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Citation

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Consensus Guidelines of Irreversible Electroporation for Pancreatic Tumors: Protocol Standardization Using the Modified Delphi Technique

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Abstract

Since no uniform treatment protocol for pancreatic irreversible electroporation (IRE) exists, the heterogeneity throughout literature complicates the comparison of results. To reach agreement among experts, a consensus study was performed. Eleven experts, recruited according to predefined criteria regarding previous IRE publications, participated anonymously in three rounds of questionnaires according to a modified Delphi technique. Consensus was defined as having reached ≥80% agreement. Response rates were 100, 64, and 64% in rounds 1 to 3, respectively; consensus was reached in 93%. Pancreatic IRE should be considered for stage III pancreatic cancer and inoperable recurrent disease after previous local treatment. Absolute contraindications are ventricular arrhythmias, implantable stimulation devices, congestive heart failure NYHA class 4, and severe ascites. The inter-electrode distance should be 10 to 20 mm and the exposure length should be 15 mm. After 10 test pulses, 90 treatment

Keywords
- irreversible electroporation
- pancreatic tumors
- modified Delphi technique
- interventional radiology

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pulses of 1,500 V/cm should be delivered continuously, with a 90-µs pulse length. The first postprocedural contrast-enhanced computed tomography should take place 1 month post-IRE, and then every 3 months. This article provides expert recommendations regarding patient selection, procedure, and follow-up for IRE treatment in pancreatic malignancies through a modified Delphi consensus study. Future studies should define the maximum tumor diameter, response evaluation criteria, and the optimal number of preoperative FOLFIRINOX cycles.

Irreversible electroporation (IRE) is a primarily non–thermal ablation technique of which the feasibility and safety has been validated by several (prospective) studies for a variety of tumors.[1–5] Other comparative, prospective trials are currently being conducted or pending publication to further assess its efficacy, such as the COLDFIRE-III for colorectal liver metastases (NCT06185556) and the CROSSFIRE trial for pancreatic cancer (NCT02791503). After placement of several needle electrodes in and around the tumor, high-voltage pulses are delivered between each needle–electrode pair.[6] The pulses create nanopores in the cellular membrane which induce apoptosis of the cells within the ablation zone.[7] Since the working mechanism of IRE is based on direct injury caused by electrical pulses instead of thermal energy, it can be used for tumors that are unamenable for thermal ablation techniques because of proximity to vital structures such as bile ducts or vessels.[8]

Pancreatic cancer is known for its dismal prognosis and aggressive growth surrounding large blood vessels and biliary structures.[9] Since surgical resection is impossible in many patients, IRE has been investigated as a treatment option for unresectable pancreatic cancer.[3–5,10–16] However, a great variety in the approach of pancreatic IRE exists throughout literature, such as the used eligibility criteria, applying IRE during laparotomy or percutaneously, using IRE as complementary treatment to resection (margin accentuation) or as solitary treatment for local control, and different procedure and follow-up protocols.[17] This variability throughout literature impedes the comparison of outcomes and the assessment of the oncological benefit of IRE for patients with pancreatic cancer.

To maintain scientific progress and optimize oncological outcome, IRE should be performed according to a uniform and systematic protocol across different studies. Therefore, all current conflicting recommendations and study designs mandate the setup of this Delphi consensus, in which consensus among a selected group of global experts regarding systematic pre- and post-treatment evaluation, strict patient selection criteria, and standardization of the IRE protocol is pursued.

Materials and Methods

Delphi Consensus

A Delphi consensus is a structured process that is used for the evaluation of expert opinion on health and medical topics. It uses a series of questionnaires that are iterated until consensus is reached. The questionnaires are answered anonymously, thereby preventing domination of one or more experts. The answers from the questionnaire are gathered and reported back to the group, encouraging the panelists to reassess their initial judgements. Subsequently, the experts are asked to answer the questionnaire again. This process is iterated until consensus has been reached. In the first round, the experts were given the opportunity to propose new items that were not yet noted in the questionnaire. In this study, the process was iterated three times, or less when reaching consensus earlier. Consensus was defined as having reached at least 80% agreement among panelists. If the experts did not reassess their judgements in the third and final questionnaires, they were asked to specify the reasons for remaining outside the consensus.

