Original Article

Pleural Effusion after Percutaneous Radiofrequency Ablation for Hepatic Malignancies

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Abstract.

Background and Aims: Radiofrequency ablation (RFA) can play an important role in the treatment of primary or metastatic liver tumors. Currently, percutaneous RFA is generally regarded as a safe, effective, and minimally invasive procedure. This study aimed to evaluate the presence and course of pleural effusion after monopolar RFA.

Methods: From October 2008 to July 2013, a total of 54 patients (28 male and 26 female, mean age 65.2) treated with monopolar RFA were included in our study. 47 patients were diagnosed with hepatocellular carcinoma, 4 patients with hepatic metastasis, and 3 patients had other diagnoses. There were a total of 115 sessions of treatment and 199 liver tumors to be treated (1.73 ± 1.02 tumors treated per session). The tumor size ranged from 0.8 cm to 5.0 cm (mean 2.31 cm, standard deviation 1.04 cm). Thereafter, a follow-up ultrasound was performed within 24 hours subsequent to ablation to evaluate the presence of pleural effusion. The degree of pleural effusion was assessed by chest X-ray.

Results: Fifteen (13.0%) treatment sessions in 14 patients showed right-sided pleural effusion after ablations. One patient had a large amount of effusion, while other patients manifested a minimal to small amount of effusion. There were 5 patients that experienced delayed resolution of pleural effusion; one patient (0.87%) had a minimal amount of pleural effusion even after one month. Overall, there was no pneumothorax, or periprocedural morality. Age, gender, tumor numbers, tumor sizes, and complete ablation of target tumors were similar among groups presenting with or without pleural effusion. Tumor locations associated with S78 segments abutting the diaphragm or right lobe of the liver were not associated with development of pleural effusion. Only the duration of ablation time had a marginal trend toward significance ($p = 0.051$).

Conclusions: The transient appearance of right-sided pleural effusion after percutaneous RFA for hepatic malignancies was not infrequent. However, refractory pleural effusion was rare.

Keywords : thermoablation, pleural effusion

原著論文

肝惡性腫瘤經皮射頻消融術後之肋膜積液表現

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中文摘要

背景：射頻消融術在治療肝臟惡性腫瘤包括原發性肝癌與肝轉移癌皆有相當的角色。經皮射頻消融術式被認為是一個安全性高、有效、且微小侵襲性的治療。本研究的目的在探討單極經皮射頻消融術後之肋膜積液表現。

方法：本研究共收入 54 位(28 位男性與 26 位女性，平均年齡 65.2 歲)接受單極經皮射頻消融術患者。其中 47 位的診斷為肝細胞癌、4 位為肝轉移癌、3 位為其他肝臟惡性腫瘤。本研究收入總共 115 次的射頻消融術治療 199 顆肝腫瘤(每次治療平均消融 1.73 ± 1.02 顆腫瘤)。腫瘤大小為 0.8 到 5.0 公分(平均 2.31 公分，標準差 1.04 公分)。在射頻消融術後 24 小時內，患者接受超音波追蹤評估是否有肋膜積液，存在肋膜積液的患者以胸部 X 光評估肋膜積液量。

結果：本研究在 14 位患者共 15 次(13.0%)射頻消融術後觀察到有右側肋膜積液。其中 1 位患者積液量為大量，其餘皆為少量積液。5 位患者肋膜積液有延遲性吸收。1 位患者在一個月後仍有微量的右側肋膜積液。本研究患者並未觀察到有氣胸或治療後短期死亡病例。經分析後，年齡、性別、腫瘤數目、腫瘤大小、與腫瘤消融率在是否產生肋膜積液的兩個患者族群均相似。腫瘤是否位在靠近橫隔膜的肝臟分段或肝臟右葉並無與是否產生肋膜積液有顯著相關。唯較長的射頻消融術治療時間有邊際傾向產生肋膜積液的趨勢(p=0.051)。

