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## Case Report

# A case of improved quality of life in a patient with inoperable pancreatic cancer after repeated RFA<sup>☆,☆☆</sup>

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## ABSTRACT

Radiofrequency ablation (RFA) has widespread popularity due to its immune-modulation effects in many cancers. Optimal settings to apply RFA in pancreatic cancer, in which the advanced stage of the tumor at the diagnosis makes various therapeutic approaches fail, are still demanding. We report the case of a patient with unresectable pancreatic cancer in which 3 repetitive RFA has been applied over a period of 3 months. Results revealed an improvement in the patient's clinical condition associated with the reduced incidence of CD4+CD45RO+ T lymphocytes and declined TGF- $\beta$  level in serum. The good quality of life and disease-free survival were maintained for the next months. Booster application of RFA procedure might be a promising option to improve the quality of life in pancreatic cancer patients.

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a leading cause of cancer-related mortality in the Western world with limited therapeutic options and a very poor prognosis. Pancreatic cancer accounts for almost as many deaths as cases since patients rarely exhibit symptoms until an advanced stage when most of the patients are diagnosed [1]. Although palliative chemotherapy and best supportive care might have some im-

pact on overall survival, still the median survival is only 3–6 months in metastatic disease at presentation [2].

Radiofrequency ablation (RFA) is a minimally invasive loco-regional therapy for tumor eradication with positive immunomodulation [3]. RFA reported as an “endogenous vaccine” for PDAC could be a rational approach to the enhancement of antigen-specific immune reactions [4,5]. However, the strength and the timing of this procedure still remain to be established for certain tumors. Short-lived effect of RFA treatment brings to the assumption that a single procedure

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might not be sufficient to raise a prolonged effective antitumor immune response. This explains that such thermal ablation rarely induces distant tumor regression.

Repetitive RFA procedures may supply the immune system with additional booster doses of cancer antigens and maintain long-term effective immune responses.

## Case report

A 75-year-old man presented with a 2-week history of high fever, epigastric pain, progressing fatigue, jaundice, tea-colored urine, and an unintentional weight loss of 7.5 kg during the previous 2 months. A clinical diagnosis of cholangitis was made on the basis of Charcot's triad. Blood analysis showed that CA 19-9 (244 U/ml); ESR (43 U/mol), Total BIL (62  $\mu\text{mol/L}$ ); direct BIL (49  $\mu\text{mol/L}$ ) were elevated.

Ultrasound and contrast-enhanced CT revealed pancreatic cancer with liver metastasis. Eastern Cooperative Oncology Group (ECOG) performance status (PS) score was 3. Patient assessed his own ECOG PS in a questionnaire by placing a mark beside the statement that most accurately reflected his functional ability over the preceding 2 weeks. Clinical oncologist recorded the patient's ECOG score using the same questionnaire throughout the treatment course (Table 1). He was not eligible for any kind of chemotherapy.

Percutaneous transhepatic biliary drainage (PTBD) was performed under the combined ultrasound-fluoroscopy guidance to relieve cholangitis. Jaundice and symptoms of cholangitis were alleviated in a few hours and eliminated in 5 days. A week after PTBD endoluminal, RFA was successfully performed under deep sedation. The bile duct obstruction secondary to invasive tumor was detected on the fluoroscopy (Fig. 1A). The first step of the RFA procedure involved the insertion of the introducer sheath over the guidewire and manipulation of the wire across the obstructed segment of common bile duct using a 5Fr diameter advantage catheter (Fig. 1B). An 8Fr endoluminal RFA catheter was inserted over the guidewire and positioned across a tumor obstructed segment in the CBD under fluoroscopic guidance.

The endoluminal RFA catheter was coupled to a radiofrequency generator to deliver 15 Watts over a duration of 2 minutes for each application. The RF energy was applied in a sequential manner along the entire length of the malignant stricture under fluoroscopic guidance for 2 minutes (Fig. 1C). Biliary patency has been restored by internal/external drain positioning. The patient coped with therapy very well.

