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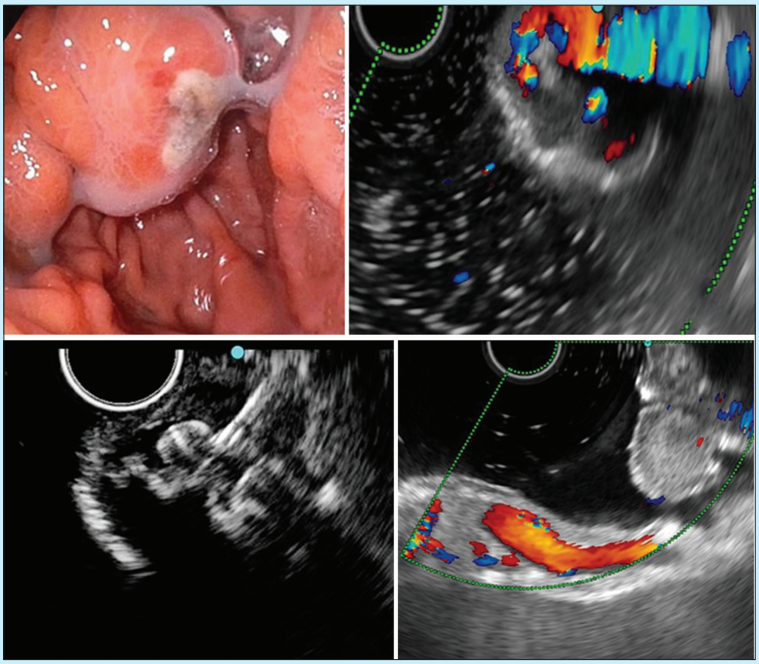

HIGHLIGHT ARTICLES

- EUS-guided *versus* percutaneous liver biopsy: Do we have a winner?
- How to perform EUS-guided biliary drainage
- Utility of contrast-enhanced harmonic EUS for diagnosis of portal vein invasion by pancreatic cancer
- *Ex vivo* comparison of electrocautery-enhanced delivery of lumen-apposing metal stents matching electrosurgical workstations during EUS-guided gallbladder drainage

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—Original Article—

EUS-guided ablation with the HybridTherm Probe as second-line treatment in patients with locally advanced pancreatic ductal adenocarcinoma: A case–control study

Sabrina Gloria Giulia Testoni[1], Maria Chiara Petrone[1], Michele Reni[2], Clelia Di Serio[3], Paola Maria Rancoita[3], Gemma Rossi[1], Gianpaolo Balzano[4], Walter Linzenbold[5], Markus Enderle[5], Emanuel Della-Torre[6], Francesco De Cobelli[7], Massimo Falconi[8], Gabriele Capurso[1], Paolo Giorgio Arcidiacono[9]

[1]Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Center, San Raffaele Hospital, Milan, Italy; [2]Department of Oncology, Pancreas Translational and Clinical Research Center, San Raffaele Hospital, Milan, Italy; [3]Vita-Salute San Raffaele University, CUSSB, University Centre for Statistics in the Biomedical Sciences, Milan, Italy; [4]Department of Pancreatic Surgery, Pancreas Translational and Clinical Research Center, San Raffaele Hospital, Milan, Italy; [5]ERBE Elektromedizin GmbH, Tübingen, Germany; [6]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, Pancreas Translational and Clinical Research Center, San Raffaele Hospital, Milan, Italy; [7]Department of Radiology and Center for Experimental Imaging, Pancreas Translational and Clinical Research Center, Vita-Salute San Raffaele University, San Raffaele Hospital, Milan, Italy; [8]Department of Pancreatic Surgery, Pancreas Translational and Clinical Research Center, Vita-Salute San Raffaele University, San Raffaele Hospital, Milan, Italy; [9]Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Center, Vita-Salute San Raffaele University, San Raffaele Hospital, Milan, Italy

ABSTRACT

Background and Objectives: Data on the clinical efficacy of EUS-guided ablation using the HybridTherm-Probe (EUS-HTP) in locally advanced pancreatic ductal adenocarcinoma (LA-PDAC) are lacking. The aim of the study was to assess the impact of EUS-HTP added to chemotherapy (CT) on overall survival (OS) and progression-free survival (PFS) of LA-PDAC patients with local disease progression (DP) after first-line therapy, compared to CT alone in controls. **Methods:** LA-PDAC cases, prospectively treated by EUS-HTP, were retrospectively compared to matched controls (1:2) receiving standard treatment. Study endpoints were the OS and PFS from local DP after first-line therapy, compared through log-rank test calculating hazard ratios and differences in restricted mean OS/PFS time (RMOST/RMPFST) within prespecified time points (4, 6, and 12 months). **Results:** Thirteen cases and 26 controls were included. Clinical, tumor, and therapy features before and after first-line therapy were case–control balanced. The median OS and PFS were not significantly improved in cases over controls (months: 7 *vs.* 5 and 5 *vs.* 3, respectively). At 4 and 6 months, the RMPFST difference was in favor of cases ($P = 0.0001$

