의학박사 학위논문

췌장암 환자에서의 내시경 초음파 유도하 RFA (Radiofrequency ablation; 고주파열치료) 및 항암치료 병행요법의 장기 추적연구

Long-term outcomes of endoscopic ultrasound-guided radiofrequency ablation for unresectable pancreatic cancer: a prospective observational study

울산대학교 대학원

의 학 과

오 동 욱

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지도교수서동완

이 논문을 의학박사학위 논문으로 제출함

2021년 2월

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목차

국문요약

췌장암 환자에서의 내시경 초음파 유도하 RFA (Radiofrequency ablation; 고주파열치료) 및 항암치료 병행요법의 장기 추적연구

연구배경: 내시경 초음파 유도하 고주파열치료는 췌장 신생물 치료에 점점 더 많이 사용되고 있다. 췌장암 치료에 있어서 내시경 초음파 유도하 고주파열치료의 역할은 아직 밝혀지지 않았다. 본 연구에서는 절제가 불가능한 췌장암에서 내시경 초음파 유도하 고주파열치료의 생존 성적을 평가하고자 한다.

방법: 2016년 5월부터 2019년 6월까지 절제가 불가능한 22명의 췌장암 환자가 내시경 초음파 유도하 고주파열치료와 함께 후속 항암화학요법을 받았다. 전체생존기간 및 무진행생존기간을 포함한 생존 성적을 평가하였다.

결과: 연구에 포함된 환자의 연령은 중앙값 60.5세 (사분위범위 56.25 – 68.75세) 였으며, 대상의 59%는 남성이었다. 22명의 환자에서 14명(63.6%)은 진단당시에 국소진행성 췌장암이었으며, 8명(36.4%)은 전이성 췌장암이었다. 대상의 모든 환자에서 내시경 초음파 유도하 고주파열치료는 성공적으로 수행할 수 있었다. 원발 종양의 크기는 중앙값 38 mm (사분위범위 32.75 – 45 mm)로 측정이 되었다. 고주파열치료 횟수의 중앙값은 5회였다 (사분위범위 3.25 – 5.75). 성공적인 내시경 초음파 유도하 고주파열치료 시술 후 후속 항암화학요법을 시행하였다. 시술 후 조기 합병증은 복막염 (n = 1) 및 복통 (n = 3)을 포함하여 총 107 회 중 4회(3.74%)에서 발생했었다. 중앙값 21.23 개월 (사분위범위 10.73 – 27.1 개월) 추적기간동안 중앙값 전체생존기간 및 무진행생존기간은 24.03 개월 (95%

신뢰구간 16 – 35.8 개월)과 16.37 개월 (95% 신뢰구간 8.87 – 19 개월)로 각각 측정이 되었다. 단변량 분석으로 분석하였을 때 무진행생존기간은 진단에서 내시경 초음파 유도하 고주파열치료까지의 시간이 유의한 예측 인자였다 (위험도: 0.993, 95% 신뢰구간 0.988 – 0.998, P = 0.004). 전체생존기간은 종양의 범위가 유의하게 관련이 있었다 (위험도: 2.978, 95% 신뢰구간 1.035 – 8.566, P = 0.043).

결론: 내시경 초음파 유도하 고주파열치료는 절제 불가능한 췌장암에서 기술적으로 가능하며 안전한 치료로 생각된다. 전신 항암화학요법과 병합한 내시경 초음파 유도하 고주파열치료는 우수한 생존 결과와 관련이 있을 것으로 생각된다. 이러한 우수한 연구 결과에 대한 확인을 위해서는 대규모의 전향적 비교 연구가 필요하다.