After 2 months from the first RFA, the patient's quality of life has improved. His ECOG PS score was 2, CA 19-9 was 222 U/ml. He became eligible for chemotherapy but declined it due to concerns about toxicity. Second RFA was successfully performed to maintain the possible immunomodulatory effect and the external-internal drain was repositioned.

After 1 month (3 months after the first procedure), the patient's clinical condition was good. Third RFA followed with 10 mm diameter self-expanding metallic stent placement was successfully performed for biliary patency final restoration (Fig. 1D). On the stent implantation procedure, stent patency was documented by contrast injection via the introducer sheath and repositioned PTBD drain. The external drain has been repositioned to maintain access to the biliary tree.

Five months after the first RFA procedure, the patient's general well-being was not declined. His ECOG PS score was 2. The patient was fully active during the next 8 months.

Blood samples for immunological studies were obtained on admission and 2, 3, and 5 months after the first RFA procedure. Results were compared to 22 healthy age-matched controls.

After 13 months from the first visit, the patient was admitted with severe fatigue, jaundice, pruritus, and epigastric pain. Serum CA19-9 level was 882 U/ml. His ECOG PS score was 3. Tumor stricture advancement with existing stent obstruction was identified (Fig. 1E). The recanalization procedure by second metal stent parallel implantation was successfully performed (Fig. 1F). Jaundice and abdominal pain were relieved. One month later ECOG PS score was 4 and his general condition gradually deteriorated. The patient died 19 months after the first visit.

**Table 1 – RFA response and disease progression.**

Parameter	Admission	After 2 months	After 3 months	After 5 months	After 13 months	After 15 months
NLR (1.97±0.59)	1.79	1.56	1.19	1.19	3	4
CD4+CD45RO+ (40.6±4.5)	79.3	27.4	27.4	3.3	3	4
TGF- $\beta$ (pg/ml) (37.7±5.2)	57.5	29.8	10.3	9.9	3	4
IL-4 (pg/ml) (2.8±1.1)	23.7	17.4	14.0	13.8	3	4
ECOG PS Score	3	2	2	2	3	4
Interventions	1 <sup>st</sup> RFA	2 <sup>nd</sup> RFA	3 <sup>rd</sup> RFA	S/P	Recanalization by 2 <sup>nd</sup> metal stent	Stent procedure

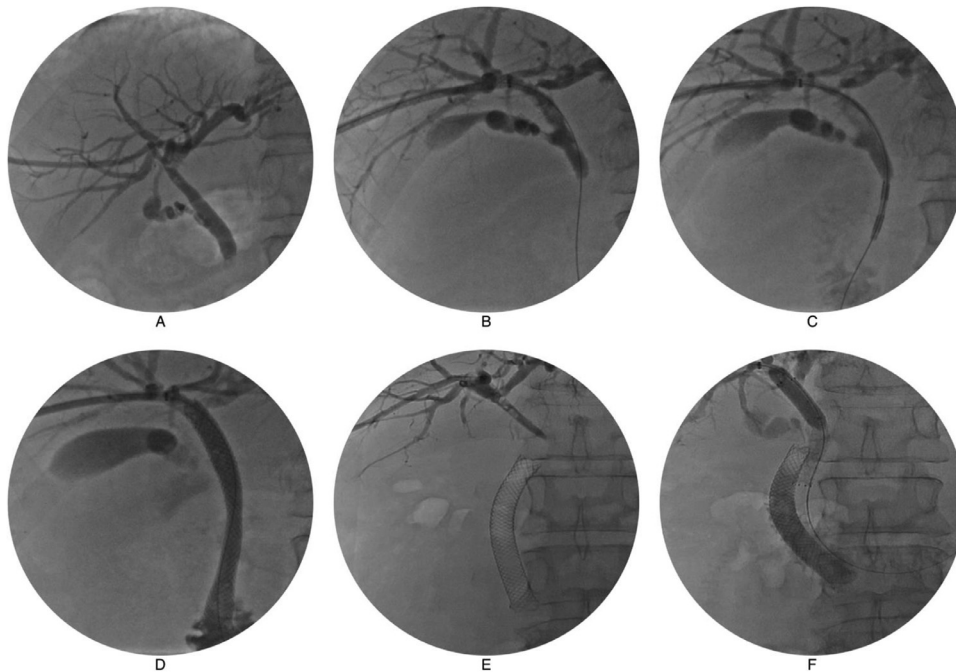
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IL, interleukin; n, reference range (values in healthy controls); NLR, neutrophil lymphocyte ratio; RFA, Radiofrequency Ablation; S/P, stent placement; TGF, tumor growth factor.