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Address for correspondence

Prof. Paolo Giorgio Arcidiacono, Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute IRCCS, Vita-Salute San Raffaele University, Via Olgettina 60, 20132, Milan, Italy.
E-mail: arcidiacono.paologiorgio@hsr.it

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and $P = 0.003$, respectively). In cases and controls not candidate to further CT ($N = 5$ and $N = 9$), the median OS and PFS were not significantly improved in cases over controls (months: 6 *vs.* 3 and 4 *vs.* 2, respectively), but the RMPFST difference was in favor of cases at 4 months ($P = 0.002$). **Conclusions:** In locally progressive PDAC patients experiencing failure of first-line therapy, EUS-HTP achieves a significantly better RMPFST up to 6 months compared to standard treatment, although without a significant impact on OS.

Key words: ablation technique, cancer of pancreas, case-comparison study, EUS, survival analysis

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) mostly presents with distant metastases (40%) or unresectable locally advanced (LA) disease (40%) at diagnosis. PDAC patients' prognosis has only marginally improved in the last decades with the development of poly-chemotherapy ± radiotherapy (CT ± RT) regimens, achieving only one-third of responsive patients.[1] So far, patients with LA-PDAC progress regardless of the frontline therapy regimen and no second-line regimen (s) showed to confer survival benefit.[2]

This unmet need increased research focusing on new therapeutic approaches for LA-PDAC, with the intent to reinforce the tumor local control, in particular in the case of persistence of tumor unresectability after first-line therapy.[3,4]

Local thermal ablation (LTA) is being investigated in this setting, based on the hypothesis of the ability to modify the tumor microenvironment with increased intratumor drug uptake[5] and better antitumor immune response.[6] Several studies, mostly case reports and series, investigated the LTA feasibility and efficacy in pancreatic tumors.[7]

However, to the best of our knowledge, the LTA clinical relevance in LA-PDAC compared with CT alone has not been evaluated, yet.

In a preliminary study involving 22 patients with LA-PDAC and local disease progression (DP) after first-line CT ± RT or unfit for CT from diagnosis, we demonstrated that EUS-guided ablation using the HybridTherm-Probe (EUS-HTP) was safe and induced a well-demarcated intratumoral necrosis with a significant tumor volume reduction at 1-month imaging and a postablation median survival of 7 months.[8,9]

The aim of the current study was, therefore, to assess the impact of the adjunct of EUS-HTP to the standard treatment on the overall survival (OS) and progression-free survival (PFS) in patients with LA-PDAC and local DP after first-line CT ± RT, through a case–control study.

MATERIAL AND METHODS

Study design and patients

Cases were consecutive patients with primary LA-PDAC, experiencing local failure of first-line therapy, treated with EUS-HTP over a 6-year period (2010–2016). These patients were enrolled in a prospective study (N. CTP2010),[8,9] approved by the Medical Ethics Committee of the San Raffaele Scientific Institute of Milan (Italy) and gave informed consent for ablation treatment and data management for scientific purposes.

The outcomes of these patients were compared in a retrospective analysis, with 1:2 ratio, with a control group including similar consecutive patients with LA-PDAC and local failure of first-line therapy, candidate to further CT ± RT, or no further CT regimens due to poor performance status or intolerance to CT. These controls were extrapolated from the observational database of patients with primary diagnosis of LA-PDAC, treated during the same time frame (2010–2016), enrolled by the Oncology Unit of the San Raffaele Scientific Institute and matched with the cases according to predefined inclusion criteria and features.

Features for the case–control comparison

The following features were compared between cases and controls, within three separate blocks: (1) before first-line therapy: age, tumor site, longest size and stage, and serum CA19.9 level; (2) after first-line therapy: type of first-line therapy (CT or CT + RT), CT regimen (number of drugs) and duration, initial radiological response to first-line CT according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST1.1), and tumor stage; (3) at

local DP after first-line therapy: time interval between LA-PDAC diagnosis and first appearance of local DP, time interval between the end of first-line CT and first appearance of local DP, tumor longest size and stage, and serum CA19.9 level.