Expert Panel

A literature search through the PubMed database was performed with the following search strategy: ((irreversible electroporation[Title/Abstract]) AND (pancr*[Title/Abstract])). Experts were selected if they had at least two peer-reviewed publications on IRE, of which at least one was a retro- or prospective patient cohort in the field of pancreatic IRE, excluding case reports and small case series (1–5 patients). Only one expert was allowed per research group.

After reviewing the search, a total of 11 experts from Europe ($n = 7$) and the United States ($n = 4$) working in 11 centers were asked to participate in the survey. The expert panel consisted of specialists from surgery and (interventional) radiology departments (Appendix 1). The questionnaires were internet-based and sent by email, to increase response rate. All experts received a deadline to fulfill the questionnaire and were sent weekly reminders to encourage participation.

Results

The response rates were 100, 64, and 64% in rounds 1, 2, and 3, respectively. Consensus was reached on 147/158 items (93%; see ►**Fig. 1**). A comprehensive overview of the results, including all items and the level of agreement, is provided in Appendix 2.

Indications and Contraindications for Pancreatic IRE

Prior to treatment with IRE, histological or cytological proof should be obtained. Pancreatic IRE can be considered for

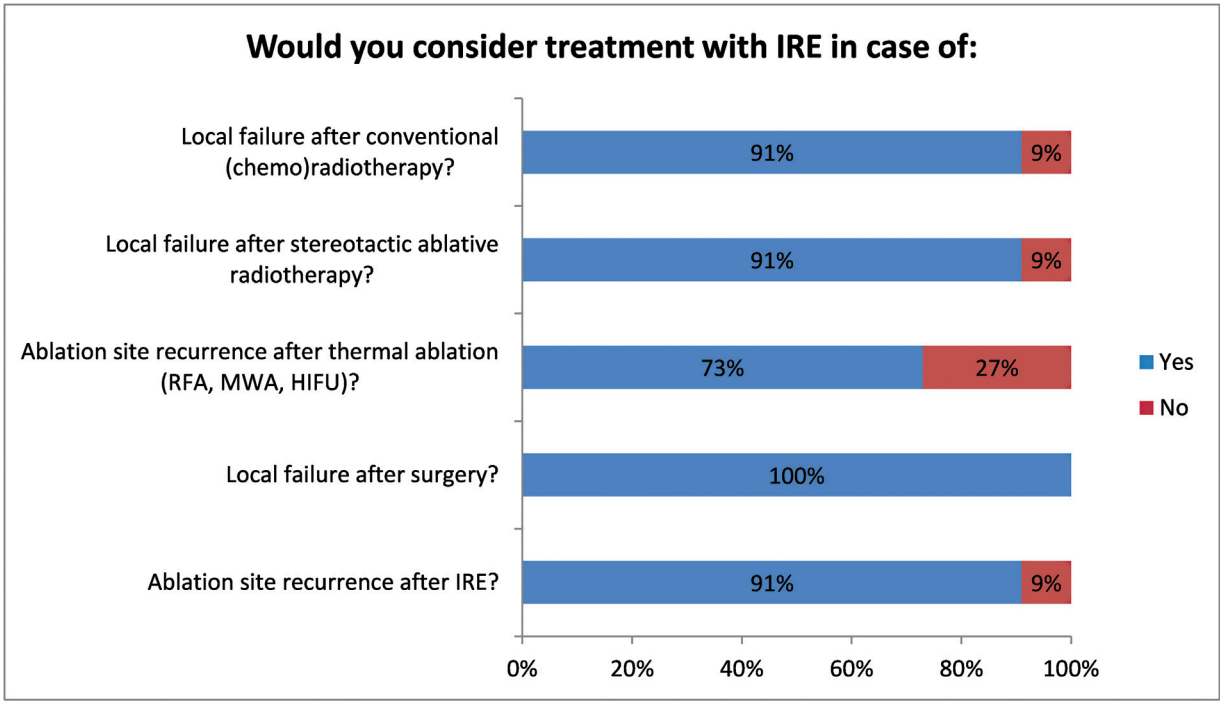

Fig. 1 Questionnaire response example. IRE, irreversible electroporation; RFA, radiofrequency ablation; MWA, microwave ablation; HIFU, high-intensity focused ultrasound.

