Original Article

# Irreversible electroporation and adjuvant chemoradiotherapy for locally advanced pancreatic carcinoma

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## ABSTRACT

**Context:** The safety and efficacy of irreversible electroporation (IRE) for locally advanced pancreatic carcinoma (LAPC) are well established. However, whether adjuvant chemoradiotherapy after IRE increases, the survival rate remains unknown. Therefore, this study evaluated the effect of chemoradiotherapy combined with IRE in patients with LAPC.

**Subjects and Methods:** We retrospectively analyzed 42 patients with LAPC between July 2015 and December 2016 at PLA General Hospital treated with IRE or IRE combined with radiation and/or chemotherapy. These patients were divided into the IRE group and the combined-therapy group. All patients underwent computed tomography (CT), magnetic resonance imaging, and positron-emission tomography-CT and no signs of metastases were found. The prognosis of these patients was observed.

**Results:** The times after operation and after diagnosis in the combined-therapy group (304.20 ± 118.54) and (334.40 ± 114.07) days, respectively, were better those than in the IRE group (214.36 ± 95.68) and (244.68 ± 110.61) days, respectively. Moreover, patients in the combined-therapy group had a significantly better survival rate than the IRE group (80 vs. 45.45%, $P < 0.05$).

**Conclusions:** IRE combined with radiotherapy or chemotherapy was superior to IRE alone for the treatment of LAPC, as it prolonged the survival time and improved the survival rate, making it worthy of wide dissemination and clinical application.

**KEY WORDS:** Chemotherapy, irreversible electroporation, pancreatic carcinoma, radiotherapy

## INTRODUCTION

Locally advanced pancreatic carcinoma (LAPC) is a highly malignant disease with poor prognosis, which accounts for 4% of cancer-related deaths worldwide.[1] The initial stage is usually asymptomatic, while the late stage is characterized by abdominal pain, jaundice or deterioration in general health. Hence, approximately 20% of cases are resectable at the time of diagnosis, with a low 5-year survival of 20%–25%.[2,3] The remaining 80% of patients receive oncologic treatment (downstaging or palliative) or best supportive care, with a dismal 5-year survival of around 2%.[4]

Vessels such as the celiac trunk, superior mesenteric artery and vein, hepatic artery, and portal vein are easily invaded by pancreatic carcinoma, which precludes radical surgery. Alternative local treatments have been investigated, including radiation therapy and various thermal and nonthermal local ablation techniques; however, they have been generally unsuccessful.[5-7] Irreversible electroporation (IRE) is a novel method without thermal ablation that is based on the transmission of short direct current pulses through the tumor through needles, leading to irreversible changes in cell membrane integrity and subsequent apoptosis.[8-12] While its safety and efficacy have been reported, issues such as improving the treatment mechanism, selecting the optimal parameters, and the treatment of residual tumor cells remain unresolved.

Hence, the combination of IRE with other treatments is necessary to be fully effective. This study combined radiotherapy, chemotherapy, and surgery to improve the survival time of



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patients with LAPC, and documented findings from our center.

## SUBJECTS AND METHODS

### Study design

All patients with LAPC were examined by a multidisciplinary team, which developed treatment plans by consensus. The criteria for vascular invasion in LAPC were as follows: tumor invading the superior mesenteric artery by more than 180°; tumor invading the abdominal trunk by more than 180°; tumor invading the first jejunal branch of the superior mesenteric artery; tumor invasion or embolization (thrombus or tumor thrombus), leading to unresectable reconstruction of the superior mesenteric or portal vein; tumor invading the proximal jejunal drainage branch of the superior mesenteric vein. Between July 2015 and December 2016, a total of 42 patients received IRE or IRE combined with chemoradiotherapy. The patients' baseline characteristics, comorbidities, and surgery details were collected retrospectively. This study was approved by the hospital ethics committee and all patients included in the study and follow-up provided informed consent before discharge. The inclusion criteria were as follows: (1) patients diagnosed with unresectable LAPC; (2) age 18–80 years; (3) Maximum tumor size <5 cm (longest axis); and (4) willing to sign an informed consent form. The exclusion criteria were as follows: (1) patients with other organ metastasis and (2) patients with incomplete basic information. Among the 46 cases, two refused follow-up investigation. As 44 cases met the exclusion criteria and two were lost to follow-up, therefore, 42 cases were included in this study.