Inclusion criteria

Inclusion criteria for this case–control study were as follows: clinically and radiologically confirmed LA-PDAC and first evidence of local DP without metastasis, through multidisciplinary evaluation including total-body contrast-enhanced multidetector computed tomography (CE-MDCT) scan, after ≥4-month first-line gemcitabine-based therapy; Karnofsky Performance Score >70%; life expectancy >3 months; tumor longitudinal axis at least 30 mm, according to the distance between electrodes on the HTP active part; and adequate bone marrow (white blood count ≥3.500/mm^3, neutrophils ≥1.500/mm^3, platelets >100.000/mm^3, and hemoglobin ≥10 g/dL), kidney (serum creatinine ≤1.5 mg/dL), and coagulative (international normalized ratio <1.5) functions. Patients with local recurrence after surgery, those who underwent other treatments different from standard CT ± RT and EUS-HTP, and those with unclear survival data were excluded.

Tumor unresectability was defined, according to internal guidelines adapted from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[10] and approved by the Institutional Review Board, as vessel wall's infiltration or contact >180° for more than 2-cm length, with vessel's initial stricture or alteration of Doppler signal, or thrombosis either of celiac axis and/or portal vein, and/or superior mesenteric artery and/or vein, and/or hepatic artery, in the absence of distant metastasis.

Treatment procedures

Ablation was performed under EUS guidance using the HTP (ERBE Elektromedizin GmbH, Tübingen, Germany), an internally carbon dioxide-cooled bipolar radiofrequency (RF) probe that can be inserted into a pancreatic lesion through the operative channel of a 3.8-mm therapeutic linear-array echoendoscope, under real-time imaging. EUS-HTP could be repeated monthly up to three sessions, accordingly to the tumor size (at least 30 mm) and the patient's clinical conditions. The HTP technology has been reported in detail in previous studies.[11-13] EUS-HTP procedures were performed by two endosonographers (PGA and MCP) with expertise in pancreatic EUS-FNA (>400/year for >10 years), administering deep sedation (i.v. propofol) under anesthesiologic monitoring, intravenous antibiotic therapy (ceftriaxone 1 g × 2/day for 5 days) to prevent infections, and prophylaxis with intravenous protease inhibitors (gabexate mesylate 500 mg in 500-ml saline solution), later replaced by rectal indomethacin (indomethacin 100 mg), to reduce risk of thermal-induced acute pancreatitis.[14] Ablation parameters were as follows: fixed RF power of 18W, fixed cooling pressure of 650 psi, and application time varying between 240 s for a 2-cm mass and 480 s for a >3-cm mass.[8] After EUS-HTP, cases were 5 days clinically surveilled as inpatients and underwent a radiological follow-up after 48 h to detect adverse events (AEs). First-line gemcitabine-based CT, used for a minimum of 4 months, and second-line CT regimens, if indicated, were administered in both the study groups at the discretion of the attending oncologists according to the Medical Oncology Italian Association (AIOM) guidelines.

Patients' follow-up

Cases underwent a 1-month follow-up visit after EUS-HTP, and both cases and controls were scheduled to undergo follow-up visits every 2 months until death, according to the oncological therapeutic program. Each follow-up visit included physical and imaging (including total-body CE-MDCT scan) examinations and serum CA19.9 level measurement. RECIST1.1[15] was used to assess the radiological response to therapy on CE-MDCT scans and define tumor progression. Partial response (PR: ≥30% decrease in the longest diameter of the target lesion, taking as reference the baseline diameter, without new lesions) and stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for DP, taking as reference the smallest long diameter on the study) findings at imaging defined the disease control. DP was defined as ≥20% increase in the longest diameter of the target lesion, taking as reference the smallest long diameter in the study, or absolute increase of at least 5 mm, or appearance of new lesions.

Study endpoints

Primary endpoint was the OS, calculated as the period between the date of first documentation of local DP after first-line therapy and the date of patient's death (or last follow-up). Secondary endpoint was the PFS, calculated as the period between the date of first documentation of local DP after first-line therapy

and the date of further documentation of DP (local and/or distant). These outcomes were case–control compared, determining the hazard ratios according to the EUS-HTP intervention as well as the restricted mean OS and PFS times (RMOST and RMPFST), as average event-free survival times up to a prespecified time point of the area under the Kaplan–Meier survival curve: 4 and 6 months and up to the maximum rounded time shorter than or equal to the lesser of the longest follow-up time for cases and controls.[16,17] As we anticipated that a part of patients, both in cases and controls, would have been unfit to further CT ± RT after first local DP, we specifically aimed at investigating the effect of EUS-HTP in this subgroup of patients.

