table 3 and Figures 2 and 3).

The mean progression-free survival (PFS) after RFA was 11.5 months and 1-, 2- year survival rates were 26.0%, 17.3%, respectively. With multivariate analysis, abnormal serum levels of CA199 (p = 0.016) and extrahepatic metastasis before RFA (p = 0.043) were identified as independent prognostic factors for PFS in patients with PALM (Table 4 and Figure 4).

**Complications**

No RFA treatment-related death was observed during the follow-up period. The occurrence of major complications was 17.4% (4/23 sessions). Two patients experienced bile fistula within 1 week after RFA treatment and recovered after 2–3 months. The treated liver tumors were located on the surface of the liver in both cases and were punctured with an RF electrode multiple times from one skin site during RFA treatment. Another major complication was liver abscess happened in two patients. These four patients all recovered after ultrasound-guided puncture and drainage. The occurrence of minor complications was 8.7% (2/23 sessions). Among them, one patient experienced minor abdominal effusion and the other patient experienced abdominal wall hematoma. Both of them recovered with conservative management.

**Discussion**

Pancreatic cancer is one of the most common diseases associated with poor prognosis [1], with estimated 5-year overall survival rates of less than 5% [19,20]. Despite treatment by curative resection, metastatic pancreatic cancer, unfortunately, still has a poor prognosis [3]. In selected patients with

### Table 2. Local tumor progression and new tumor development in 20 patients with pancreatic adenocarcinoma liver metastasis after RFA.

| Variables | Local tumor progression (n = 3) | New tumor development (n = 10) |
|-----------|--------------------------------|-------------------------------|
| Distribution of liver lobe | Single (2) | Intrahepatic metastases (7) |
| | Multiple (1) | Extrahepatic metastases (3) |
| Time to progression | ≤6 months (1) | ≤12 months (7) |
| | >6 months (2) | >12 months (3) |
| Treatment after progression | Second RFA combined with chemotherapy (1) | Chemotherapy (4) |
| | TACE (1) | Radiotherapy combined with TACE (1) |
| | Second RFA combined with radiotherapy (1) | None (5) |

Note: RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.

### Table 3. Multivariate analysis of overall survival prognostic factors with Cox proportional hazards in patients with PALM after RFA.

| Variables | Hazard ratio | Standard error | Wald value | P value | 95% confidence interval |
|-----------|--------------|----------------|------------|---------|------------------------|
| Serum level of CA199 | 2.074 | 0.911 | 5.180 | 0.023 | 1.334–47.504 |
| Extrahepatic metastases before RFA | 1.513 | 0.729 | 4.305 | 0.038 | 1.087–18.969 |

RFA: radiofrequency ablation; PALM: pancreatic adenocarcinoma liver metastasis.
limited tumor burden, local regional treatment, such as radiofrequency ablation (RFA), may improve survival. However, the seemingly beneficial effect of RFA is controversial [16]. Our study sought to explore the value of RFA in patients with PALM.

Previous studies have shown that the technical efficacy of RFA in treating primary or metastatic liver tumors was 90%–96% [16,21,22], which was similar to our finding (96.6%). Furthermore, the local tumor progression (LTP) in liver metastasis from pancreatic cancer during the follow-up after RFA was 15% (3/20) in our study, which was lower than that previously reported (38.3%) [23]. To our knowledge, tumor size was significantly associated with LTP after RFA. In the present study, 70% (14/20) of patients had PALMs less than 3 cm. This might be the reason that the LTP in our study was comparatively lower.

The mean overall survival (OS) after RFA and the 2-year OS rate in our study was 14.6 months and 18.1%, respectively. Regarding other treatments for PALM, previous studies reported that the median OS of patients after hepatic resection was 5.6–14 months [24,25], which was similar to our results. The median survival of patients who received transcatheter arterial chemoembolization (TACE) was 7.5 months [26], and that for patients who received FOLFIRINOX for advanced pancreatic cancer was 11.1 months [27]. Thus, in our experience, RFA as a feasible treatment for selected patients with PALM may prolong OS or reduce the tumor burden of the liver.

Our results showed that abnormal serum of CA199 indicated a worse prognosis for patients with PALM, which is consistent with previous studies [23,28]. Groot VP et al. [29] found that a preoperative level of CA199 >210U/ml was a risk factor for early recurrence. Several reports [30,31] have also proven that patients with elevated preoperative CA199 serum levels have worse median survival. This may be because elevated CA199 serum levels can provide evidence of a large tumor load and indicate the possibility of micrometastasis.