### Treatments

Potential IRE patients underwent a detailed preoperative evaluation, and careful perioperative management including chest X-ray, electrocardiogram, echocardiography, dynamic contrast-enhanced computed tomography (CT), dynamic contrast-enhanced magnetic resonance imaging, positron-emission tomography-CT, routine blood examination, and measurements of tumor marker levels, and liver and kidney function.

We used a Nanoknife IRE system (Angiodynamics, Queensbury, New York, USA). The distance between the two electrodes affected the voltage, and the electrode length was 1.0–1.5 cm. The system can produce high-voltage direct current electrical pulses, in the present study; the delivery was at least 1500V/cm at 90 μs, typically for a total of 100 pulses in ten sets of ten pulses between each paired probe. All patients underwent IRE under general anesthesia with deep neuromuscular block. Three-dimensional reconstruction was used to assess the relationship between tumor and vessels before the operation, which also helped us to determine the electrode placement. All needles were placed under ultrasound guidance, to determine the needle position and the distance between needles. The electrode pairs were placed in caudal to cranial or ventral to dorsal directions. The direction was selected mainly based on the tumor size and location; the caudal to cranial direction was used when the dorsal side of the tumor had a larger blood vessel or the anterior and posterior diameters of the tumor were small, while the ventral to dorsal direction was selected for cases in which the tumor was large and without major blood vessel or digestive tract involvement. Ten pulses were initially administered. The resulting current was checked and the machine's settings were adjusted accordingly before actual treatment pulses were administered to maximize the ablation zone; the electrodes were separated by 2 cm. Pullback was performed if the target ablation zone was >2 cm so that the overlapping ablation allowed for complete coverage of the entire target. An intraoperative fine-needle biopsy was obtained to histologically verify the LAPC diagnosis. Tumors in the pancreatic head may lead to the bile duct and duodenal obstructions, which require treatment by cholangioenterostomy or gastroenterostomy. All IRE procedures were performed by a board-certified surgeon trained to operate the IRE device.

The patients were divided into IRE and combined-therapy groups (IRE combined with radiotherapy or chemotherapy) according to the treatment received. LAPC was defined as superior mesenteric artery or celiac encasement, aortic invasion, unresectable superior mesenteric or portal vein involvement, with no evidence of metastatic disease in abdominal and thoracic CT.[13] The 20 patients in the combined-therapy group received radiotherapy and/or chemotherapy before or after IRE treatment. Of these, six received chemotherapy, three received radiotherapy, and 11 received both radiotherapy and chemotherapy. Chemotherapy and/or radiotherapy began after the recovery of pancreas function, including restoration of amylase and lipase levels to normal values. Each cycle of the chemotherapy regimen consisted of gemcitabine combined with cisplatin, and gemcitabine (1000 mg/m$^2$) administered intravenously in 30 min on days one and five, with an intravenous infusion of cisplatin (20 mg/m$^2$) on days 1–3. When the white blood cell counts returned to normal levels and gastrointestinal tract and other side effects disappeared, the next chemotherapy cycle was started. According to the patient's general condition, tumor situation, lymph node metastasis, cost, and preference (some patients refused chemotherapy), 17 patients in the combined therapy group received chemotherapy, six patients received four cycles of chemotherapy, three received five cycles, six received six cycles, one received seven cycles and one patient received eight cycles. After the simulator was located, the 15-mV X-ray was administered *in vitro*. The radiation range included the first stage: the 1–2 cm and the adjacent lymph drainage area outside the primary focus, the ventral front field and the backfield, the irradiated area 7 × 11–8 × 13 cm, TD40–45 Gy, 1.7–1.9 Gy each time; in the second stage, if patients tolerated radiotherapy to one side or bilateral ventral field, close to the edge of the lump, the radiation area: 6 × 10–7 × 11 cm, supplemental TD10–25 Gy, each time 1.7–1.9 Gy.

### Clinical data collection

We collected the detailed preoperative, intraoperative, and postoperative data and monitored changes in tumor markers and imaging test findings. The key data included the time after diagnosis, time after the operation, carbohydrate antigen (CA) 19-9 levels, and recurrence, metastasis and survival rates.

