

# Necrosis volume and Choi criteria predict the response to endoscopic ultrasonography-guided HybridTherm ablation of locally advanced pancreatic cancer



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## ABSTRACT

**Background and study aims** Endoscopic ultrasound (EUS)-guided ablation of pancreatic ductal adenocarcinoma (PDAC) with HybridTherm-Probe (EUS-HTP) is feasible and safe, but the radiological response and ideal tool to measure it have not been investigated yet. The aims of this study were to: 1) assess the radiological response to EUS-HTP evaluating the vital tumor volume reduction rate, Response Evaluation Criteria in Solid Tumors (RECIST1.1) and Choi criteria; 2) determine the prognostic predictive yield of these criteria.

**Patients and methods** A retrospective analysis was performed of patients with locally advanced PDAC after primary treatment or unfit for chemotherapy prospectively treated by EUS-HTP. Computed tomography scan was performed 1 month after EUS-HTP to evaluate: 1) vital tumor volume reduction rate (VTVRR) by measuring necrosis and tumor volumes through a computer-aided detection system; and 2) RECIST1.1 and Choi criteria.

**Results** EUS-HTP was feasible in 22 of 31 patients (71%), with no severe adverse events. Median post-HTP survival was 7 months (1–35). Compared to pre-HTP tumor volume, a significant 1-month VTVRR (mean 21.4%) was observed after EUS-HTP ( $P=0.005$ ). We identified through ROC analysis a VTVRR > 11.46% as the best cut-off to determine post-HTP 6-month survival outcome (AUC = 0.733; sensitivity = 70.0%, specificity = 83.3%). This cut-off was significantly associated with longer overall survival (HR = 0.372;  $P=0.039$ ). According to RECIST1.1 and Choi criteria,

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good responders to EUS-HTP were 60% and 46.7%, respectively. Good responders according to Choi, but not to RECIST1.1, had longer survival (HR = 0.407;  $P = 0.04$ ).

**Conclusions** EUS-HTP induces a significant 1-month VTVRR. This effect is assessed accurately by evaluation of necrosis and tumor volumes. Use of VTVRR and Choi criteria, but not RECIST 1.1 criteria, might identify patients who could benefit clinically from EUS-HTP.

## Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of 5% to 10%, with 80% of patients having metastatic or locally advanced (LA) disease at diagnosis. New poly-chemotherapy regimens achieve tumor downsizing in only 10% to 35% of cases [1]. In light of this poor outcome, local ablative treatments may represent additional options in PDAC with persistent, stable, LA disease after initial chemotherapy or a tendency to further local growth only [1, 2]. Potential benefits of such treatments might include reduction of metastatic spread and increase of chemotherapy activity through tumor and microenvironment modification [3]. Radiofrequency ablation (RFA) results in thermal irreversible protein denaturation, cellular damage, and coagulative necrosis. Cryoablation results in in-situ freezing-related destruction of cellular ultra-structures and indirect actions such as vascular injury and apoptosis [4]. It has been reported to be safe and effective in solid tumors, including PDAC, possibly promoting an antitumor immune reaction [5, 6].

Recently, application of a CO<sub>2</sub>-cooled bipolar RFA device, the HybridTherm Probe (HTP, Erbe Elektromedizin GmbH, Tübingen, Germany), used under endoscopic ultrasound (EUS) guidance in pancreatic lesions has been evaluated in our center [7–10]. HTP-ablation of pancreatic tissue in live pigs was safe and efficient in tissue destruction.

EUS-HTP feasibility and safety were preliminarily demonstrated in a study involving 22 patients with LA-PDAC after chemotherapy±radiotherapy. One of the drawbacks of this study was the difficulty in defining tumor margins and necrosis area after ablation using contrast-enhanced multi-detector computed tomography (CE-MDCT) scan. This was possible in only 37.5% of treated patients, possibly due to PDAC hypovascularity hindering accurate measurement of necrosis [10].

Tumor volumetry represents a powerful tool for measuring treatment response, providing more accurate quantification of tumor size changes after treatment in rectal and renal cell cancer [11, 12]. Tumor size changes are also the basis for Response Evaluation Criteria in Solid Tumors (RECIST1.1), which is the most widely used radiological response assessment tool [13]. In patients with advanced hepatocellular carcinoma (HCC) treated with antiangiogenic multikinase-inhibitors, the response rate according to RECIST1.1 criteria did not reflect the survival benefit obtained with these agents [14]. On the other hand, also in other tumor types, Choi criteria showed better correlation with improved clinical outcome compared to RECIST1.1 [14–16]. Decreased tumor density on CT scan was correlated with necrosis development, reflecting tumor activity.

Recent improvements in advanced visualization computer-aided detection (CAD) systems have further increased diagnostic accuracy of cancer detection and volumetric assessment [17, 18]. None of these CAD tools have been employed to evaluate the effect of EUS-guided treatments for PDAC so far.