Statistical analysis

Variables are presented as mean ± standard deviation or median with interquartile range if continuous, or as absolute numbers or percentages if categorical. Parametric or nonparametric tests were used to analyze group differences: *t*-test for independent normally distributed samples and Mann–Whitney rank-sum test for independent not normally distributed samples. Chi-squared test was used to compare proportions. Kaplan–Meier product limit estimates were used to construct survival curves, compared using the log-rank test with the calculation of the hazard ratios with 95% confidence interval (HR, 95% CI) and the RMOST and RMPFST (95% CI) difference. Two-tailed $P < 0.05$ was considered statistically significant. Statistical calculations were done by using MedCalc version 19.2.1 (MedCalc Statistical Software bvba, Ostend, Belgium).

RESULTS

Patient and treatment features

Thirteen cases were compared with 26 controls. Patients' flow diagram is reported in Figure 1. All cases were treated with ≥4-month first-line gemcitabine-based CT, associated with RT consolidation in 8 patients (61.5%), before local DP and were subsequently treated with EUS-HTP. In all cases, EUS-HTP was successful, with a mean application time of 125 ± 75 s. Five cases (38.5%) received more than one session of EUS-HTP, accordingly to the tumor lesion size and clinical conditions, and the other 8 cases (61.5%) received only one session, due to technical impossibility to perform the second EUS-HTP session ($n = 4$), local DP ($n = 1$), poor general conditions ($n = 1$), and choice to undergo RT ($n = 2$). Neither severe AEs nor signs of acute pancreatitis were observed following EUS-HTP. Five out of eight cases with pancreatic head tumor location had biliary stenting, without affecting the EUS-HTP feasibility.

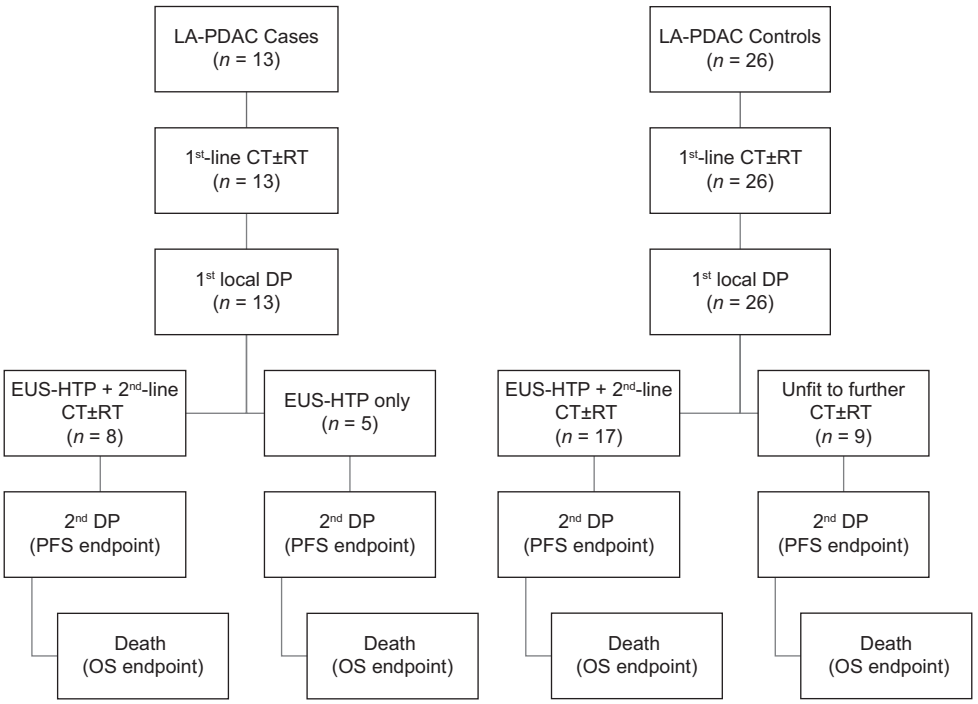

Figure 1. Flow diagram of included cases and controls. LA-PDAC: locally advanced pancreatic ductal adenocarcinoma; CT ± RT: chemotherapy ± radiotherapy DP: disease progression; EUS-HTP: EUS-guided ablation with the HybridTherm Probe; PFS: progression-free survival; OS: overall survival

All controls had local DP after ≥4-month first-line gemcitabine-based CT, associated with consolidation with RT in 18 patients (69.2%).

The three separate blocks of features for the case–control comparison were evenly balanced between the two populations. Detailed data and significance analyses are reported in Table 1.

Three cases (23.1%) and seven controls (26.9%) experienced local DP during the 4-month first-line CT ($P = 0.80$).

After the first-line therapy, eight cases (61.5%) underwent second-line therapy, with one-drug CT regimen in two patients, associated with RT in other two, two-drug CT regimen in two patients, associated with RT in another one, and three-drug CT regimen in one patient. The other five cases (38.5%) were considered unfit to further CT ± RT regimens and underwent EUS-HTP alone.