중심단어: 췌장암, 내시경 초음파, 고주파열치료, 치료 성적

약어목록: OS, overall survival; EUS, endoscopic ultrasound; RFA, radiofrequency ablation; RF, radiofrequency; LAPC, locally advanced pancreatic cancer; SMA, superior mesenteric artery; CA, celiac axis; SMV, superior mesenteric vein; PV, portal vein; PFS, progression-free survival; FFLP, freedom from local disease progression; IQR, interquartile range; CI, confidence interval

INTRODUCTION

Pancreatic cancer has a poor prognosis, with a 5-year overall survival (OS) rate of about 9%.[1] Surgery can provide long-term survival, with 5-year OS rates of 18% to 24%. However, most patients present with unresectable pancreatic cancer at the time of diagnosis because of locally advanced or distant metastasis. To date, clinical outcomes with chemotherapy or chemoradiation therapy are unsatisfactory for the management of unresectable pancreatic cancer.

Recently, endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) has been applied for the management of pancreatic neoplasms. EUS-RFA can offer real-time imaging of the target lesion, and RFA may result in safe tissue ablation. Recently, several reports have demonstrated that EUS-RFA is effective and has an acceptable safety profile for the treatment of benign pancreatic tumors.[2-4] In our preliminary study, EUS-RFA combined with systemic chemotherapy was technically feasible and safe in patients with metastatic pancreatic cancer. However, despite encouraging results, the efficacy and long-term clinical outcomes of EUS-RFA have not been evaluated.[5,6]

This study aimed to evaluate the long-term survival outcomes of EUS-RFA in patients with unresectable pancreatic cancer.

METHODS

Patients

This study was a single-center, prospective observational study conducted between May 2016 and June 2019. The study was approved by the Institutional Review Board at Asan Medical Center, and all patients signed a written informed consent form before enrollment. The inclusion criteria were as follows: (1) histopathologically confirmed pancreatic cancer, and (2) at an unresectable stage due to locally advanced or metastatic disease. Exclusion criteria were as follows: (1) advanced heart or lung disease precluding adequate sedation, (2) surgically altered anatomies, (3) poor performance, (4) uncontrolled coagulopathy, and (5) informed consent not given.

EUS-RFA procedures

All patients were treated with EUS-RFA by an experienced endosonographer (D.W.S) under conscious sedation using midazolam and meperidine. Prophylactic antibiotics were administered intravenously before each procedure.

EUS-RFA was performed using a 19-gauge RFA needle (140-cm long) and a VIVA radiofrequency (RF) generator (STARmed, Koyang, Korea). The RFA needle was inserted into the target lesion under EUS guidance to avoid intervening vessels. After puncturing the target lesion, the RF generator was activated to deliver 50W of ablation power. Ablation was continued until the hyperechoic zone around the RFA needle tip sufficiently covered the tumor. The RFA needle was then repositioned to ablate another zone. RFA was usually started at the right distal portion of the tumor on the EUS image while the RFA needle was withdrawn, after which the RFA needle was reinserted and RFA was repeated at the left side of the previous site.[5] After successful EUS-RFA, subsequent systemic chemotherapy was performed on the same day. If procedure-related adverse events occurred, systemic chemotherapy was delayed until the adverse events were resolved.

A simple abdominal radiograph and blood tests, including complete blood count, liver function tests, and serum amylase and/or lipase were checked for adverse events on the following day. After the EUS-RFA, all patients were followed-up at intervals of 2 to 3 months. At each follow-up, complete blood counts, biochemical profiles, tumor markers, and imaging studies were checked.

Outcome parameters and definitions

Unresectable locally advanced pancreatic cancer (LAPC) was defined as follows: (1) lesions of the pancreatic head/uncinate process including solid tumor contact with the superior mesenteric artery (SMA) > 180°, solid tumor contact with the celiac axis (CA) > 180°, solid tumor contact with the first jejunal SMA branch, an unreconstructible superior mesenteric vein (SMV)/portal vein (PV) due to tumor involvement or occlusion, or contact with the most proximal jejunal branch draining into the SMV; and (2) lesions in the body and tail of the pancreas including solid tumor contact > 180° with the SMA or CA, solid tumor contact with the CA and aortic involvement, or unreconstructible SMV/PV due to tumor involvement or occlusion.[7]