The primary aim of this study was to evaluate radiological response to EUS-HTP in LA-PDAC according to CAD-assisted evaluation of necrosis and tumor volumetries and assessment of RECIST1.1 and Choi criteria. The secondary aim was to determine which radiological response assessment criteria correlates better with the post-ablation patients survival outcome.

## Patients and methods

### Study design and population

This was a retrospective study carried out in a consecutive series of prospectively enrolled patients with documented LA-PDAC who were unfit for chemotherapy due to comorbidities, or had local progression (no signs of extrapancreatic spread) after first-line chemotherapy±radiotherapy, or local recurrence after surgery, who were treated with EUS-HTP at a single center over 5 years.

The study evaluating EUS-HTP feasibility and safety (prot. CTP2010) was approved by the medical Ethics Committee of San Raffaele Hospital (Milan, Italy) before it started [10]. Inclusion criteria were: radiological and pathological proven LA-PDAC; completion of first-line chemotherapy; ineligibility for chemotherapy due to comorbidities; lesion size  $\geq 30$  mm or more; age  $> 18$  years; life expectancy  $> 3$  months; platelet count  $> 100.000/\text{mm}^3$ ; international normalized ratio  $< 1.5$ ; and completion of informed consent for procedure and data management for scientific purposes. Exclusion criteria were distant metastasis; severe alterations of hemostasis; infection and/or severe leukopenia; acute pancreatitis; and pregnancy.

Unresectability of PDAC was determined during multidisciplinary evaluations according to National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) [19]. LA-PDAC was defined as local disease, with no distant metastasis, presenting encasement (vessel wall infiltration or contact  $> 180^\circ$  for more than 2 cm, with initial vessel stricture or alteration of Doppler signal) or thrombosis of celiac axis and/or portal vein and/or superior mesenteric artery and/or vein and/or hepatic artery.

### Study endpoints

The primary endpoint was assessment of radiological response to EUS-HTP at 1 month post-treatment imaging, by measuring: 1) reduction rate of the vital tumor volume (VTVRR), using an

advanced visualization software to measure tumor and necrosis volumes; and 2) RECIST1.1 and Choi criteria.

Secondary endpoints were determination of the predictive yield of the radiological response assessed by the above mentioned methods on patient survival.

### EUS-guided HTP procedure

HTP, a needle-shaped (14-gauge) flexible internally CO<sub>2</sub>-cooled bipolar RF-ablation probe, was used to treat LA-PDAC under EUS guidance. HTP has been described in previous studies [7–10]. During the procedure, the probe was passed through the 3.8-mm operative channel of a therapeutic linear-array echoendoscope (Pentax Medical Endoscopic Ultrasound EG3870UTK, Pentax Europe GmbH, Hamburg, Germany) and the active tip was placed directly into the target lesion under EUS guidance. Power for heating was delivered by the VIO 300 D RF-system and cooling of the electrodes was provided by the ERBECRYO2 system (Erbe Elektromedizin GmbH, Tübingen, Germany). Ablation parameters and application time were set based on previous studies [7–9]: fixed RF power of 18 W, fixed cooling pressure of 650 psi, and application time varying between 240 seconds for a 2-cm mass and 480 seconds for a >3-cm mass. A computerized system automatically stopped the ablation before the calculated application time when the electric resistance, induced by desiccation and devitalization of the tumor tissue, increased.

All the procedures were performed by two endosonographers (PGA, MCP) who were highly experienced in pancreatic EUS-FNA/FNB (>400/year) under deep sedation administered by an anesthesiologist.

To prevent infections and thermal-induced pancreatitis, all patients were treated with antibiotic (ceftriaxone 1 g × 2/day for 5 days) and antiprotease prophylaxis (gabexate mesylate 500 mg in 500 mL saline solution), more recently replaced by rectal indomethacin before EUS-HTP (Metacen 100 mg) [20].

### Post-procedure follow-up

After EUS-HTP, patients were followed for 5 days as inpatients with blood tests (complete blood count, amylase, blood glucose, C-reactive protein, creatinine) and 48-hour CE-MDCT scan to detect possible adverse events (AEs).

AE severity classification was defined according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon for endoscopic AEs [21]. Early AEs were defined as occurring during treatment or within the first 2 weeks after EUS-HTP. Potentially related late AEs were considered as occurring after the first 2 weeks or within 3 months after EUS-HTP.

After discharge, in case of late AE onset, patients were readmitted. Clinical follow-up by the oncology team on an outpatient basis was planned until their deaths.

### Radiological response assessment

Investigation of the radiological response to EUS-HTP was planned at 1-month with CE-MDCT scan; it was determined by assessing the vital tumor volume reduction rate, RECIST1.1 and Choi criteria [13–16].

► **Table 1** Radiological response of target lesions to therapy according to RECIST1.1 and Choi criteria.