Seventeen controls (65.4%) underwent second-line therapy, with a one-drug CT regimen in two patients, associated with RT in other three, a two-drug CT regimen in four patients, associated with RT in other five patients, a three-drug CT regimen in one patient, and a four-drug CT regimen in two patients. The other nine controls (34.6%) were considered unfit to further CT ± RT regimens.

The rates of cases and controls undergoing a second-line therapy were similar ($P = 0.81$).

Comparison of overall survival

The median OS time was 7 (95% CI: 6–15) and 5 (95% CI: 4–25) months in cases and controls, respectively,

Table 1. Demographic, clinical, tumor, and therapeutical features of cases and controls at the diagnosis of locally advanced pancreatic ductal adenocarcinoma and after first-line therapy

	Cases (*n*=13), *n* (%)	Controls (*n*=26), *n* (%)	*P*
Features before first-line therapy			
Age, mean±SD	64.8±7.8	63.8±8.7	0.73
Pancreatic lesion site			
Head	8 (61.5)	19 (73.1)	0.47
Body/tail	5 (38.5)	7 (26.9)	
Pancreatic lesion size (mm), mean±SD	42.3±13.9	42.9±19.8	0.92
Serum CA19.9 levels (U/l), median (IQR)	292 (133-548)	204.5 (54-817)	0.68
Features after first-line therapy			
Type of first-line therapy			
CT	5 (38.5)	8 (30.8)	0.64
CRT	8 (61.5)	18 (69.2)	0.64
CT drug number			
4 drugs	9 (69.2)	17 (65.4)	0.81
3 drugs	0	1 (3.9)	0.48
2 drugs	4 (30.8)	9 (34.6)	0.81
CT regimen			
PEXG/PAXG	9 (69.2)	17 (65.4)	0.81
Nab-paclitaxel + gemcitabine	2 (16.7)	7 (26.9)	0.48
XELIRI + gemcitabine	0	1 (3.9)	0.48
XELODA + gemcitabine	2 (16.7)	1 (3.9)	0.17
CT duration (months), mean±SD	5.5±1.2	5.2±1.1	0.43
RECIST1.1 radiological response to 4-month CT			
Partial response	6 (46.2)	12 (46.2)	1.00
Stable disease	7 (53.8)	14 (53.8)	1.00
Features at local DP after first-line therapy			
Time between PDAC diagnosis and local DP (months), mean±SD	10.4±5.3	10.5±4.5	0.93
Time between end of first-line CT and local DP (months), mean±SD	4.2±4.5	4.7±4	0.76
Pancreatic lesion size (mm), mean±SD	37.9±13	38.6±11.5	0.53
Serum CA19.9 levels (U/l), median (IQR)	354 (106.5-811)	180.5 (122-532)	0.81

SD: Standard deviation; IQR: Interquartile range; CT: Chemotherapy; CRT: Chemoradiotherapy; PDAC: Pancreatic ductal adenocarcinoma; DP: Disease progression; PEXG: Cisplatin, epirubicin, capecitabine, and gemcitabine; PAXG: Cisplatin, capecitabine, gemcitabine, and nab-paclitaxel; XELIRI: Capecitabine and irinotecan; XELODA: Capecitabine; RECIST1.1: Response Evaluation Criteria in Solid Tumors, version 1.1

without a statistically significant difference (log-rank test: $P = 0.96$). The HR of controls/cases for death was of 1.02 (95% CI 0.52–1.98) [Figure 2a].

Analyzing the RMOST (months), its difference between cases and controls was not significantly in favor of cases up to 15 months [Table 2].

Comparison of progression-free survival

The median PFS time resulted of 5 (95% CI: 3–8) and 3 (95% CI: 2–12) months in cases and controls, respectively, without a statistically significant difference (log-rank test: $P = 0.50$). The HR of controls/cases for DP was of 1.27 (95% CI: 0.65–2.46) [Figure 2b]. Analyzing the RMPFST (months), its difference between cases and controls was significantly in favor of cases up to 6 months ($P = 0.0001$ at 4 months and $P = 0.003$ at 6 months) [Table 2]. The rate of further local DP and distant DP (metastatic disease) was similar between the two patient groups, being respectively of 61.5% (8/13) and 73.1% (19/26) for local DP, and 61.5% (8/13) and 69.2% (18/26) for distant DP, in cases and controls ($P = 0.47$ and $P = 0.64$). In 23.1% of cases (3/13) and 26.9% of controls (7/26), overlapping of local and distant DP occurred. The median time to further local DP was of 5 (95% CI: 3–8) and 3 (95% CI: 2–12) months in cases and controls, respectively (log-rank test: Chi-squared = 0.58, $P = 0.45$), with a HR of controls/cases for local DP of 1.38 (95% CI: 0.63–3.01). The median time to distant DP was of 5 (95% CI: 3–9) and 3 (95% CI: 2–21) months in cases and controls, respectively (log-rank test: Chi-squared = 0.6, $P = 0.44$), with a HR of controls/cases for distant DP of 1.39 (95% CI: 0.63–3.06).