結論：在經皮射頻消融術治療肝惡性腫瘤後之右側肋膜積液並不罕見。這些肋膜積液大多數在短時間內會自動吸收而不需要抽吸，在一個月後仍存有肋膜積液的病例則極為少見。

關鍵字: 射頻消融、肋膜積液

INTRODUCTION

Liver cancer has been one of the leading causes of cancer-related morality worldwide [1]. Within the liver cancer category, hepatocellular carcinoma (HCC) was the most commonly diagnosed primary liver cancer. Local ablation therapies were considered to be effective treatments for early stage HCC [2,3]. Radiofrequency ablation (RFA) was deemed more effective than other local ablation modalities in HCC treatment for its high rate of technique effectiveness, low local recurrence rate, and good prognosis [4]. Recently, RFA was reported to be an effective treatment for small and medium-sized HCCs using the multiple electrode switching system [5]. Secondary liver tu-

mors are malignant tumors that metastasize into the liver from other sites of the body. Percutaneous RFA was reported to achieve local control of secondary liver tumors such as colorectal and breast metastases [6,7]. The mid-term and long-term survival rates of patients with treated hepatic metastases were comparable to those survival rates of patients with resected hepatic metastases [6,8,9].

Percutaneous RFA had been regarded as a safe and minimally invasive procedure. The reported complications associated with RFA include ascites, hemorrhage, pleural effusion, abscess formation, biloma, subcapsular hematoma, and liver failure [10]. The reported major complication rate ranged from 3.54 to 4.4% [10,11], and thoracic-related major complications including hemohydrothorax, hepatohydrothorax, or pneumothorax were rare. Most notably, the mortality rate related to RFA was reported as less than 0.5% [10,11].

The presence of pleural effusion was rarely discussed in the list of complications related to percutaneous RFA for hepatic malignancies. The course and nature of pleural effusion or subsequent pleural effusion has not yet to be addressed as a stand-alone topic. This study aimed to evaluate the presence and course of pleural effusion after RFA for hepatic malignancies.

MATERIALS AND METHODS

Patients

This study retrospectively evaluated and included patients who underwent RFA procedures for hepatic malignancies from October 2008 to July 2013. The

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following inclusion criteria were used: (1) primary or secondary malignancies were diagnosed by pathological studies except HCC, which can be diagnosed according to the criteria from the guidelines of the American Association for the Study of Liver Diseases published in 2010 (typical enhancing patterns in computed tomography or magnetic resonance imaging studies) [3], (2) diameter of the largest tumor was less than 5 cm regardless of tumor numbers. A patient was excluded from this study if there were pre-existing pleural effusion, or iatrogenic injection of pleural effusion or ascites during ablation procedure.

Radiofrequency Ablations (RFA)

The internally cooled 17-gauge monopolar radiofrequency electrode (ValleyLab) with an electrically active tip was placed under real time sonographic monitoring with a 1-5 MHz convex probe (C5-1, Philip) on an iU22 ultrasound system (Philips), by way of a percutaneous puncture through the intercostal space or upper abdomen to the liver by a single experienced operator. The radiofrequency energy was generated with a 480-kHz power generator (Series CC-1, ValleyLab) with a maximum power of 200 watts and delivered to each electrode. The delivery of energy was regulated with a feedback algorithm according to tissue impedance. For larger tumors in this study, two or three electrodes were inserted and an additional switcher shifted the ablation energy between the electrodes. Regardless of the number of electrodes, RF energy was delivered only via one electrode once at same time for 30 seconds unless the tissue impedance had an abrupt rise when the energy output was switched to the next electrode. A pump (model PEPM, ValleyLab) maintained continuous circulation of chilled distilled water through the electrodes to keep the electrode tip temperature within 0 to 10°C. During the process of electrode removal, tract ablation was performed. A single operator performed all the RFA procedures in this study. For conscious sedation, the patients received either meperidine in

Table 1. Patient characteristics at the baseline of radio frequency ablation

	Patients (n=54)
Age (year)	65.2 ± 11.2 (39.6-84.9)
Gender	
Male	28 (51.9%)
Female	26 (48.1%)
Etiology of liver cancer	
Hepatocellular carcinoma	47 (87.0%)
Hepatic metastasis	4 (7.4%)
Cholangiocarcinoma	1 (1.9%)
Others	2 (3.7%)
Size of largest tumor (cm)	2.31 ± 1.04 (0.8-5.0)
Follow-up (months)	27.2 ± 16.9 (2-64)

Note. Data presented with plus–minus values are means ± SD

addition to midazolam, or intravenous general anesthesia without endotracheal intubation or mechanical ventilation. We monitored patient vital signs, electrocardiogram, and oxygen saturation during RFA.