	RECIST1.1	Choi Criteria
<b>CR</b>	Disappearance of target lesions. No new lesions.	Disappearance of target lesions. No new lesions.
<b>PR</b>	≥ 30% decrease in longest diameter of the target lesion, taking as reference the baseline diameter. No new lesions.	≥ 10% decrease in the longest diameter or ≥ 15% decrease in tumor density of the target lesion. No new lesions.
<b>SD</b>	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest long diameter on study.	Does not meet the criteria for CR, PR or PD.
<b>PD</b>	≥ 20% increase in the longest diameter of the target lesion, taking as reference the smallest long diameter in study, as well as an absolute increase of at least 5 mm. New lesions.	≥ 10% increase in tumor longest diameter and does not meet the criteria of PR by tumor density (HU) on CT scan. New lesions.

RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HU, Hounsfield unit; CT, computed tomography

With regards to volumetry, the following measurements were determined: 1) pre- and post-HTP tumor volume; 2) post-HTP ablation-induced necrosis volume; 3) post-HTP vital tumor volume (VTV), defined as the difference between pre-HTP tumor volume and post-HTP necrosis volume; and 4) rate of reduction rate of VTV (VTVRR) calculated as follows: [(pre-HTP tumor volume – post-HTP VTV)/pre-HTP tumor volume] × 100 [22].

Patients who had complete response (CR), partial response (PR) or stable disease (SD) after treatment according to RECIST1.1 and Choi criteria (► **Table 1**) were defined as good responders, whereas those with progressive disease (PD) were defined as poor responders.

Tumor and induced necrosis dimensions and volumes were assessed using the CADsystem IntelliSpace Portal 7.0 (ISP7.0, Philips Healthcare) [23,24]. A dedicated tool, named Multi Modality Tumor Tracking, was used to review tumor images, applying tumor semi-automatic segmentation and tracing 3D-ROIs (three-dimensional region-of-interest). This software enables quantitative parameters of target lesions, such as tumor size, volume and mean density (attenuation coefficient in Hounsfield Units), both in pre-contrastographic phase and post-contrastographic arterial, portal, and venous phases.

In patients with previous allergy to iodized contrast medium, contrast-enhanced magnetic resonance imaging (CE-MRI) was planned in place of CE-MDCT scan and necrosis and tumor volumes were still obtained using ISP7.0, but Choi criteria could not be assessed.

All measurements were double-checked by two radiologists (MB, SG) who are experts in pancreatic imaging.

## Statistical analysis

Data are presented as mean±SD if not otherwise specified. For group differences and correlation analysis, *t*-test and Pearson correlation coefficient were used for normally distributed samples and Mann-Whitney or Wilcoxon test and Spearman correlation coefficient were used for not-normally distributed samples. For assessment of the prognostic predictive yield of VTVRR related to post-HTP 6-month survival, a receiving operator characteristics (ROC) curve was constructed with identification of an associated criterion as cut-off for VTVRR. For assessment of the prognostic predictive yield of VTVRR, RECIST1.1 and Choi criteria related to the overall survival (OS), Kaplan-Me-

ier product limit estimates were used to construct survival curves, compared using Log-rank Mantel-Cox test. Statistical calculations were done with GraphPadPRISM8.0 software (GraphPad Software Inc, California, USA), with  $P < 0.05$  was defined as statistically significant.

## Results

### Patients and lesions characteristics

Thirty-one LA-PDAC patients (mean  $64 \pm 11.5$  years) were enrolled (► **Table 2**). The tumor mass was located in the pancreatic head in 15 patients (48.4%). Before enrollment, all but five patients had received first-line gemcitabine-based chemotherapy (for mean  $6 \pm 1.9$  months), with initial partial response in 14 and stable disease in 12 patients and subsequent local progression. Eighteen (58.1%) also underwent radiotherapy. Two patients (6.4%) had post-surgery local disease relapse. Median time from LA-PDAC diagnosis and from first-line treatment to EUS-HTP treatment were 12 (range 1–26) and 5 months (range 1–19), respectively. Five patients did not receive other treatments before EUS-HTP (16.1%) because of concomitant comorbidities (3), refusal of chemotherapy (1) and advanced age (1).

### Feasibility of EUS-HTP treatment

EUS-HTP was feasible in 22 of 31 patients (71%). EUS-HTP was not possible in nine patients due to tumor hardness (6), gastrointestinal wall stiffness (1), vessel interposition (1), and post-surgical altered anatomy (1). Of these nine patients, four (44.4%) and five (55.6%) had tumor location at pancreatic head and body, respectively, and eight (88.9%) had received chemotherapy + radiotherapy before EUS-HTP.

Seven of 22 patients had a biliary stent (6 metal and 1 plastic) and one a percutaneous biliary catheter at the time of EUS-HTP, without affecting its feasibility.