### Follow-up

All patients were followed up monthly during the study. Data on survival, recurrence, metastasis, chemotherapy, and radiotherapy were collected during follow-up, on outpatient hospital readmission or by telephone. The follow-up was performed by an experienced abdominal imaging diagnostic physician; LAPC-related deaths were defined as those due to infection, multiple organ failure, malignant consumption, for digestive tract hemorrhage.

### Statistical analysis

The measured data were represented as means ± standard deviation or medians (first and third quartiles) based on tests of normality, and compared using *t* or Wilcoxon rank tests between groups. The categorical variables were shown as counts (percentage), and differences between groups were assessed using Chi-square or Fisher's exact tests. Kaplan–Meier curves were built for both groups and the difference in survival rates was assessed by log-rank tests. We then performed Cox proportional hazards regression for unadjusted and adjusted effects of the group. Potential confounders were included if they individually caused >10% change in the estimated hazard ratio (HR). In addition, variables with clinical plausibility were retained in the final regression model. Finally, multivariate models were progressively adjusted for age, sex, body mass index (BMI), tumor location, tumor size, T-stage, N-stage, operation time, and pullbacks. Data were analyzed using SPSS statistics for windows software (version 17.0; SPSS, Inc., Chicago, USA) and $P < 0.05$ was considered statistically significant.

## RESULTS

The clinicopathological characteristics of 42 patients are shown in Table 1. In this study, the IRE group tumors were mainly located in the pancreatic head, but the difference between groups was not statistically significant. There were no major differences in tumor size and vascular invasion between the two groups. The time from diagnosis to treatment was more than 1 month because most patients received ultrasound-guided percutaneous transhepatic biliary drainage to reduce jaundice.

The related complications during and after the operation are shown in Table 2. Because IRE is a treatment involving electricity, transient hypotension, hypertension, and supraventricular tachycardia are possible. The postoperative complications were categorized based on Clavien-Dindo classifications, and no deaths were directly attributed to IRE. There was no loss during follow-up. At the 180-day follow-up, 12 participants in the IRE group ($n = 22$) and 15 participants in the combined therapy group ($n = 22$) were at risk [Table 3]. The Kaplan–Meier curves showed better survival in the combined therapy group compared to than in the IRE group [Figure 1, log-rank test $P = 0.008 < 0.05$]. The 1-year survival in the combined-therapy group (76.86%) was better than that in the IRE group (18.19%). A series of progressive Cox proportional hazards regressions [Table 4] showed a crude HR and 95% confidence interval (CI) (combined therapy vs. IRE) of 0.24 (0.08, 0.76) ($P = 0.15$) in Model 1. The adjusted HRs for age, sex, and BMI were marginally significant ($P = 0.064$) in Model 2. The adjusted HR and 95% CI in the finale model including all measured potential confounders was 0.19 (0.05, 0.80) ($P = 0.23$).

The median time from diagnosis and operation to the end of the study in the IRE group was 211 and 199 days, respectively, which were significantly shorter than those in the combined therapy group (326 and 291.5 days). The relapse rate was significantly higher in the IRE group (12/22) than that in the combined-therapy group (3/20). Seven cases (31.82%) in the IRE group and three cases (15.00%) in the combined-therapy group had distant metastases ($P = 0.201$), the distant metastases in the IR group included the liver ($n = 4$), lung ($n = 1$), bone marrow ($n = 1$), and adrenal gland ($n = 1$); the liver was the only metastatic site in the combined-therapy group ($n = 3$). Serum CA19-9 levels were higher on the first postoperative day in both groups. In the IRE group, CA19-9 levels frequently fluctuated; in contrast, the levels gradually reduced after surgery and then increased 3 months after the operation [Table 5]. The univariable regression analysis showed that age, N-stage, IRE time, operation time, and treatment modality were associated with end-point events [Supplement Table 1].