Subgroup analysis of patients not candidate to second-line therapy

In cases and controls who were unfit to further CT regimens after first-line therapy because of poor general conditions or intolerance to CT ($n = 5$ and $n = 9$), the adjunct of EUS-HTP was followed by a median OS of 6 months (95% CI: 2–10) *versus* 3 months (95% CI: 1–6) in controls (log-rank test: $P = 0.12$), with

Table 2. Restricted mean survival time (95% confidence interval) and difference (95% confidence interval) in the restricted mean survival time of cases and controls for both overall survival and progression-free survival from the date of local disease progression after first-line therapy

Max t (months)	RMST cases (95% CI)	RMST controls (95% CI)	Diff. RMST (95% CI)	*P*
		OS (months)		
4	3.77 (3.46-4.08)	3.62 (3.33-3.89)	0.15 (−0.27-0.58)	0.48
6	5.46 (4.77-6.16)	4.69 (4.11-5.27)	0.77 (−0.14-1.68)	0.1
12	7.39 (5.92-8.86)	6.54 (5.14-7.94)	0.85 (−1.19-2.88)	0.41
15	7.62 (5.89-9.34)	6.92 (5.27-8.57)	0.69 (−1.7-3.08)	0.57
		PFS (months)		
4	3.8 (3.62-4.04)	2.8 (2.38-3.23)	1.03 (0.55-1.5)	0.0001
6	4.83 (4.23-5.44)	3.41 (2.69-4.12)	1.43 (0.49-2.36)	0.003
8	5 (4.23-5.77)	3.79 (2.84-4.74)	1.21 (−0.01-2.43)	0.05

Max t: maximum time; RMST: Restricted mean survival time; Diff. RMST: Difference of RMST between cases and controls; CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival

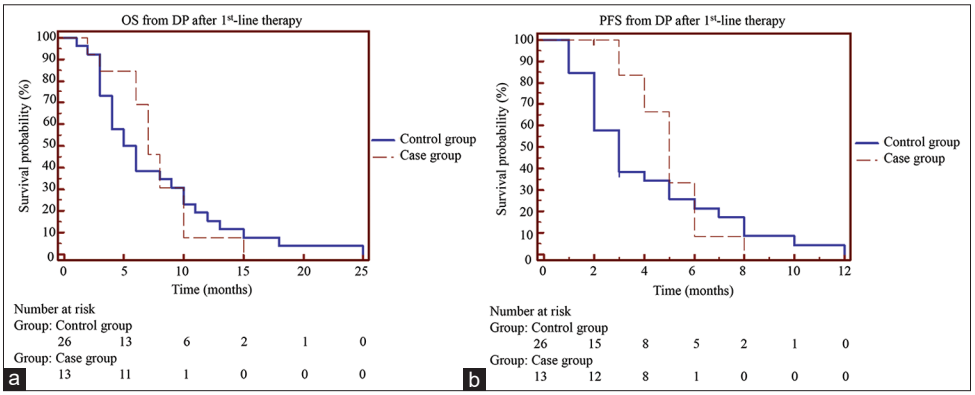

Figure 2. Kaplan–Meier curves of cases and controls from the date of local DP after first-line therapy: (a) OS: HR of controls/cases = 1.02 (95% CI: 0.52–1.98; log-rank test: Chi-squared = 0.003, $P = 0.96$). (b) PFS: HR of controls/cases = 1.27 (95% CI: 0.65–2.46; log-rank test: Chi-squared = 0.46, $P = 0.50$). DP: Disease progression; OS: Overall survival; HR: hazard ratio; PFS: Progression-free survival; CI: Confidence interval

a HR of controls/cases for death of 2.32 (95% CI: 0.81–6.67) [Figure 3a]. In these patients, the median PFS time was of 4 (95% CI: 3–8) and 2 (95% CI: 1–6) months in cases and controls, respectively (log-rank test: $P = 0.15$), with a HR of controls/cases for DP of 2.34 (95% CI: 0.75–7.27) [Figure 3b].

There was a significant difference in the RMPFST (months) in favor of cases at 4 months ($P = 0.002$) [Table 3].