Follow-up

A follow-up ultrasound was performed within 24 hours after the procedure to evaluate the complications and the presence of pleural effusion. Upright chest X-ray was performed if the presence of pleural effusion was detected by ultrasound, and thereafter evaluated by an experienced pneumologist to assess the degree of pleural effusion. The amount of pleural effusion was estimated based on the patient's chest X-ray. A minimal amount of pleural effusion was defined as the posterior costophrenic sulcus being obscured. Small amount was defined as obliteration of the lateral costophrenic sulcus. Moderate amount was defined as haziness of the diaphragmatic contour. The effusion above the level of the 4th anterior rib in upright chest X ray was defined as large amount [12]. One month after the procedure, a contrast-enhanced CT or MR imaging was performed to assess the RFA effectiveness. Multi-phase imaging studies including unenhanced, arterial, portal, and venous phases were

applied if the malignancy being treated was HCC. Complete ablation was defined as the target lesions being surrounded by non-enhanced areas on contrast-enhanced CT or MR. Delayed resolution of pleural effusion was defined as the presence of pleural effusion after one week but not at the one-month imaging follow-up. Refractory pleural effusion was defined as the presence of pleural effusion at the one-month imaging follow-up. The patients were then regularly followed every 3 months with either ultrasound or contrast-enhanced CT or MR imaging.

Statistical Analysis

We compared age, numbers and sizes of tumors, and RF ablation time between the treatment sessions with and without occurrence of pleural effusion after RFA using the Wilcoxon rank sum test. Fisher's exact test was applied to the categories of gender and the occurrence of pleural effusion. The described statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 20.0. A two-tailed probability value of less than 0.05 was defined as statistically significant.

Table 2. Characteristics of pleural effusion

Variables	No. of patient
Amount of effusion (minimal/small/moderate/large)	7/6/0/1
Location of pleural effusion (right/left)	14/0
Delayed resolution of effusion	5 (35.7%)
Refractory pleural effusion	1 (7.1%)

RESULTS

Patient Characteristics

This study included a total of 54 patients (28 male and 26 female). Patient age at baseline of treatment ranged from 39.6 to 84.9 (mean 65.2) years old. There were 47 patients that had hepatocellular carcinoma, 4 patients had hepatic metastasis, 1 patient had cholangiocarcinoma, 1 patient had neuroendocrine tumor, and 1 patient had malignant angiomyolipoma. A total of 115 sessions of treatment were included in this study. A total of 199 liver tumors were treated (1.73 ± 1.02 tumors treated per session) with tumor sizes ranging from 0.8 cm to 5.0 cm (mean 2.31 cm, standard deviation 1.04 cm). Table 1 provides a summary of the patient characteristics.

Pleural Effusion

Pleural effusion was noted after ablation procedures in 15 treatment sessions from 14 patients. All of these pleural effusions presented on the right side. Seven patients had a minimal amount of pleural effusion, and six patients had a small amount. Only 1 patient had a large amount of effusion. Delayed resolution of pleural effusion 1 week after treatment was noted in 5 patients, but the pleural effusion was completely resolved on the imaging studies 1 month after RFA. Only 1 female patient had minimal amount of pleural effusion one month after RFA. She received 2 consecutive RFA sessions and had a moderate amount of pleural effusion after RFA. There was no pneumothorax or periprocedural morality that occurred in this study. None of the patients in this study had evidence of pleural seeding of HCC in their clinical course following RFA.