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## Discussion

In a reported case, a pancreatic cancer patient with distant metastases was treated with 3-repeated RFA. At the time of diagnosis, the patient had increased frequency of blood CD4+CD45RO+ cells and elevated levels of serum cytokines (IL-4, TNF- $\alpha$ , IL-10, IL-17, TGF- $\beta$ ) compared to healthy controls (Table 1). A stable decrease of cells with activated memory phenotype - CD4+CD45RO+ and the level of TGF- $\beta$  were observed all over the repeated RFA. It was correlated with an improvement of the quality of life. Diminished CD4+CD39+ cells, known as immunosuppressive by nature, was observed after the first and second RFA procedures.

The decrease of CD4+CD45RO+ cells might be the result of memory Treg cells reduction since 90%-95% of circulating CD4+Foxp3+Treg are CD45RO+ and secrete TGF- $\beta$ , promoting PDAC progression [6]. TGF- $\beta$  enhances pancreatic cancer invasiveness and metastatic potential while suppressing cancer-



**Fig. 1 – Fluoroscopy images of the patient in dynamics. (A) Contrast injected via introducer sheath showed obstruction in PD secondary to the dense tumor. (B) The guidewire conducted into the duodenum through the obstructed segment. (C) Application of radiofrequency at the level of the tumor. (D) A 10 mm SEMS was placed in succession at the end of the third RFA procedure. (E) 13 months after first visit, the patient underwent de novo PTBD procedure after jaundice onset. Contrast injection via PTBD catheter shows the biliary stricture above the implanted stent. (F) Fluoroscopic image shows the newly positioned stent post dilatation by balloon.**

directed immune mechanisms [7]. TGF- $\beta$  blockage contributes to tumor control [8].

Since our patient did not receive any other treatment, we suppose that the RFA procedure was responsible for the disease-free period (13 months) accompanied with diminution of TGF- $\beta$  and IL-4 (Table 1).

Lymphopenia most likely indicates a favorable environment for tumor growth. Either due to lymphopenia or neutrophilia increased levels of neutrophil/lymphocyte (NLR), platelets/lymphocyte (PLR) and monocyte/lymphocyte (MLR) ratios suggest the immune system inefficacy to suppress cancer progression. NLR, MLR, PLR have been proposed as cancer prognostic markers [9,10]. We suppose that levels of NLR, MLR, and PLR at diagnosis, comparable with the healthy controls (NLR- $1.97 \pm 0.59$ , PLR- $121.62 \pm 25.27$ ; MLR- $0.24 \pm 0.07$ ) were favorable for RFA treatment and prolonged cancer-free survival in our patient.

While this case study is encouraging, limitations should be acknowledged. A more comprehensive immune subset analysis is warranted in the future. FoxP3 expression within CD4+CD45RO+ cells ought to be determined to call them regulatory in nature.

This case report describes the improved quality of life in a patient with inoperable pancreatic cancer after a booster administration of RFA. Larger scale studies are needed to convince the immunomodulatory outcome of repeated RFA which might become a promising option to improve the quality of life and disease-free survival in advanced pancreatic cancer.

### Ethics statements

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent and consent for publication is provided from a study participant. The study protocol was approved by Tbilisi State Medical University Ethical Committee on Human Research.

### Informed consent and consent for publication

Informed consent was obtained from a patient included in the study. Consent for publication was obtained for a person's data included in the study.

### Patient consent

I give my consent for the Material about me to appear in scientific journals. I understand that the Material will be published without my name attached; however, I understand that complete anonymity cannot be guaranteed. It is possible that

somebody somewhere—for example, somebody who looked after me or a relative—may recognize me. [Signed].

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