DISCUSSION

In LA-PDAC patients, irreversible electroporation, a nonthermal ablation technique, following CT showed to achieve better PFS and OS than CT alone.[18]

Conversely, the actual clinical relevance of LTA combined with systemic CT for the treatment of LA-PDAC compared to CT alone has not yet been evaluated.

In the present study, we aimed at retrospectively assessing the OS and PFS in a series of LA-PDAC patients who had local DP after first-line CT ± RT and were prospectively treated with EUS-HTP, eventually followed by further CT ± RT, compared with patients with similar characteristics undergoing second-line CT ± RT not associated with EUS-HTP or unfit to further CT regimens due to intolerance.

To compare the clinical outcomes of cases and controls, the latter patients were carefully selected according to the defined inclusion criteria. Features at diagnosis, after first-line therapy, and at local DP time after first-line therapy were evenly case–control balanced. Moreover, these patients were treated in the same time frame and hospital, by the same physicians.

Overall, in cases undergoing first-line CT ± RT followed by EUS-HTP, associated or not with second-line therapy, there was a slight, yet not significant, improvement of median OS and PFS compared with controls. The OS and PFS curves crossed over at 8- and 6-month follow-up, respectively, indicating overlap of the 95% CI and violation of the assumption of proportional hazards. Thus, we calculated

Table 3. Restricted mean survival time (95% confidence interval) and difference (95% confidence interval) in the restricted mean survival time for both overall survival and progression-free survival from the date of local disease progression after first-line therapy in 5 cases and 10 controls unfit to further chemotherapy regimens after first-line therapy

Max t (months)	RMST cases (95% CI)	RMST controls (95% CI)	Diff. RMST (95% CI)	*P*
		OS (months)		
4	3.6 (2.89-4.3)	3.1 (2.46-3.76)	0.5 (−0.47-1.44)	0.32
6	5.2 (3.79-6.6)	3.6 (2.53-4.58)	1.6 (−0.09-3.38)	0.06
		PFS (months)		
4	3.8 (3.33-4.17)	2.4 (1.75-3.14)	1.3 (0.49-2.12)	0.002
6	4.3 (3.18-5.32)	2.9 (1.72-4.06)	1.4 (−0.22-2.95)	0.09

Max t: maximum time; RMST: Restricted mean survival time; Diff. RMST: Difference of RMST between cases and controls; CI: Confidence interval; OS: Overall survival; PFS: Progression-free survival

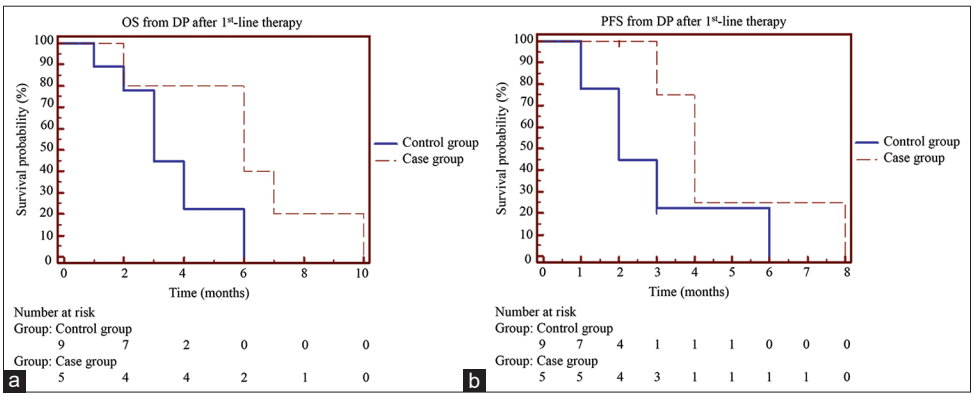

Figure 3. Kaplan–Meier curves from the date of local DP after first-line therapy in cases and controls unfit to further chemotherapy regimens: (a) OS: HR of controls/cases = 2.32 (95% CI: 0.81–6.67; Log-rank test: Chi-squared = 2.41, $P = 0.12$). (b) PFS: HR of controls/cases = 2.34 (95% CI: 0.75–7.27; Log-rank test: Chi-squared = 2.04, $P = 0.15$). DP: Disease progression; OS: Overall survival; HR: hazard ratio; PFS: Progression-free survival; CI: Confidence interval

the RMOST and RMPFST in order to quantify the magnitude of survival benefits of EUS-HTP and standard therapy within specified time points without model assumptions as complementary measurement of the treatment effect. This analysis confirmed the direction of the effect from added EUS-HTP, up to 15 months. In particular, even if the case–control RMOST difference was not statistically significant, the RMPFST difference was significantly in favor of cases within 6 months over controls. Cases also showed an 11.6% improvement in the disease local control over controls, even if the rate of distant DP was similar.

