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Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy

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Abstract

Background: Irreversible electroporation (IRE) is a non-thermal based tumor ablation method used close to vessels and ducts and has the potential of treating locally advanced pancreatic cancer (LAPC). The aim of this study was to evaluate the efficacy and safety of IRE in patients with LAPC after chemo- and/or radio-chemotherapy.
Method: Twenty-four patients with biopsy proven LAPC and who had received chemo- and/or radio-chemotherapy with no signs of metastases were included and treated with ultrasound guided percutaneous IRE under general anesthesia.
Results: The median overall survival from diagnosis of LAPC was 17.9 months; this included 7.0 months after IRE. Median time from IRE was 6.1 months to local progression and 2.7 months to observation of metastases. Local control was observed in nine patients. IRE related complications were observed in 11 patients, three of which were serious complications. There was no IRE related mortality.
Conclusion: Percutaneous IRE is reasonably safe in LAPC after chemo-/radio-chemotherapy and with promising results regarding efficacy.

Keywords: Pancreatic neoplasms; Electroporation; Interventional ultrasonography

Introduction

The prognosis for pancreatic adenocarcinoma is poor, with an overall 5-year survival of less than 4%. The only hope for cure is radical surgery, which can only be performed in less than 20% of cases[1] due to metastatic disease (40%) or locally advanced pancreatic cancer (LAPC: 40–50%).[2] When resection cannot be performed, the median survival is 3–6 months for metastatic disease and 6–10 months for LAPC.[1] The prognosis is the same for patients treated with gemcitabine, with a median survival of 4.4 months in metastatic disease and 6.6 months in LAPC.[3]

Due to poor survival in LAPC, different ablation methods are used for treating LAPC, including radiofrequency ablation, microwave ablation, cryoablation, and photodynamic ablation. However, there is a considerable risk for complications due to injuries to adjacent structures.[1] With thermal ablation, there is also a risk that heat close to the vessels is insufficient to ablate all tumor cells, the so called heat-sink effect, especially since LAPC per definition include major vessels.[4]

Irreversible electroporation (IRE) is a non-thermal based ablation technique and is based on the transmission of short direct current pulses through the tumor via needles, leading to irreversible change in cell membrane integrity and subsequent apoptosis.[5–9] A unique feature of IRE is that although some heat is generated collagen structures such as blood vessels and bile ducts are not destroyed. IRE is performed under general anesthesia with relatively few anesthetic complications.[10] In a prospective study by Martin et al.[5] intraoperative IRE is favored over historical controls treated with chemotherapy or radiochemotherapy. With IRE local progression free survival was 14 months

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(6 months for treatment with chemo-/radio-chemotherapy), distant-progression free survival was 15 months (9 months with chemo-/radio-chemotherapy), and overall survival was 20 months (13 months with chemo-/radio-chemotherapy).[5]

In contrast to previous studies with IRE in LAPC which used intraoperative IRE, or were guided by computer tomography, in this study we used ultrasound guidance with Doppler for IRE administration. Our initial feasibility experience with this technique for LAPC was recently published.[8] We now present our expanded experience from ultrasound guided IRE for treatment of LAPC after chemo- and or radio-chemotherapy with the aim to evaluate efficacy and report additional data on safety.

Patients and methods

Patients

Patients over 18 years old with biopsy proven and still unresectable LAPC after chemotherapy and/or radiochemotherapy were included. LAPC was defined as superior mesenteric artery or celiac encasement, aortic invasion, unreconstructable superior mesenteric or portal vein involvement, with no evidence of metastatic disease from abdominal and thoracic computer tomography.[11] Exclusion criteria were implanted electronic devices, ASA-score IV, expected survival <3 months, pregnancy, epilepsy, severe heart disease, and tumor diameter >5.0 cm. All patients signed informed consent before treatment. The study was approved by the Uppsala Regional Ethics Committee, Uppsala, Sweden (Dnr 2011/298).

Twenty-four patients were included in the study, three of which were also included in the phase 1 part of the study previously reported, the three patients from our initial study were included because we now have data on their survival.[8] The patients were 42−77 years old (median 65 years) and 12 were female. Before IRE, all patients were discussed during a multidisciplinary team conference and were still considered unresectable after oncological treatment: patient demographics are summarized in Table 1. Five patients were considered too locally advanced for resection after laparotomy with curative intent was performed.

All patients had prior chemotherapy and/or radiochemotherapy. Three patients had only prior radiochemotherapy and seven patients had chemotherapy induction followed by radiochemotherapy before IRE treatment see Table 1. In six patients, the tumor was considered potentially resectable before chemotherapy/radiochemotherapy.

IRE procedure

The NanoKnife IRE equipment from Angiodynamics System (Queensbury, NY, USA) was used. In all patients, the needle placement outlined the tumor, with a needle also placed in the center of the tumor when tumor diameter exceeded 2.0 cm. If a needle was placed in the center of the tumor we tried to place it as close to the center as possible without causing direct mechanical injury to vital structures e.g. blood vessels encased in the tumor. The procedure was conducted under general anesthesia with deep neuromuscular block (posttetanic count of zero). The needles were placed percutaneously and transabdominally, through ultrasound guidance and initially with the tips at the deep aspect of the tumor. All needles were placed under ultrasound guidance and thus both the needle position and the distance between needles were determined in this way. The electrical parameters are calculated by the machine in order to compensate for any error in the assessment of the needle distance. Ten pulses were given initially and the resulting current was checked on the machine and the machine's settings (mainly V/cm) and were adjusted accordingly before actual treatment pulses were given. Needles were not deliberately placed through either stomach or bowel. Six needles were used in 20 patients, four needles in two patients, and three needles in the remaining two patients. Active needle length was 1.5 cm in all cases. A minimum of 90 pulses was delivered between each adequate needle pair, defined as a distance between the needles not exceeding 2.5 cm. After completion of the treatment cycles in the deep portions of the tumors, the needles were pulled back 1.5 cm and another treatment with the same parameters was performed in the superficial portion of the tumor. The machine settings were adjusted so that an end current of around 40 A, and never less than 30 A, was achieved. We used the recommended settings by the manufacture of the machine.

We did no not record the total time of the treatments, but we estimate it to be between 1.5 and 3.5 h, mainly dependent on the tissues electric conductivity.

In hospital assessments and follow-up

After IRE treatment, all patients were observed for at least 3 days in hospital for safety reasons. Observation included clinical assessment twice daily by a surgeon and daily blood tests. Before discharge, an abdominal ultrasound was used to check for complications.

One month after the treatment, patients underwent physical examination and assessment for adverse effects through contrast enhanced abdominal ultrasound. The patients were assessed every three months for radiological signs of local progression and occurrence of metastatic disease through contrast enhanced abdominal ultrasound and computed tomography of the thorax and abdomen. Due to the limited experience of how an ablated area looks post-IRE it was deemed a local recurrence when the ablated zone started to grow or new contrast enhancing areas were seen. If clear radiological signs of progressive disease were observed, surveillance was discontinued. Serious complications were defined as Dindo−Clavien >2 within 30 days of treatment[12] and time of death was retrieved from the patients' charts.