## DISCUSSION

The results of this study showed that the survival time was longer by almost 3 months in the combined-therapy group, along with a significantly increased survival rate. These findings showed that radiotherapy and chemotherapy

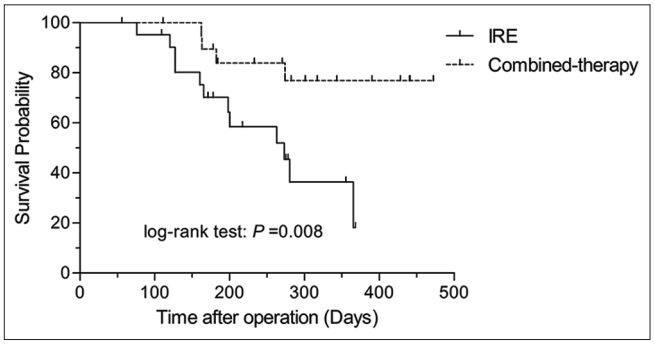


**Figure 1:** Kaplan–Meier curves of the irreversible electroporation and combined-therapy groups

**Table 1: Baseline characteristics of the patients in the two groups**

| | IRE (*n*=22) | Combined therapy (*n*=20) | *P* |
|---|---|---|---|
| Age (years) | 58.82±10.00 | 57.80±7.54 | 0.714 |
| Gender (male/female), *n* (%) | | | |
| Female | 6 (27.27) | 9 (45.00) | 0.231 |
| Male | 16 (72.73) | 11 (55.00) | |
| BMI (kg/m$^2$) | 21.85±3.24 | 22.54±2.77 | 0.461 |
| Preoperative total bilirubin | 69.55±53.25 | 53.59±62.79 | 0.217 |
| Preoperative direct bilirubin | 58.57±51.82 | 45.81±55.46 | 0.540 |
| Tumour location, *n* (%) | | | |
| Head | 17 (77.270) | 10 (50.00) | 0.065 |
| Body/neck | 5 (22.73) | 10 (50.00) | |
| Tumour size (cm) | 3.82±1.16 | 4.30±1.69 | 0.285 |
| Vascular invasion, *n* (%) | | | |
| Celiac only | 6 (27.27) | 8 (40.00) | 0.214 |
| SMA only | 6 (27.27) | 3 (15.00) | |
| Celiac/SMA | 3 (13.64) | 0 (0.00) | |
| PV/SMV occlusion | 6 (27.27) | 9 (45.00) | |
| Celiac/SMA and PV/SMV occlusion | 1 (4.55) | 0 (0.00) | |
| Operation, *n* (%) | | | |
| IRE | 10 (45.45) | 9 (45.00) | 0.976 |
| IRE and bypass surgery | 12 (54.55) | 11 (55.00) | |
| Direction of the needle, *n* (%) | | | |
| Anterior to posterior | 12 (54.55) | 9 (45.00) | 0.537 |
| Caudal to cranial | 10 (45.45) | 11 (55.00) | |
| IRE time (min) | 32.5 (29.0-38.0) | 36.0 (28.5-54.5) | 0.504 |
| Operation time (min) | 215.0 (190.0-230.0) | 200.0 (165.0-250.0) | 0.313 |
| Probes | 3.0 (2.0-4.0) | 3.0 (2.5-4.0) | 0.444 |
| Pullbacks, *n* (%) | | | |
| 1 | 13 (59.09) | 7 (35.00) | 0.273 |
| 2 | 7 (31.82) | 11 (55.00) | |
| 3 | 2 (9.09) | 2 (10.00) | |
| Probe exposure (cm), *n* (%) | | | |
| 1 | 7 (31.82) | 9 (45.00) | 0.380 |
| 1.5 | 15 (68.18) | 11 (55.00) | |
| Time from diagnosis to treatment (days) | 22.5 (12.0-33.0) | 19.00 (15.0-36.0) | 0.734 |

BMI=Body mass index, PV=Portal vein, IRE=Irreversible electroporation, SMV=Superior mesenteric vein, SMA=Superior mesenteric artery

**Table 2: Complications after irreversible electroporation**

| Type | IRE (*n*=22) | Combined therapy (*n*=20) | Clavien-Dindo classification |
|---|---|---|---|
| Intraoperative complications | | | |
| Transient hypotension | 1 | 1 | - |
| Transient hypertension | 1 | 0 | - |
| Transient supraventricular tachycardia | 1 | 1 | - |
| Postoperative complications | | | |
| Pancreatic fistula (Grade A) | 1 | 1 | Grade 1 |
| Acute pancreatitis | 2 | 1 | Grade 2 |
| Upper gastrointestinal haemorrhage | 1 | 0 | Grade 3 |
| Delayed gastric emptying | 1 | 1 | Grade 2 |
| PV thrombosis | 1 | 0 | Grade 3 |