OS and progression-free survival (PFS) were estimated from the date of diagnosis of pancreatic cancer to the date of death or last follow-up examination, and to the date of any site of tumor progression, respectively. Local control was defined as the absence of radiologic or clinical disease progression or recurrence within the treatment field. Freedom from local disease progression (FFLP) was calculated from the date of diagnosis to the date of local disease progression.[8] The following factors were evaluated for their impact on the different survival endpoints: age, sex, nodal metastasis, tumor size, tumor location, tumor extent (LAPC vs. metastatic), pre-EUS-RFA CA19-9 level, and chemotherapy. Procedure-related adverse events were classified and graded according to the American Society for Gastrointestinal Endoscopy workshop reports.[9] Early procedural adverse events were defined as any procedure-related adverse event that occurred within 2 weeks, including bleeding, pancreatitis, and perforation. Late procedural adverse events were defined as those that occurred 2 weeks after EUS-RFA.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL, USA). The results are expressed as means and standard deviations or medians and interquartile ranges (IQRs). The probability of cumulative survival was calculated using the Kaplan-Meier method. A P-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the patients are summarized in Table 1. A total of 22 patients with unresectable pancreatic cancer (n = 14, locally advanced unresectable; n = 8, metastatic) underwent EUS-RFA. The median CA 19-9 level before RFA was 200.8 U/mL (IQR, 15.9 – 901.3). Among these patients, CA 19-9 levels were > 200 U/mL in 11 patients (50%). Pancreatic cancer was located in the head of the pancreas in 14 patients (63.6%), in the pancreas body in 4 patients (18.2%), in the tail of the pancreas in 3 patients (13.6%), and in the resection margin in 1 patient (4.5%). The median size of the primary tumor was 38 mm (IQR, 32.75 – 45). Sixteen patients (72.7%) had nodal involvement. All patients underwent gemcitabine-based chemotherapy before (n = 19) and after (n = 3) EUS-RFA. Among these patients, 18 (81.8%) received induction chemotherapy.

Clinical outcomes

Clinical outcomes are summarized in Table 2. EUS-RFA was performed successfully in all patients. The median number of RFA sessions was 5 (IQR, 3.25 – 5.75). Three patients underwent 1 session of RFA, 1 underwent 2 sessions, 2 underwent 3 sessions, 4 underwent 4 sessions, 6 underwent 5 sessions, 2 underwent 6 sessions, and the rest of the patients each underwent 8, 9, 10 and 11 sessions, respectively. The median time interval from diagnosis to EUS-RFA was 4.73 months (IQR, 2.66 – 9.65). Over a median follow-up period of 21.23 months (IQR, 10.73 – 27.1), 17 patients (77.3%) died due to disease progression. Twenty patients (95.5%) experienced treatment failure. Among these patients, treatment failure was first associated with local progression in 13 patients (59.1%), distant metastasis in 7 patients (31.8%), and both in one patient (4.5%).

Early procedure-related adverse events occurred in 4 out of 107 sessions (3.74%), including peritonitis (n = 1) and abdominal pain (n = 3). There were no severe adverse events and patients improved completely after conservative treatment. Subsequent systemic chemotherapy was performed within 2 days.

Univariate analysis results are summarized in Table 3. The median OS, PFS, and FFLP were 24.03 months (95% confidence interval [CI], 16 – 35.8), 16.37 months (95% CI, 8.87 - 19), and 6.83 months

(95% CI, 6.6 – not estimable), respectively (Fig 1). The 1-year OS and PFS rates were 72.7% (95% CI, 56.3 – 93.9%) and 62.2% (95% CI, 44.6 – 86.8%), respectively. The 1-year FFLP rate was 25.3% (95% CI, 10.5 – 60.6%).