### Radiological response to EUS-HTP treatment

Mean HTP application time was  $125.05 \pm 75.0$  seconds. As reported previously [19], tumor short axis length significantly correlated with HTP application time ( $R = 0.45$ ,  $P = 0.04$ ). Moreover, post-HTP necrosis volume significantly correlated with HTP application time ( $R = 0.58$ ,  $P = 0.02$ ) and pre-HTP tumor volume ( $R = 0.48$ ,  $P = 0.03$ ).

Post-HTP 1-month imaging was performed in 18 of 22 patients (81.8%), after mean  $38.15 \pm 15.9$  days. In three cases CE-MRI was performed instead of CE-MDCT scan. Four patients did not undergo 1-month imaging because of death (one esophageal and duodenal variceal bleeding in a patient with previous severe portal hypertension due to vessel tumoral infiltration of the splenic vein, superior mesenteric vein and portal vein, and one rapidly degenerative general condition in a 66-year old patient after pancreatic surgery) or loss to follow-up (2). Necrosis volume was measurable in 16 of 18 patients (88.9%). The typical radiological finding at ablation site was an inhomogeneous, hypodense, and not vascularized intra-tumor area, confirmed after intravenous injection of contrast medium, compatible with colliquative necrosis. In two patients, it was difficult to precisely assess the ablation area size and volume because of

► **Table 2** Baseline characteristics of the 31 enrolled patients with locally advanced pancreatic adenocarcinoma.

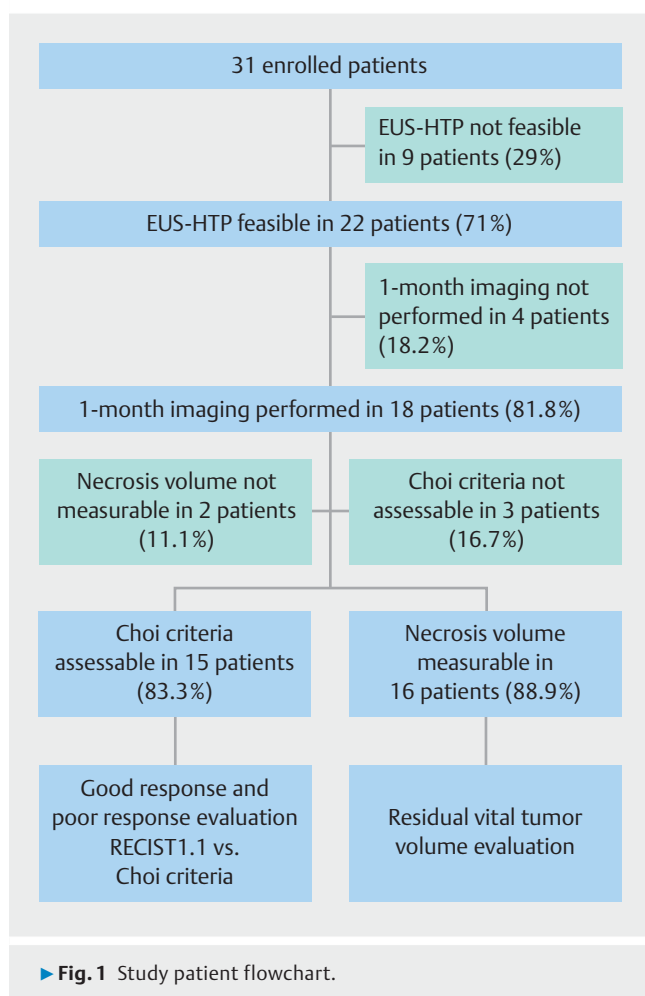
Sex, N. (%)	
Male	21 (67.7)
▪ Female	10 (32.3)
▪ Age (years), mean ± SD	64 ± 11.5
Pancreatic tumor site, N. (%)	
▪ Head	14 (45.2)
▪ Body	13 (41.9)
▪ Body – Tail	3 (9.7)
▪ Head – Body	1 (3.2)
Pretreatment, N. (%)	
▪ Chemotherapy	8 (25.8)
▪ Chemoradiotherapy	18 (58.1)
▪ Not performed	5 (16.1)
Pretreatment scheme, N. (%)	
▪ PEXG	17 (54.8)
▪ PAXG	2 (6.4)
▪ Gemcitabine + XELIRI	1 (3.2)
▪ Gemcitabine + XELODA	4 (12.9)
▪ Gemcitabine + cisplatin	1 (3.2)
▪ Gemcitabine + abraxane	1 (3.2)
▪ Time (months) of chemotherapy, mean ± SD	6 ± 1.9
Response to pretreatment (RECIST 1.1), N. (%)	
▪ Stable disease	12 (46.15)
▪ Partial response	14 (53.8)
Time (months) from first treatment, median (range)	5 (1–19)

SD, standard deviation; MDCT, multi-detector computed tomography; PEXG, gemcitabine, cisplatin, capecitabine, epirubicin; PAXG, nab-paclitaxel, gemcitabine, capecitabine, cisplatin; XELIRI, irinotecan, capecitabine; XELODA, capecitabine; RECIST, Response Evaluation Criteria in Solid Tumors

► **Table 3** Radiological response to endoscopic ultrasound-guided cryothermal ablation treatment according to RECIST1.1 and Choi criteria 1 – month, evaluated in 15 patients in whom both the criteria could be assessed.