-=Not applicable, PV=Portal vein, IRE=Irreversible electroporation

**Table 3: Number of participants at risk during follow-up**

| Number at risk | Time point (days) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 90 | 180 | 270 | 360 | 450 |
| IRE group | 22 | 20 | 12 | 7 | 2 | 0 |
| Combined-therapy group | 20 | 20 | 15 | 12 | 7 | 2 |

IRE=Irreversible electroporation

combined with IRE were effective in improving the prognosis of patients with LAPC.

Given the retroperitoneal position of the pancreas, the tumor tends to spread quickly to the superior mesenteric and/or hepatic artery and/or celiac trunk and/or junction of the mesenteric and portal vessels.[14] Therefore, despite surgery, locoregional therapy, chemotherapy and molecular therapies, the overall median survival of pancreatic cancer is <1 year from diagnosis, highlighting the need for better therapeutic options.[15] Hence, systematic and new treatments are important. Our results showed that IRE improved prognosis and suggested that combined therapy had a better survival benefit than IRE alone.

IRE has been used for >30 years[16] and was initially used to destroy microorganisms or introduce drugs into cells *in vitro*.

It is a new technique that induces cell death with proven safety and efficacy. It uses very high voltage, maximum of 3000 volts, delivered in 70–80 μs pulses. These ultrashort electrical pulses create microscopic holes within the cell membrane, resulting in irreversible cell damage due to interference with homeostatic mechanisms.[17] Thus, the cells are destroyed while the collagen architecture of the vascular, biliary, or neuronal structures is preserved.[18]

The postoperative local recurrence rate is as high as 80%.[19,20] Hishinuma *et al*.[21] showed that 75% of patients had local recurrence at the time of death. Among patients treated with adjuvant chemoradiotherapy after radical surgery, the number of positive lymph nodes, age ≤60 years and a microscopically margin negative resection were all independently associated with improved survival in multivariate analysis.[22] Therefore, adjuvant therapy is necessary.

Adjuvant chemotherapy was shown in randomized settings to improve survival as compared to observation.[23] The first clinical trial was conducted 30 years ago,[24] in which 42 patients were randomized into adjuvant 5-fluorouracil-based chemoradiotherapy observation groups. The results showed median overall survival times of 20 and 11 months, respectively. Chemotherapy is well documented to alleviate symptoms, improve quality of life, and prolong survival time. The recurrence rates in the two groups were 56.20% and 35.70%, and the survival rates were 50% and 71.40%, respectively. These results are more promising than those previously reported.

**Table 4: Association of combined therapy versus irreversible electroporation with the risk of death**

| | HR (95% CI) P | | |
|---|---|---|---|
| | Unadjusted model | Model 1[a] | Model 2[b] |
| IRE | Reference | Reference | Reference |
| Combined therapy | 0.24 (0.08-0.76)<br>0.015 | 0.23 (0.06-0.84)<br>0.026 | 0.14 (0.03-0.72)<br>0.019 |

[a]Adjusted for age, sex, BMI, T stage and N stage, [b]Adjusted variables in Model 1 plus tumour location, tumour size, operation time and pullbacks. HR=Hazard ratio, CI=Confidence interval, IRE=Irreversible electroporation, BMI=Body mass index

Unlike chemotherapy, the use of radiotherapy remains controversial. Chemoradiotherapy or radiotherapy after induction chemotherapy could alleviate symptoms and prolong survival.[24] Radiotherapy may also improve the quality of life in patients with metastatic pancreatic cancer accompanied by obstruction, oppression, or pain.[23] However, no randomized controlled trials have evaluated the efficacy of chemotherapy in adjuvant therapy. Multiple research trials[25-28] have shown that radiotherapy did not improve survival. These findings may reduce the application of radiotherapy in patients with LAP. Hence, further studies are needed to confirm the present results.

Few studies have assessed the combination of IRE and chemotherapy or radiotherapy; moreover, the present study is a retrospective study with small sample size and short follow-up duration. Hence, further studies with larger sample sizes and long-term follow-up are needed.