On univariate analysis, the tumor extent was also associated with OS ($P = 0.043$). The time interval from diagnosis to EUS-RFA was associated with PFS ($P = 0.019$). Although statistically insignificant, the number of RFA sessions tended to be associated with PFS (P = 0.051). Tumor classification was also associated with FFLP (P = 0.048).

On subgroup analysis, the median OS (LAPC, 26.63 months [95% CI, 18.1 – not estimable] vs. metastatic, 15.05 months [95% CI, 10.13 – not estimable]), PFS (LAPC, 16.57 months [95% CI, 9.3 – not estimable] vs. metastatic, 10.86 months [95% CI, 6.9 – not estimable]), and FFLP (LAPC, 8.57 months [95% CI, 6.67 – not estimable] vs. metastatic, 5.17 months [95% CI, 2.7 – not estimable]) were longer in patients with LAPC than in patients with metastatic pancreatic cancer.

DISCUSSION

EUS-RFA has emerged as a promising treatment modality for various pancreatic tumors, including pancreatic cancer. Previous reports have shown that EUS-RFA can be applied for ablation of pancreatic tumors; however, the efficacy and safety of EUS-RFA still remains questionable with there being a potential risk of damage to the surrounding structures.[2,3,5,10] Our study demonstrated that EUS-RFA combined with subsequent systemic chemotherapy was technically feasible and had an acceptable range of adverse events in patients with unresectable pancreatic cancer. These results also suggested that EUS-RFA may increase survival outcomes by enhancing systemic chemotherapeutic effects.

In this series, a median of 5 sessions (IQR, 3.25 – 5.75) of EUS-RFA followed by chemotherapy within 2 days was performed successfully in all patients. Procedure-related adverse events occurred in 4 out of 107 (3.74%) sessions, including 1 episode of peritonitis and 3 episodes of abdominal pain. Except for one patient who had peritonitis, subsequent systemic chemotherapy was possible in patients who underwent EUS-RFA. In our previous study on benign solid pancreatic tumors, acute pancreatitis developed in one patient after ablation of a tumor that was close to the pancreatic duct.[3] In the current study, acute pancreatitis did not occur in any patient. As per experience accumulated through previous studies, EUS-RFA was performed while maintaining a minimum safety margin of 5 mm from the main pancreatic duct.[3] Furthermore, in patients with pancreatic cancer, chronic pancreatitis was also present at the time of presentation. Therefore, it is possible that post-procedural pancreatitis is less likely in a chronically scarred gland having severe fibrosis and atrophy.[11]

Local tumor control is important issue; therefore, the current standard of care in patients with LAPC includes a combination of chemotherapy and radiotherapy.[12] However, 1-year FFLP rate was 25.3% (95% CI, 10.5 – 60.6%). Considering the potential risk of thermal injury to adjacent organs and the relatively large size of tumors as compared with that reported in previous studies, the primary tumor was not completely ablated. As a tradeoff for incomplete ablation of the primary tumor, the incidence of postprocedural adverse events was low (4 out of 107 sessions, 3.74%). On subgroup analysis, tumor extent (locally advanced vs. metastatic pancreatic cancer) was associated with local progression (LAPC, 8.57 months [IQR, 5.56 – 11.56] vs. metastatic, 5.16 months [IQR, 0.5 – 9.83], $P = 0.222$). With regard to local control of pancreatic cancer, EUS-RFA may be more helpful in patients with LAPC than in patients with metastatic pancreatic cancer.