Age and gender were not statistically related to the presence of pleural effusion. The numbers and sizes of tumors to be treated were also not related to the presence of pleural effusion. Tumor locations regarding S78 segments abutting the diaphragm or right lobe of liver were not associated with development of pleural effusion. Only the total ablation time defined by the duration of ablation time had a marginal trend toward significance (p = 0.051). The presence of pleural effusion did not have impacts on the technique effectiveness assessed at 1 month after RFA.

DISCUSSION

RFA was regarded as a safe, effective, but less invasive procedure for treating hepatic malignancies. The published literatures for complications of RFA were limited. In a previous multicenter study including 2320 patients in Italy, the mortality rate and overall complication rate of percutaneous RFA in treating malignant liver tumors were 0.3% and 7.1% respectively [13]. In a recent Japanese multicenter study including 16,346 treated nodules reported that the mortality rate was 0.038% and the overall complication rate was 3.54% in percutaneous RFA of hepatocellular carcinoma. The reported complications included 276 hepatic injuries (1.69%), 113 extrahepatic organ injuries, 78 hemorrhages (0.477%), and 27 tumor progressions (0.17%). Among the extrahepatic organ injuries, there were a total of 43 cases of refractory pleural effusion (0.263%) reported. However, this study did not mention the prevalence, nature, and course of post-

Table 3. Characteristics of RFA procedures in patients with and without pleural effusion

	Presence of pleural effusion after RFA (no. of treatment session)		
	Yes (n=15)	No (n=100)	*P*-value
Age at treatment (year)	63.8 ± 8.0	66.7 ± 10.8	0.229
Gender (M/F)	6/9	52/48	0.420
Number of tumors to treat	1.93 ± 1.22	1.70 ± 0.99	0.490
Size of tumors to treat (cm)	2.57 ± 1.39	2.27 ± 0.98	0.714
Tumor pathology (HCC / others)	13/2	86/14	1.000
Tumor location			
Right liver (yes/no)*	13/2	74/26	0.354
S7/8 (yes/no)*	9/6	42/58	0.266
Ablation time (minutes)	32.6 ± 18.76	23.38 ± 13.65	0.051
Effectiveness at 1 month (yes/no)	13/2	89/7	0.606

* At least one ablated tumor in the treatment session was located in the designated location

RFA, radiofrequency ablation

RFA pleural effusions [11].

In our study, the transient appearance of pleural effusion in patients receiving percutaneous RFA for hepatic malignancies was quite frequent. Most of the pleural effusion was right-sided and the amount of fluid was limited. None of these patients with transient and minimal amount of pleural effusion required therapeutic thoracentesis. We did not observe major mortality contributed to pleural effusion in this study or periprocedure mortality related to RFA in this study. A longer duration of ablation time might have a marginal trend toward formation of pleural effusion after RFA.

The pleural liquid was normally originated from circulation of the pleural membranes. The fluid was finally reabsorbed by the lymphatics in the parietal pleura. The formation and reabsorption of pleural effusion was general in equilibrium. Breaking the equilibrium toward either increasing formation or decreasing reabsorption of fluid may cause accumulation of pleural effusion in the pleural space. However, the pleural effusion was commonly a result of combination of troubles in both formation and reabsorption. Increased permeability of pleural membrane, increased vascular pressure of pleural microcirculation, decreased osmotic pressure of the third space, or decreased pressure in the pleural cavity can lead to increased formation of pleural fluid [14].

The lymphatic function was pivotal in reabsorption of pleural effusion [15]. Multiple factors were reported to interfere lymphatic function. These factors can be divided into intrinsic and extrinsic categories. The intrinsic ones were usually related to lymphatic functions. The common factors in this category were reported as inflammation or injuries of lymphatic duct, endocrine disorders, or cancer invasion of lymphatic duct. The extrinsic factors including diaphragm paralysis, pneumothorax, pleural fibrosis, or increases in venous pressure hindered the lymphatic drainage without direct involvement of the lymphatic structures. Mostly, the development of pleural effusion originated from multiple factors comprising both intrinsic and extrinsic ones.