Radiological Response	1-Month RECIST1.1	1-Month Choi Criteria
Good responders (PR + SD)	9/15 (60.0%) (9 SD)	7/15 (46.7%) (2 PR – 5 SD)
Poor responders (PD)	6/15 (40.0%)	8/15 (53.3%)

RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease



artifacts and HTP-induced edema or because the ablation area was no longer clearly visible.

Creating a necrosis area with median volume of 5.3 cc (range 0.26–48.75), the mean post-HTP VTV was significantly reduced compared to pre-HTP tumor volume (24.8 ± 12.3 vs. 30.5 ± 13.8 cc;  $P=0.005$ ), with a mean VTVRR of 21.4% (range 2.0–80.5).

Excluding three of 18 patients on whom CE-MRI was performed, the radiological response rate was: 60% in good responders (9/15 patients) and 40% in poor responders (6/15 pa-

tients) using RECIST1.1 criteria; 46.7% in good responders (7/15 patients) and 53.3% in poor responders (8/15 patients) using Choi criteria (► **Table 3**). Three patients (21.4%) developed liver metastasis. ► **Fig. 1** is a flowchart of the study patients.

### Prognostic predictive yield of the radiological response criteria

Median post-HTP survival was 7 months (range 1–35). One patient, with postsurgical disease relapse to the residual pancreas of a mixed ductal-acinar pancreatic adenocarcinoma, was still alive 35 months after one EUS-HTP session associated with chemotherapy and radiotherapy. Excluding this long-term survivor, the median post-HTP survival was 6.5 months (range 1–19) ( $P=0.79$  compared with all-patient survival outcome).

Analyzing accuracy of 1-month post-HTP VTVRR (16 patients) in predicting subsequent patient 6-month survival outcome, the area under the receiver operating characteristic curve (AUC) was 0.733 (95% CI 0.459–0.918) ( $P=0.115$ ). An associated criterion for VTVRR of more than 11.46% was identified as the best cut-off to determine the potential post-HTP 6-month survival outcome, with sensitivity of 70.00% (95% CI 34.8–93.3) and specificity of 83.33% (95% CI 35.9–99.6) (► **Fig. 2a**). As appreciated in the Kaplan-Meier OS curves (► **Fig. 2b**), this VTVRR cut-off was able to separate groups of patients with different outcomes (OS median 10 [range 5–35] vs. 6 [range 3–18] months; Log-rank Mantel-Cox test = 5.5;  $P=0.039$ ), with hazard ratio (HR) of 0.372 (95% CI 0.124–1.121).

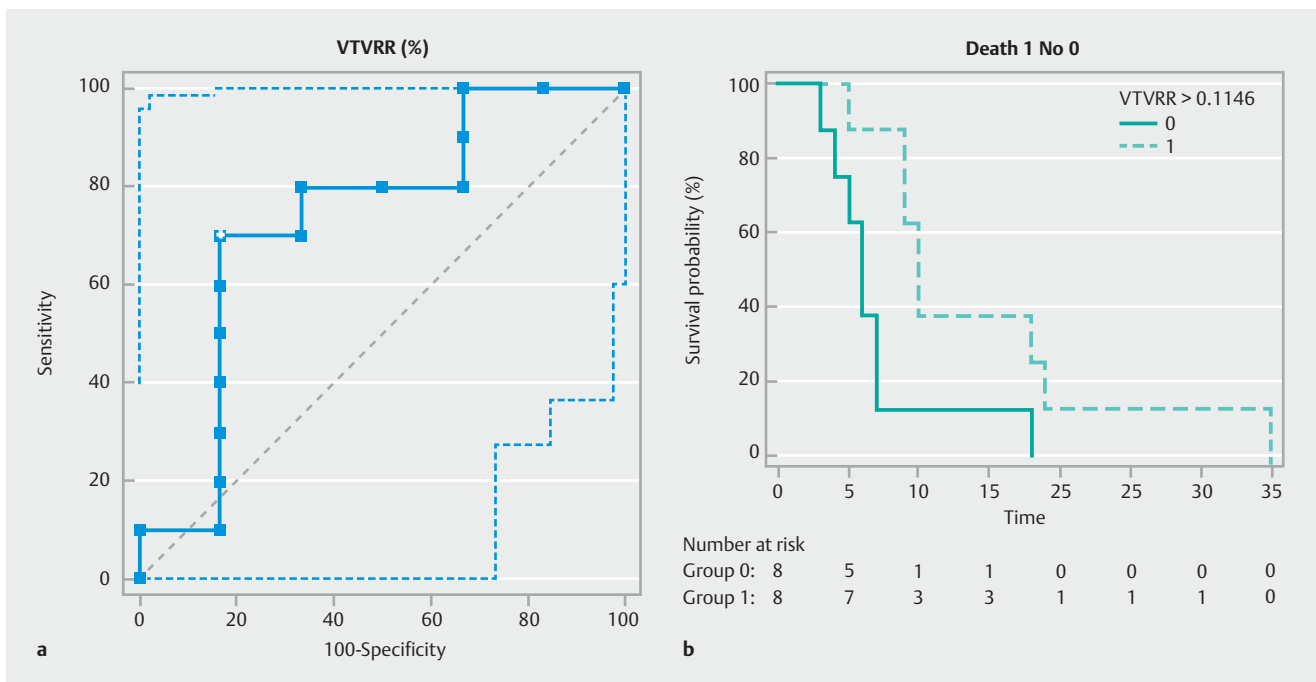
As for the 1-month radiological response using RECIST1.1 or Choi criteria (15 patients), Kaplan-Meier OS curves with patients classified as good responders according with Choi criteria showed significantly better post-HTP survival outcome compared to those classified as poor responders (median 9 [range 4–35] vs. 6 [range 2–10] months; Log-rank Mantel-Cox test = 4.2;  $P=0.04$ ), with HR of 0.407 (95% CI 0.137–1.206) (► **Fig. 3a**). This was not the case for patients classified as good or poor responders according with RECIST1.1 criteria (median 8 [range 3–35] vs. 6 [range 2–10] months; Log-rank Mantel-Cox test = 2.1;  $P=0.15$ ), with HR of 0.509 (95% CI 0.159–1.629) (► **Fig. 3b**).