In terms of PFS and OS, the time interval from the diagnosis to EUS-RFA (hazard ratio [HR] 1.001;

95% CI, 0.997 – 1.005; $P = 0.004$) and tumor extent (HR, 2.978; 95% CI 1.035 – 8.566; $P = 0.043$) were statistically significant. In the current study, 86.4% of patients underwent systemic chemotherapy before EUS-RFA. The median time interval from diagnosis to EUS-RFA was 4.73 months (IQR, 2.66 – 9.65). These results are thought to be due to the fact that EUS-RFA was not performed at the time of diagnosis and was additionally performed when the tumor did not decrease to systemic chemotherapy. The number of RFA sessions also tended to be associated with PFS (HR 1.188; 95% CI. 0.999 – 1.412; $P = 0.051$). The median number of RFA sessions was 5 (IQR, 3.25 – 5.75). When the therapeutic effect of EUS-RFA was unsatisfactory, the procedure was performed repeatedly to reduce the tumor burden. These clinical practices may have affected the results. In this study, the median OS was 24.03 months in patients with unresectable pancreatic cancer, including LAPC and metastatic pancreatic cancer. In addition, the median OS was 26.63 months in patients with unresectable LAPC and 15.05 months in patients with metastatic pancreatic cancer. Considering the heterogeneity of enrolled patients, our results had relatively favorable survival outcomes compared with the median OS of 8.6 - 18.8 months in patients with LAPC and the median OS of 6.7 – 11.1 months in patients with metastatic pancreatic cancer from previous reports.[13-17] In a study by Haen et al., thermal ablation could induce an immune response towards the tumor, determined by the release of necrotic cell content in the extracellular space that stimulated the host's antitumor immunity.[18] A more recent study documented increased blood flow around the ablated area.[5] Therefore, even suboptimal RFA treatment could affect these post-procedural tumor changes associated with systemic antitumor immune response.

There are some limitations in this study. First, the number of enrolled patients was small and our study was a single arm, non-comparative study. Therefore, large scale randomized controlled studies comparing chemotherapy alone and EUS-RFA combined with chemotherapy are necessary to confirm our favorable results. Second, the systemic chemotherapy used in this study was inferior to that of current practice which uses a more effective regimen such as FOLFIRINOX and gemcitabine plus abraxane. In addition, there was a discrepancy between PFS/OS and FFLP. These discrepancies may be due to the median 4.73 months of time gap between the initial diagnosis and EUS-RFA. If EUS-RFA combined with systemic chemotherapy is initiated at the time of diagnosis, the results may change.

In conclusion, EUS-RFA is technically feasible and safe with favorable OS in concordance with systemic chemotherapy in patients with unresectable pancreatic cancer. Our results suggest that EUS-RFA combined with systemic chemotherapy is a promising treatment approach for patients with unresected pancreatic cancer. EUS-RFA with a more aggressive chemotherapy regimen may improve

clinical outcomes and requires further investigation.

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Tables

Table 1. Baseline characteristics of patients who underwent EUS-RFA

Characteristics	**No. of patients**
Age, median (IQR), y	60.5 (56.25 – 68.75)
Sex, M:F	13:9
Tumor extent, n (%)	
Locally advanced	14 (63.6)
Metastatic	8 (36.4)
Location, n (%)	
Head	14 (63.6)
Body	4 (18.2)
Tail	3 (13.6)
Distal pancreatectomy resection margin	1 (4.5)
Tumor size, median (IQR), mm	38 (32.75 – 45)
Initial CA 19-9, median (IQR), U/mL	200.8 (15.9 – 901.3)
CA 19-9 > 200 U/mL, n (%)	11 (50)
Nodal metastasis, n (%)	16 (72.7)
Sequential chemotherapy, n (%)	
Before EUS-RFA	19 (86.4)
After EUS-RFA	3 (13.6)
Induction chemotherapy, n (%)	18 (81.8)

IQR, interquartile range; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation

Table 2. Clinical outcomes of patients who underwent EUS-RFA combined with systemic chemotherapy

Characteristics	**No. of patients**
Number of RFA sessions, median (IQR)	5 (3.25 – 5.75)
Time interval from diagnosis to EUS-RFA, median (IQR), months	4.73 (2.66 – 9.65)
Follow-up period, median (IQR), months	21.23 (10.73 – 27.1)
Treatment failure, n (%)	20 (95.5)
Local progression	13 (59.1)
Distant metastasis	7 (31.8)
Both	1 (4.5)
Adverse events, n (%)	4/107 (3.74)
Abdominal pain	3
Peritonitis	1