One of the possible mechanisms for pleural effusion after RFA was caused by transient pleurisy related to thermal effects. The direct thermal damage of pleural membranes might cause increased pleural capillary filtration and interferes with parietal pleural
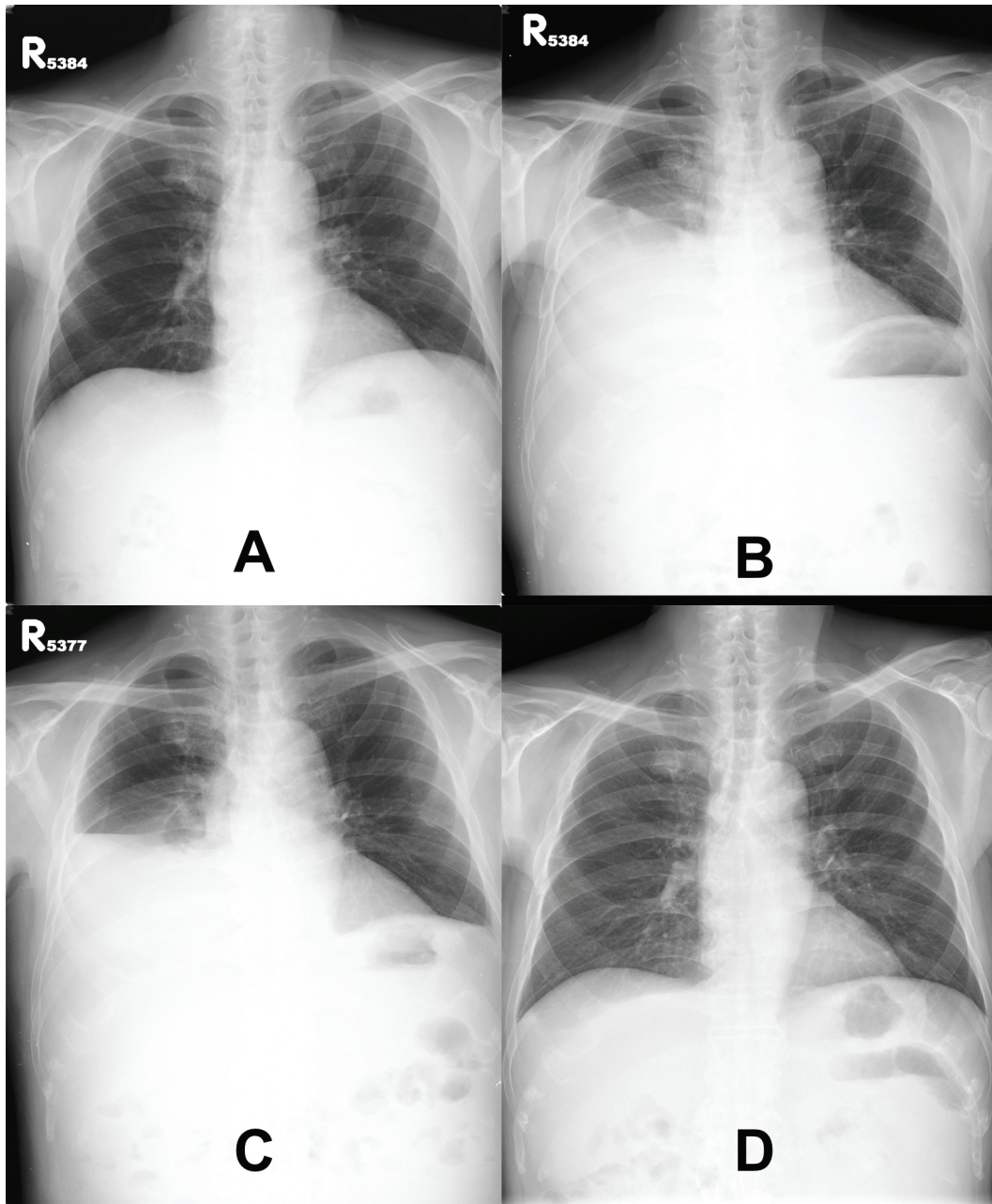
Figure 1. Periprocedural chest X-rays. (A) absence of pleural effusion before RFA (B) large amount of pleural effusion, 2 days after RFA (C) partial regression of right pleural effusion, 9 days after RFA (D) complete resolution of right-sided pleural effusion one month after RFA without thoracentesis