### Safety of EUS-HTP treatment

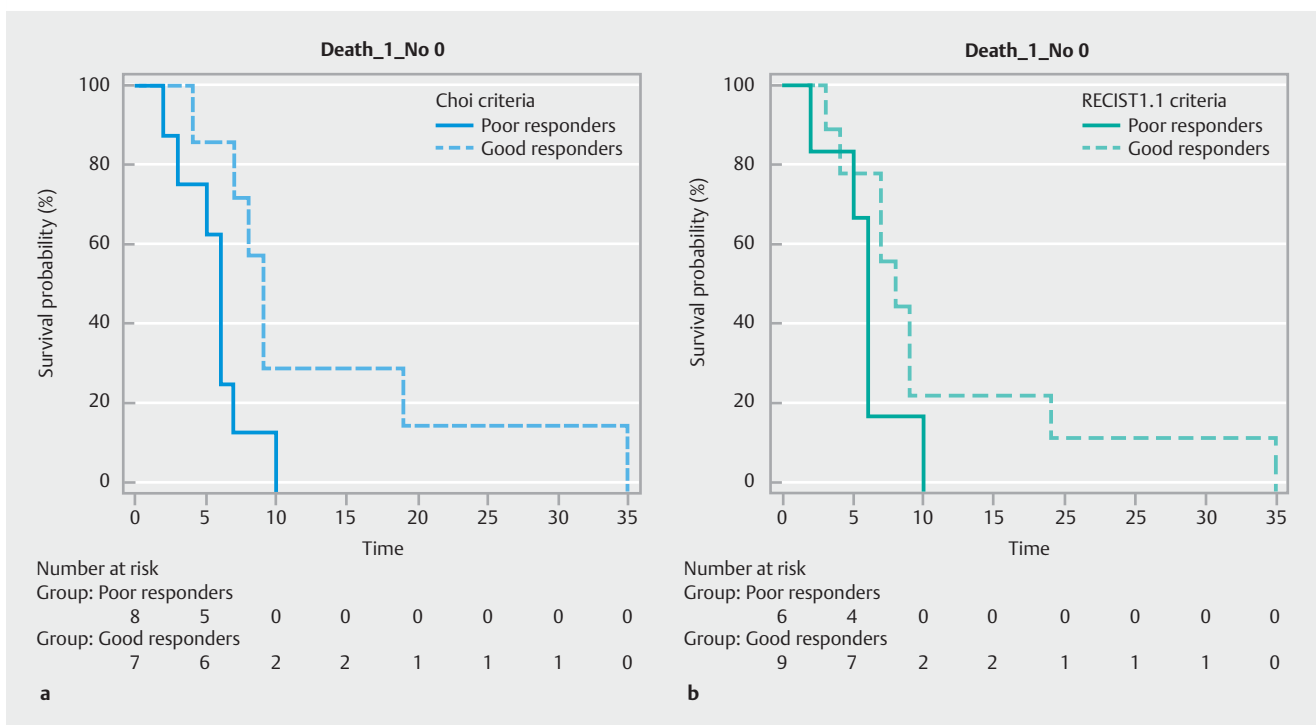
All treated patients underwent post-HTP 48-hour imaging to exclude AEs. No severe periprocedure-related AEs and no signs of acute pancreatitis were observed.