IQR, interquartile range; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation

Table 3. Univariate analysis of covariates associated with FFLP, PFS, and OS

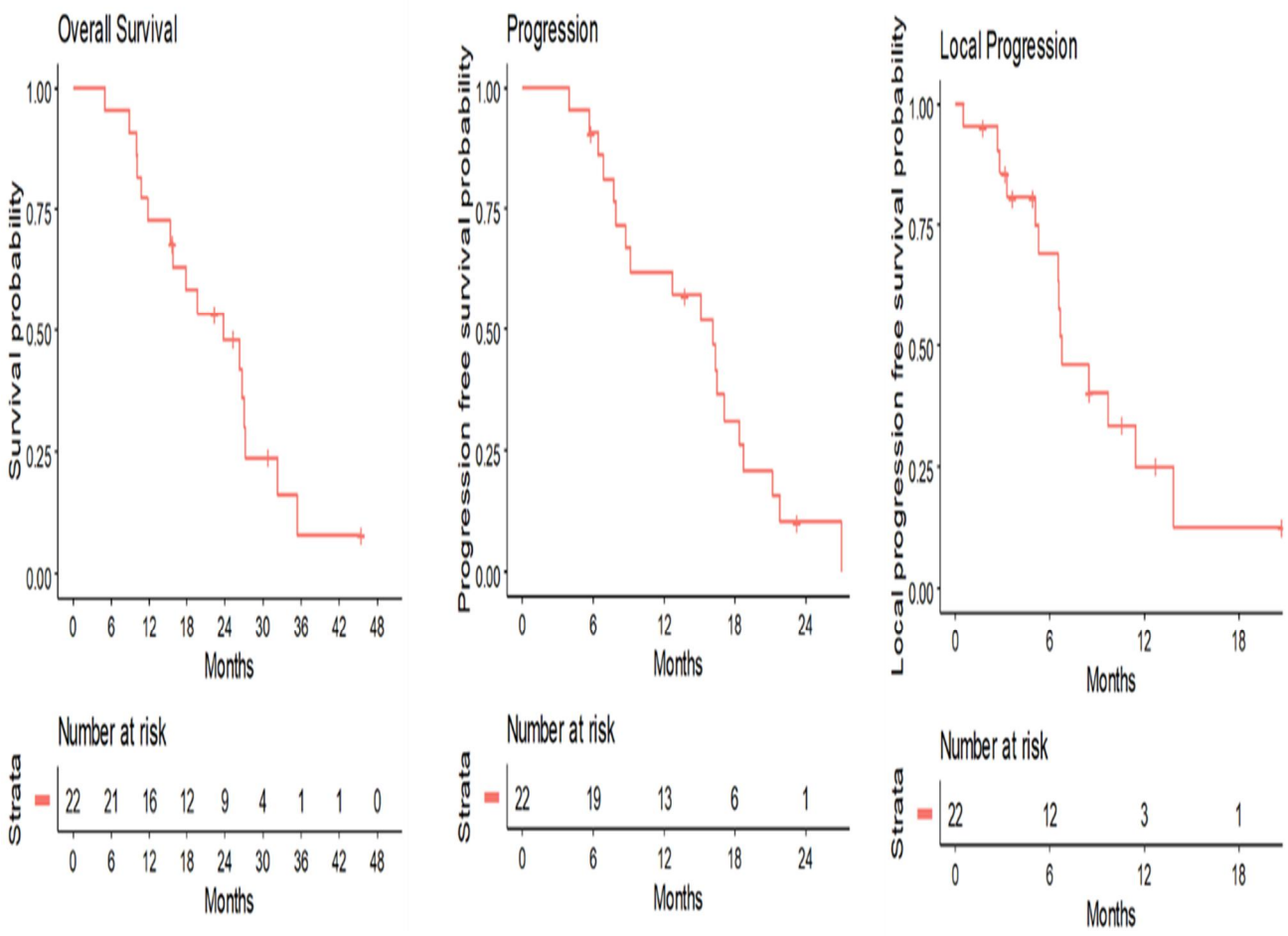
Variables	**FFLP**			**PFS**			**OS**		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	0.942	0.868 – 1.023	0.155	0.995	0.938 – 1.055	0.869	0.999	0.939 – 1.064	0.987
Sex	1.028	0.310 – 3408	0.964	0.449	0.167 – 1.205	0.112	0.477	0.180 – 1.261	0.136
Tumor extent	3.247	1.011 – 10.425	0.048	1.190	0.443 – 3.195	0.730	2.978	1.035 – 8.566	0.043
Tumor size	1.011	0.978 – 1.045	0.533	0.996	0.975 – 1.017	0.691	1.015	0.992 – 1.040	0.206
Tumor location	0.440	0.140 – 1.378	0.159	0.550	0.207 – 1.457	0.229	0.454	0.167 – 1.229	0.120
Nodal metastasis	1.102	0.338 – 3.592	0.872	0.437	0.150 – 1.278	0.131	0.535	0.178 – 1.612	0.266
Distant	1.998	0.645 –	0.23	0.610	0.212 –	0.359	2.498	0.852 –	0.095