The effects of radiotherapy or chemotherapy after surgery should be separately compared. Furthermore, extending the survival of patients as well as improving their quality of life should be emphasized.

## CONCLUSIONS

Since IRE is an effective treatment for LAPC, we found that the combination of IRE and radiotherapy and chemotherapy offered advantages over IRE alone by prolonging survival time and increasing the survival rate; however, these findings require verification.

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Nil.

**Table 5: Surgical outcomes between irreversible electroporation and combined therapy group**

| | IRE (*n*=22) | Combined therapy (*n*=20) | *P* |
|---|---|---|---|
| Time from diagnosis to end of study (days) | 211.0 (107.0-553.0) | 326.0 (131.0-516.0) | 0.013 |
| Time from operation to end of study (days) | 199.0 (56.0-368.0) | 291.50 (111.0-472.0) | 0.010 |
| Recurrence, *n* (%) | | | |
| Yes | 12 (54.55) | 3 (15.00) | 0.008 |
| No | 10 (45.45) | 17 (85.00) | |
| Metastasis, *n* (%) | | | |
| Yes | 7 (31.82) | 3 (15.00) | 0.201 |
| No | 15 (68.18) | 17 (85.00) | |
| CA19-9 (u/mL) | | | |
| At admission | 73.07 (64.95-891.20) | 128.95 (46.81-444.65) | 0.659 |
| Day 1 after IRE | 74.46 (60.00-900.32) | 166.74 (50.96-455.15) | 1.000 |
| Day 7 after IRE | 60.64 (40.01-876.90) | 150.59 (42.77-518.70) | 0.850 |
| Day 30 after IRE | 52.38 (37.56-867.30) | 121.58 (40.10-374.55) | 0.860 |
| Day 90 after IRE | 80.79 (65.00-986.20) | 119.13 (30.12-1340.50) | 0.632 |
| Overall hospital stay (days) | 18.5 (14.0-20.0) | 17.0 (16.0-22.5) | 0.830 |
| Postoperative hospital stay (days) | 11.0 (10.0-14.0) | 10.00 (9.00-11.5) | 0.122 |

IRE=Irreversible electroporation, CA=Carbohydrate antigen

## Conflicts of interest

There are no conflicts of interest.

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**Supplemental Table 1: Univariate cox regression analyses of the associations between each variable and follow-up survival**

| | HR (95% CI) *P* |
|---|---|
| Age (for 1 year increase) | 1.16 (1.03-1.29) 0.01 |
| Male versus female | 2.20 (0.56-8.69) 0.26 |
| BMI (for 1 kg/m$^2$ increase) | 1.01 (0.82-1.24) 0.94 |
| CA199 at admission | 1.00 (1.00-1.00) 0.59 |
| Preoperative total bilirubin (for 1 umol/L increase) | 1.00 (0.99-1.01) 0.79 |
| Preoperative directive bilirubin (for 1 umol/L increase) | 1.00 (0.99-1.01) 0.90 |
| Tumor location | |
| Head | Reference |
| Body/neck | 0.45 (0.12-1.79) 0.26 |
| Tumor size (for 1 cm increase) | 1.50 (0.92-2.46) 0.10 |
| T-stage | |
| 1 | Reference |
| 2 | 3.11 (0.57-17.02) 0.19 |
| N-stage | |
| 1 | Reference |
| 2 | 0.17 (0.04-0.80) 0.02 |
| Direction of the needle | |
| Anterior to posterior | Reference |
| Caudal to cranial | 1.50 (0.43-5.25) 0.52 |
| IRE time (for 1-min increase) | 1.03 (1.00-1.07) 0.07 |
| Operation time (for 1-min increase) | 1.02 (1.00-1.03) 0.02 |
| Probes (for 1 increase) | 1.98 (0.99-3.97) 0.05 |
| Pullbacks | |
| 1 | Reference |
| 2 | 0.75 (0.20-2.83) 0.67 |
| 3 | 1.50 (0.17-12.94) 0.71 |
| Probe exposure (cm) | |
| 1 | Reference |
| 1.5 | 4.33 (0.99-18.89) 0.05 |
| Treatment modalities | |
| IRE | Reference |
| Combined therapy | 0.24 (0.08-0.76) 0.01 |

IRE=Irreversible electroporation, BMI=Body mass index, CA=Carbohydrate antigen