Early AEs occurred after 13 of 31 procedures (41.9%) and were all mild requiring conservative treatment or resolving spontaneously within 48 to 72 hours (1 duodenal wall ischemic injury, 9 abdominal pain or fever, 6 amylase levels rise with a mean 2.5-fold increase [range 137 U/L–653 U/L] over the upper normal value, 2 asymptomatic retroperitoneal fluid collections), except for one moderate case (minor bleeding in duodenal lumen treated endoscopically). Among these, the patient who experienced duodenal wall ischemic injury, treated conservatively, had a metal stent put in place.

EUS-HTP related late AEs occurred after three of 31 procedures (9.7%): one mild (asymptomatic retroperitoneal fluid collection) and two moderate (1 jaundice with haemobilia 3 weeks



► **Fig. 2a** ROC curve for the 1-month post-ablation of the vital tumor volume reduction rate (VTERR) in 16 patients related to the post-ablation 6-month overall survival: AUC = 0.733 (95% CI 0.4590 – 0.9178), associated criterion > 11.46%, sensitivity = 70.00% (95% CI 34.8 – 93.3), specificity = 83.33% (95% CI 35.9 – 99.6) ( $P=0.115$ ). **b** Kaplan-Meier survival curve for post-ablation overall survival (months) using the VTERR cut-off > 11.46%: median overall survival 10 vs. 6 months, Log-rank test = 5.5 ( $P=0.039$ ), HR = 0.3723 (95% CI 0.1237 – 1.1207).



► **Fig. 3** Kaplan-Meier survival curves of patients classified as Good Responders (partial responder + stable disease) and Poor Responders (progressive disease) according to **a** Choi criteria: median 9 vs. 6 months (Log-rank = 4.2;  $p=0.04$ ), with HR = 0.4066 (95% CI 0.1370 to 1.2060) and **b** RECIST1.1: median 8 vs. 6 months (Log-rank = 2.1;  $p=0.15$ ), with HR = 0.5088 (95% CI 0.1589 to 1.6290).

after EUS-HTP requiring ERCP for biliary removal of clots and replacement of biliary metal stent, one duodenal stricture 1 month after EUS-HTP with duodenal wall ischemic injury requiring endoscopic duodenal stenting).

## Discussion

The current study aimed to evaluate radiological response in patients with LA-PDAC with EUS-HTP, according to CAD-assisted evaluation of necrosis and tumor volumetries with measurement of the vital tumor volume reduction rate (VTVRR), RECIST1.1 and Choi criteria. Further aims were to determine which radiological response assessment criteria correlated better with post-HTP patient survival.

HTP was successfully applied under EUS guidance in 71 % of patients with LA-PDAC and, with the aid of an advanced visualization CAD system, radiologists were able to calculate necrotic and tumor volumes after 1 month in 89 % of cases after EUS-HTP.

A significant VTVRR, defined as the percentage difference between post-HTP VTV and pre-HTP tumor volume, was demonstrated after EUS-HTP ( $P = 0.005$ ), with a mean rate of 21.4 %. Moreover, we aimed to identify the best VTVRR cut-off to potentially predict the post-HTP 6-month survival outcome in a receiver operating characteristic analysis (► **Fig. 2a**). The identified cut-off has a sensitivity of 70.00 % and a specificity of 83.33 % and at first post-HTP imaging at 1-month, was significantly associated with post-HTP OS outcome (median 10 vs. 6 months,  $P = 0.039$ ; ► **Fig. 2b**). However, these data should be considered with caution as explorative and with need of validation in larger datasets, as the AUC is not statistically significant and the lower limit of the 95 % CI of the AUC for the ROC analysis is below 0.5. The necrosis volume is significantly correlated both with pre-HTP tumor volume ( $P = 0.03$ ) and with HTP application time ( $P = 0.02$ ).

Use of Choi rather than RECIST1.1 criteria better identified patients with clinical benefit from EUS-HTP. At post-HTP 1-month CE-MDCT-scan, good response was observed in 60 % and 46.7 % of patients according to RECIST1.1 and Choi criteria, respectively. In line with these differences, good responders had significantly better post-HTP OS compared to poor responders (median 9 vs. 6 months,  $P = 0.04$ ) according to Choi criteria (► **Fig. 3a**), whereas this was not the case according to RECIST1.1 (► **Fig. 3b**).

Our findings are in keeping with previous data suggesting that Choi criteria on MDCT scan, combining tumor size and attenuation changes, have shown to have better prognostic predictive yield in patients with advanced HCC and gastrointestinal stromal and gastroenteropancreatic neuroendocrine tumors treated with antineoplastic agents than RECIST1.1, based on a single dimensional parameter [14–16].

Indeed, RECIST1.1 may underestimate clinically meaningful responses to cytostatic targeted therapies that can induce tumor necrosis without substantial tumor size changes, in contrast with previous reports [11, 12, 22] suggesting that volumetry of the entire tumor mass is able to predict the prognosis of patients treated with molecular targeted therapies.