To the best of our knowledge, the presentation of multi-organ metastasis indicates a late stage of a malignant tumor. We also found that extrahepatic metastasis before RFA was an independent prognostic factor both for OS and RFS, which is consistent with the study by Dr. Lee [23], liver-only metastasis arising from pancreatic cancer was reported to benefit from RFA treatment. Dr. Xiu-Mei Bai [21] also reported RFA is a safe and locally effective method for the treatment of BCLM, especially in patients with no extrahepatic metastasis (p < 0.001).

Dr. Wei Yang reported that RFA was more likely to achieve acceptable outcomes for HCC patients with a single tumor (p = 0.003) [32]. In the study by Xi-mei Bai [21], the median OS of patients with 3–5 liver metastases from the breast was shorter than that of patients with 1–2 liver metastases (17 months vs. 29 months) (p = 0.030). Multiple metastases are often associated with more progressive biological behavior [33]. However, our results showed there was no
significant difference on survival with different tumor numbers. In our study, 70.0% (14/20) patients developed multiple metastases before RFA and received RFA as a palliative treatment.

Previous findings [23,34,35] also showed that tumor size was significantly related to OS and LTP in patients with hepatic malignancies. It is [36] reported that the OS in patients with tumors ≤3 cm was 36.2 months compared with 23.2 months in those with at least one lesion >3 cm ($p = 0.006$). However, our study did not find that metastasis tumor size affected OS or PFS. We think that other factors affect survival more than tumor size in these cases, such as the degree of tumor progression. This issue would be further evaluated in future studies with larger samples. Evidence from previous studies has demonstrated that the incidence of RFA-associated complications ranges from 3.54% to 20% [23,37,38], which is similar to our results. The study by Hua YQ et al. [16] reported that the incidence of major complications was 0% with RFA in treating hepatic oligometastatic pancreatic cancer, which was better than the 17.4% in our study. This was probably related to the fact that 85.0% (17/20) of patients with tumors in difficult locations in our study. The difficult location of liver lesions may increase the risk of complications in RFA [18]. In our study, two patients experienced bile fistula within 1 week after RFA treatment, which may be caused by multiple punctures from one skin site and the tumor was located on the surface of the liver. Therefore, increasing puncture points and performing multidirectional

![Figure 3](image-url)

**Figure 3.** Kaplan-Meier curves for overall survival of 20 patients with 29 PALMs after RFA. Overall survival curve of 20 patients with 29 PALMs after RFA (A). Overall survival curve of patients with normal or abnormal serum level of CA199 ($p = 0.037$) (B). Overall survival curve of patients with or without extrahepatic metastasis before RFA ($p = 0.091$) (C). PALM: pancreatic adenocarcinoma liver metastasis; RFA: radiofrequency ablation.

| Variables                                      | Hazard ratio | Standard error | Wald value | $P$ value | 95% confidence interval |
|------------------------------------------------|--------------|----------------|------------|-----------|------------------------|
| Serum level of CA199                           | 2.415        | 1.000          | 5.838      | 0.016     | 1.578–79.403            |
| Extrahepatic metastases before RFA             | 1.674        | 0.826          | 4.112      | 0.043     | 1.058–26.908            |

RFA: radiofrequency ablation; PALM: pancreatic adenocarcinoma liver metastasis.
Needle insertion [38] may provide a solution to this problem. Based on our experience, pancreatic cancer liver metastasis located under the liver capsule was comparatively contradictory to RFA treatment. The risk of bile fistula was increased because of the endocrine function of pancreatic tumors.

The limitations of our study were as follows. First, the patient sample was small and single-institution research was performed due to its retrospective nature. Local treatment of pancreatic adenocarcinoma liver metastasis is still in the exploratory stage; thus far we could not enroll a number of patients for this study. With medical advancements, an increasing number of patients would benefit from local treatment for liver metastasis. The role of RFA in pancreatic adenocarcinoma liver metastasis could be confirmed with patient recruitment. Another limitation was the lack of a control group because of ethics issues. Additionally, 85.0% of the patients received chemotherapy. The prolongation of survival in patients with pancreatic adenocarcinoma liver metastasis compared with related literature may be a result of a combination of systematic therapy and local ablation. Third, US-guided RFA is more convenient and flexible during operation than CT/MRI-guided RFA. It can monitor the puncture pathway to avoid injury to surrounding main structures under real-time multidimensional scans [39,40]. CT/MRI-guided images can provide accurate localization, especially when lesions are at the top of the diaphragm or other sites, which are always obscured by hyperechoic of the lung or ribs [41].

In conclusion, RFA can be a safe and effective local treatment in patients who cannot tolerate the surgical resection of liver metastases from pancreatic cancer, especially in patients with normal serum levels of CA199 or the patients without extrahepatic metastases before RFA.

**Disclosure statement**

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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