metastasis		6.196			1.756			7.326	
Pre-EUS-RFA CA 19-9	1.521	0.514 – 4.501	0.449	1.825	0.712 – 4.677	0.210	2.021	0.759 – 5.382	0.159
Time interval from diagnosis to EUS-RFA	1.001	0.997 – 1.005	0.526	0.993	0.988 – 0.998	0.004	0.999	0.997 – 1.002	0.513
Number of EUS-RFA session	1.158	0.961 – 1.396	0.123	1.188	0.999 – 1.412	0.051	1.094	0.953 – 1.257	0.202
Induction chemotherapy	5.277	0.671 – 41.486	0.114	1.074	0.300 – 3.846	0.913	3.269	0.737 – 14.500	0.119

FFLP, freedom free local progression; PSF, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation

Figures

Figure 1. Kaplan-Meier curves of (A) overall survival, (B) progression-free survival, and (C) freedom from local disease progression overall survival in patients underwent EUS-RFA with chemotherapy



ENGLISH ABSTRACT

Background and study aims: Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) has been increasingly used for the treatment of pancreatic neoplasms. The role of EUS-RFA in the management of pancreatic cancer has not yet been elucidated. This study aimed to evaluate the survival impact of EUS-RFA in unresectable pancreatic cancer.

Patients and methods: Twenty-two patients (n = 14, locally advanced unresectable; n = 8, metastatic) with unresectable pancreatic cancer underwent EUS-RFA combined with subsequent chemotherapy between May 2016 and June 2019. Survival outcomes, including overall survival (OS) and progression free survival (PFS) were evaluated.

Results: EUS-RFA was successful in all patients. The median number of RFA sessions was 5 (interquartile range, [IQR], 3.25 – 5.75). After successful EUS-RFA, subsequent gemcitabine-based chemotherapy was performed. Early procedure-related adverse events occurred in 4 out of 107 sessions (3.74%), including peritonitis (n = 1) and abdominal pain (n = 3). During follow-up over a median of 21.23 months (IQR, 10.73 – 27.1), the median OS and PFS were 24.03 months (95% confidence interval [CI], 16 – 35.8) and 16.37 months (95% CI, 8.87 - 19), respectively.

Conclusions: EUS-RFA is technically feasible and safe for the management of unresectable pancreatic cancer. EUS-RFA combined with systemic chemotherapy may be associated with favorable survival outcomes. Further larger-scale prospective comparative study is required to confirm these findings.

KEYWORDS: Pancreatic Neoplasms; Endoscopic Ultrasound, Radiofrequency Ablation, Treatment Outcome