lymphatic fluid removal. That explanation was supported by the findings in this study that RFA procedures with the presence of pleural effusion after treatment had longer duration of ablation time than those without pleural effusion. Some maneuvers were

reported to reduce damages to the diaphragm. First, increasing visibility of hepatic tumors near the hepatic dome could decrease the probabilities of unintentional direct damages caused by improper positioning of electrodes. The visibility of hepatic tumors in the he-

patic dome treated by percutaneous RFA could be enhanced through creating artificial ascites or pleural effusion [16,17]. Second, separating the diaphragm and the liver by fluid could decrease the collateral thermal injuries. In vivo porcine studies showed that the injection of artificial ascites decreased thermal damage caused by RFA near the diaphragm [18]. A recent study showed that artificial ascites significantly reduced thermal damage to the diaphragm caused by RFA for HCC in the hepatic dome without compromising technique effectiveness [19].

Additionally, liquid can move across the diaphragm. Peritoneal liquid can reach the pleural space by diffusing across the mesothelial layers. Defects in the diaphragm may lead to rapid movement of liquid across the diaphragm [20]. The patient who developed a large amount pleural effusion after RFA had liver cirrhosis with massive, refractory ascites prior to the RFA treatment. The rapid movement of fluid into the pleural cavity might be related to damage of the diaphragm. Although the patient had mild respiratory distress on exertion in the first week after RFA, the symptoms were not severe enough to require a therapeutic thoracentesis. The patient refused diagnostic thoracentesis due to underlying thrombocytopenia. The pleural effusion was resolved completely and spontaneously in the CT imaging one month after RFA. Thus, the damage to the diaphragm was likely to be healed completely.

In the present study, the majority of the pleural effusion developed after RFA, was right-sided and minimal to small amount. Thereafter, the effusion reabsorbed spontaneously within 3 to 7 days. The only case with refractory pleural effusion after RFA had a moderate to massive amount of pleural effusion with delay resolution. The patient underwent a thoracentesis 2 weeks later after the first session of RFA treatment. The effusion was exudative with high protein ratio based on Light's criteria. The microbiology and cytology studies were unremarkable. However, the patient had tumor invasion of major vessels and multiple distant metastases found within 1 month after RFA. The invasion of major vessels may imply involvement of the lymphatic system adjacent to the liver, which could hamper the lymphatic function and contribute to the poor resolution of pleural effusion.

This study had some limitations. The characteristics of the pleural effusion were not evaluated in every case due to technically difficulties and potential complications in aspirating a minimal amount of effusion. Also, this study might not detect the presence of pleural effusion if the fluid was below the detectable limit of a chest X-ray. The study was retrospective in design. Thus, we cannot confirm all the pleural effusion was exudative or transudative, and we cannot completely rule out complications such as hemothorax, chylothorax, or bile duct fistula formation. However, chylothorax or bile duct fistula usually had a more complicated course and the pleural fluid in those situations was usually refractory. The only patient with refractory pleural effusion received thoracentesis to confirm the nature of pleural effusion. Moreover, after pleural effusion was first recognized, the follow-up chest X-ray film was based on decisions of the primary care physician according to the patient's symptoms.

In summary, the development of pleural effusion after RFA was not uncommon. The pleural effusion was predominantly right-sided. Most pleural effusion occurred after RFA was well tolerated and was resolved spontaneously without requirement of thoracentesis. Refractory pleural effusion was rare. Thermal injuries related to pleurisy and injuries to the diaphragm were potential mechanisms related to formation of pleural effusion after RFA treatment.

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