Notably, in patients who were unfit to further CT protocols after first-line therapy, EUS-HTP led to not significantly longer OS and PFS than those of controls, with a statistically significant RMPFST difference in favor of the EUS-HTP adjunct at 4 months. These results may suggest that EUS-HTP contributes to a better local disease control. In our previous studies,[11-13] HTP application caused a central necrotic area, containing amorphous material and cellular debris, surrounded by an inflammatory wall, consisting of granulation tissue with fibroblastic reaction and new blood vessels. Moreover, we reported that EUS-HTP induced a significant tumor volume reduction at radiological evaluation 1 month after ablation.[9] In five cases who were unfit for first-line CT at LA-PDAC diagnosis time due to comorbidities, and were treated with EUS-HTP only, the median OS from ablation was 10 months (95% CI: 2–18). These data may suggest that EUS-HTP is a particularly interesting minimal invasive option in patients with LA-PDAC who are unfit to CT either after failure of first-line therapy or at the diagnosis time.

Combined therapeutic schemes demonstrated a modest impact on survival outcome in PDAC.[19-21] In a Cochrane meta-analysis, the FOLFIRINOX arms presented an OS of 10.8–11.1 months, and the OS differences between patients undergoing anticancer therapy or best supportive care were modest.[21] The median PFS and OS of LA-PDAC patients treated with second-line therapy after DP on nab-paclitaxel plus gemcitabine CT[22] were of only 3.29 months and 7.33 months. Moreover, RT combined with gemcitabine or 5-fluorouracil CT did not improve the survival outcome of PDAC patients, compared to CT alone.[23-25]

Currently, there is no definitive consensus regarding the standard of care after DP following first-line therapy in LA-PDAC patients.[26]

In this context, LTA may be a potentially interesting option within a multimodality therapeutic strategy. This thermal-based therapeutic approach relies on the direct insertion of needles into the tumor target aiming at inducing tumor cytoreductive effects as well as biological changes, potentially enhancing the systemic activity offered by CT, whose effect can be limited by the PDAC microenvironment's desmoplasia as well as lack of tumor antigenicity.[5,7,27]

Few studies investigated the survival outcome following LTA. The available reported median OS in patients with unresectable PDAC was of 7 months following cryoablation, with a better outcome if associated with immunotherapy (13 months),[28] and 7.4 months following laser ablation.[29]

Better results have been achieved with concomitant high-intensity focused ultrasound and gemcitabine-based CT with a median survival of 12.6 months.[30] Non-RCTs showed promising OS up to 25.6 months after RFA in LA-PDAC patients pretreated with systemic therapy.[31,32]

The survival results from the present study are in keeping with the above-reported data. The enrolled patients presented with local DP after first-line therapy, some of whom with poor general conditions, thus with a reduced life expectancy and little chance of falling into resectability criteria on EUS-HTP treatment and/or second-line therapy.

The positioning and timing of LTA remain matters of debate. From no head-to-head comparisons, second-line RFA for LA-PDAC resulted in significant OS benefit (14.7 *vs.* 25.6 months)[33] and higher PFS rate (31% *vs.* 17%)[34] compared to upfront RFA followed by postoperative CT.

However, no significant OS and PFS differences were observed between short-term CT followed by RFA and upfront RFA.[35]

The limitations of this study, as the study population type, the heterogeneity of first-line and second-line therapies, the retrospective design, and the small sample size for both the cases and controls, hindering the possibility to use the propensity score matching analysis, could provide the risk of selection bias and difficulty in evaluating the actual effectiveness of EUS-HTP, thus not allowing us to draw solid conclusions about the survival

effects induced by added EUS-HTP compared with CT alone. With respect to the study period (2010–2016), more active CT regimens, such as nab-paclitaxel plus gemcitabine, became predominant for unresectable PDAC, but showed to marginally improve the survival of these patients,[1,2] as well as the therapeutic approach following failure of first-line therapy in LA-PDAC patients has not yet been consensually established.[26]

In addition, the RMOST and RMPFST clinical outcomes are not universally used, even if their clinical relevance is being increasingly recognized as they overcome limitations of current measures of survival benefits, directly capturing information of the entire area under Kaplan–Meier survival curves up to prespecified clinically important time points.[16,17]

CONCLUSIONS

Despite these limitations, the results from the present study might suggest that EUS-HTP could be a safe and feasible treatment for patients with LA-PDAC unresponsive to first-line CT, with slowly progressive or stable disease. The actual clinical effectiveness of LTA in the PDAC, as systemic disease, needs further investigation in randomized studies on a large number of patients.

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Conflicts of interest
Paolo Giorgio Arcidiacono is an Associate Editor of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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