In our previous animal and human ex-vivo studies [7, 9], after HTP application, the histopathology specimens showed a central area with coagulative necrosis demarcated from the surrounding untreated tissue by an interposed area with edema and cellular damage, whose diameter was significantly dependent on HTP application time.

Thus, radiological assessment based on tumor volumetry and axial dimensions may not be the ideal tools for evaluating radiological response to local ablative therapies, as opposed to tools based on tissue changes and tumor density. This assumption is reinforced by the current finding of lack of a significant difference in the post-HTP OS between patients with increased tumor volume (9 patients) and those in whom it did not increase (7 patients) after EUS-HTP (median 8 (range 3–18) vs. 7 (range 2–35) months; Log-rank Mantel-Cox test = 1.06,  $P = 0.30$ ). In these two groups of patients, there was no significant difference between mean pre-HTP and post-HTP tumor volumes (including both necrosis volume and residual vital tumor volume) ( $P = 0.33$ ), supporting the hypothesis that the post-HTP tumor volume does not reflect the true amount of vital tumor tissue.

MRI with functional imaging tools such as diffusion weighted imaging (DWI) sequences has been shown to be able to distinguish different kinds of tissue (inflammatory vs. tumor vs. fibrosis), combining anatomic, physiologic and molecular information [25, 26].

The current results suggest the potential clinical utility of a radiological response assessment to ablation treatment after one month on the basis of necrosis volumetry and a VTVRR, as well as Choi criteria as a predictive factor for the overall survival of PDAC patients treated with ablation.

In our cohort, median post-HTP survival was 7 months. All enrolled patients but five unfit for chemotherapy presented with local progressive disease after primary therapy at enrollment for EUS-HTP, and therefore, had a reduced life expectancy and little chance of meeting the resectability criteria prior to EUS-HTP. These selection criteria, in addition to presence of heterogeneity regarding the type of primary treatment before EUS-HTP and tumor location as well as inclusion of patients unfit for chemotherapy, could explain our disappointing survival results after EUS-HTP and do not allow us to make solid conclusions about EUS-HTP impact on survival.

With respect to EUS-HTP feasibility, the major technical difficulty was gastrointestinal wall or tumor mass stiffness. Notably, all patients but one with such difficulties had previously undergone radiotherapy, with induced tissue fibrosis hindering the HTP insertion.

Pancreatic RFA has been used in a few human clinical trials, with percutaneous or intraoperative routes [4, 27–29], resulting in high rates of morbidity (28 %) and mortality (3 %). Presence of a metal stent is considered an absolute contraindication for RFA of pancreatic cancer at the head, due to the heat spread to surrounding structures as a consequence of the metal conductive capacity, potentially leading to serious AEs of the biliary tree or duodenum [30]. In the current study, there were no HTP-related major AEs and only 9.7 % moderate AEs occurred, which resolved with endoscopic reintervention, one of which was a

case with a biliary partially covered metal stent. In other patients with biliary stents, EUS-HTP was safe and successful (85.7%). This may be due to the heat sink effect [30–33] or to the HTP cooling system preventing thermal injury to the surrounding vascular structures and organs, or due to an EUS approach that enables precise targeting of pancreatic tumor with minimal invasivity and procedure monitoring in real time [34, 35].

This study has several limitations, such as the relatively small sample size, lack of a control group, and retrospective design causing heterogeneity in terms of time frames between tumor diagnosis and end of primary therapy to EUS-HTP onset, type of first-line treatment before EUS-HTP and indications for EUS-HTP. Some results should be considered with caution, and need further validation.

Among its strengths is the novel specific evaluation of the radiological response based on tumor and necrosis volumes through a CAD tool in PDAC treated with EUS-HTP, with calculation of an ideal prognostic predictive cut-off of the VTVRR. Moreover, this study presents, to the best of our knowledge, the largest case study for both thermal ablation treatment under EUS-guidance of locally advanced PDAC and evaluation of radiological response to EUS-guided local thermal ablation.

## Conclusion

The current results suggest that: 1) EUS-HTP resulted in a significant VTVRR compared to pre-HTP tumor volume, supporting its further evaluation in patients with LA-PDAC after failure of first-line treatment or in those unfit for chemotherapy; and 2) assessment of radiological response in this context should include evaluation of necrosis and tumor volumes by VTVRR and Choi criteria, as they help early identification of patients who benefit more from EUS-HTP.

The clinical efficacy and impact on survival outcome of EUS-HTP in patients with unresectable PDAC would be better assessed through an ongoing case-control study comparing survival of patients treated with EUS-HTP to a matched cohort that underwent standard treatments. A randomized controlled trial comparing up-front EUS-HTP plus chemotherapy to chemotherapy alone is also underway at our Center.

## Competing interests

Prof. M. Enderle and Dr. W. Linzenbold are employees of the research department of Erbe Elektromedizin GmbH, Tübingen, Germany.

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