adenocarcinoma and neuroendocrine tumors of the pancreas. Stage III pancreatic cancer (according to the American Joint Committee on Cancer [AJCC] staging system[18]) is eligible for treatment with IRE, in contrast to stages I, II, and IV. Also, treatment of metastases within the pancreas from renal cell carcinoma or melanoma can be considered if this is deemed oncologically beneficial and no other treatment options are available. The panelists believe that intraductal papillary mucinous neoplasms of the pancreas should not be treated with IRE.

The panelists agreed that local recurrent disease after surgery, conventional (chemo)radiotherapy, stereotactic ablative radiotherapy (SABR), or IRE are good indications for pancreatic (re-)IRE. This also applies in case of *early* local recurrence (<6 months). Although size progression (>20% longest diameter tumor growth) under chemotherapy is a poor prognostic sign, no consensus is reached to consider size progression under chemotherapy a contraindication.

►**Table 1** provides an overview of the comorbidities that were designated as no contraindication, relative contraindication, and absolute contraindication as judged by the panelists. A minimum platelet count of 50×10^9/L is required for treatment with IRE. An upper international normalized ratio (INR) of >1.6 should be considered an absolute contraindication and an INR between 1.2 and 1.6 a relative contraindication. Although the manufacturer of the NanoKnife system deems a metal Wallstent as an absolute contraindication, the panelists agreed that if the metal Wallstent lies outside the center of the ablation zone IRE can be performed since the electrical field lines do not interfere with the stent.

Table 1 Contraindications for pancreatic IRE

Absolute contraindication	Relative contraindication	No contraindication
Cardiac • Ventricular cardiac arrhythmias • Pacemaker/ICD • Congestive heart failure NYHA Class 4	*Cardiac* • Active coronary artery disease (i.e., instable angina pectoris/myocardial infarction <6 mo prior to IRE) • Congestive heart failure NYHA Class 2 and Class 3 • Atrial fibrillation	*Cardiac* • History of coronary artery disease (i.e., instable angina pectoris/myocardial infarction ≥6 mo prior to IRE)
Other • Severe ascites	*Other* • Non–medication-induced coagulation disorder • Moderate ascites	*Other* • Epilepsy • Minimal ascites

Abbreviations: ICD, implantable cardioversion defibrillator; IRE, irreversible electroporation; NYHA, New York Heart Association.

Tumor Characteristics

The final consensus percentage for a maximum tumor diameter of 4 cm was 71%, which should therefore be considered as norm for maximum tumor diameter, but not as *absolute* limit. Transmucosal tumor invasions into surrounding gastrointestinal structures (stomach, duodenum, and colon) are solid reasons to refrain from treatment with IRE.

Enlarged lymph nodes are suspect for malignancy from 15 mm and larger. The experts agreed that in case of histologically proven malignant lymph nodes, IRE can still be performed if these nodes are within the estimated ablation zone. Furthermore, histological proof should not necessarily be obtained in case of *locoregional* lymph nodes that are suspect for malignancy and lie within the expected ablation zone.

Low-grade stenosis ($< 70\%$) of arterial and venous vessels is not considered contraindications. IRE can be performed in case of an *occlusion* or *high-grade stenosis* ($>70\%$) of the superior mesenteric vein or portal vein (PV) and in case of a *high-grade stenosis* ($> 70\%$) of the superior mesenteric artery, celiac or hepatic artery. However, in case of both *high-grade* arterial and venous stenosis, the panelists agreed not to perform IRE because of the high risk of acute liver failure in case of acute total vessel occlusion due to swelling or thrombosis caused by the IRE treatment.

Induction Chemotherapy

All the expert panelists use the definitions of LAPC and borderline resectable disease as stated by the NCCN guidelines. Before IRE is considered in patients with locally advanced (see ►**Fig. 2**) and borderline resectable disease (see ►**Fig. 3**), neo-adjuvant chemotherapy should be administered to identify and exclude patients with biologically unfavorable tumors (i.e., patients with rapid progression under chemotherapy that would likely not benefit from IRE treatment) and to downsize the tumor. Preferably four cycles of FOLFIRINOX should be given as neo-adjuvant/induction chemotherapy. For patients who are unable to receive FOLFIRINOX because of comorbidities, suboptimal performance status and/or advanced biological age, three cycles of gemcitabine (with or without nab-paclitaxel) are recommended. In case of stable disease or partial response after neoadjuvant chemotherapy for borderline resectable disease, the expert panel recommends surgical exploration for primary surgical resection. In case of persistent locally advanced disease without distant metastases, pancreatic IRE is suggested. After IRE, adjuvant chemotherapy is routinely recommended for those who are still eligible, up to 12 cycles of FOLFIRINOX chemotherapy in total.

Workup

Standard workup prior to IRE should always include a general health history review (demographics, past medical history, allergies, intoxications, medications), assessment of performance status and pain, electrocardiography, tumor board review, and a general anesthetic review. A diagnostic laparoscopy to rule out peritoneal depositions or other metastatic disease should not be included in the standard workup prior to percutaneous IRE, but should only be performed in case of high suspicion of distant disease (indeterminate depositions on imaging, inexplicable ascites, high CA 19–9 level). Patients with an ECOG performance status 0 to 2 are eligible for IRE, while it is discouraged to treat patients with a performance status of grade 3 or higher. Patients with an American Society of Anesthesiologists (ASA) score of maximum 2 are eligible for treatment with IRE. For patients with an ASA score of 3, eligibility depends on the specific comorbidity and the availability of alternative treatment options.

A contrast-enhanced computed tomography (ceCT) scan including an arterial and portal venous phase is the recommended imaging modality for pretreatment planning. The upper slice thickness is 3 mm and the upper time limit between the last ceCT and treatment with IRE should be 4 weeks. Laboratory tests that should be performed prior to IRE are given in ►**Table 2**.

If preprocedural biliary drainage is required, an endoscopic retrograde cholangiopancreatography approach should be favored, using preferably a plastic biliary endoprosthesis, although a self-expandable metal Wallstent may be considered for patients at risk for obstruction of the plastic endoprosthesis.

Procedure

Perioperative antibiotic prophylaxis is recommended (e.g., cefuroxime plus metronidazole), while the use of a nasogastric tube seems irrelevant. The needles should be placed at a minimum and maximum distance of 10 and 20 mm, respectively, with the exposure length set at 15 mm. After 10 test pulses, 90 treatment pulses of 1,500 V/cm are delivered continuously (10–90 pulses) with a pulse length of 90 µs (►**Table 3**). In case of (pending) under- or overcurrent, it is recommended to adjust the voltage settings at first. Second, if the desired amperage is still not reached, pulse length should be adjusted. The panelists agreed that the increase in current that occurs during pulse delivery should currently not be recommended as endpoint for a successful ablation.

Post-IRE

Thrombosis prophylaxis is recommended for all patients post-IRE and may be considered in a therapeutic dose for patients at high risk for PV thrombosis, although definite consensus was not reached on the latter (71%). Patients should be admitted to the hospital for at least 2 days post-IRE. During this period, it is recommended to perform postprocedural cross-sectional imaging within 24 hours after open IRE and for percutaneous patients at least before discharge. Routine follow-up should include laboratory tests (►**Table 2**) and ceCT; at first ~1 month after IRE and then every 3 months.

Training and Supervision

No consensus was reached on the number of supervised procedures by a proctor, which varied between 3, 5, and 10 procedures. However, the panelists agreed that physicians performing IRE should have a master's degree in image-

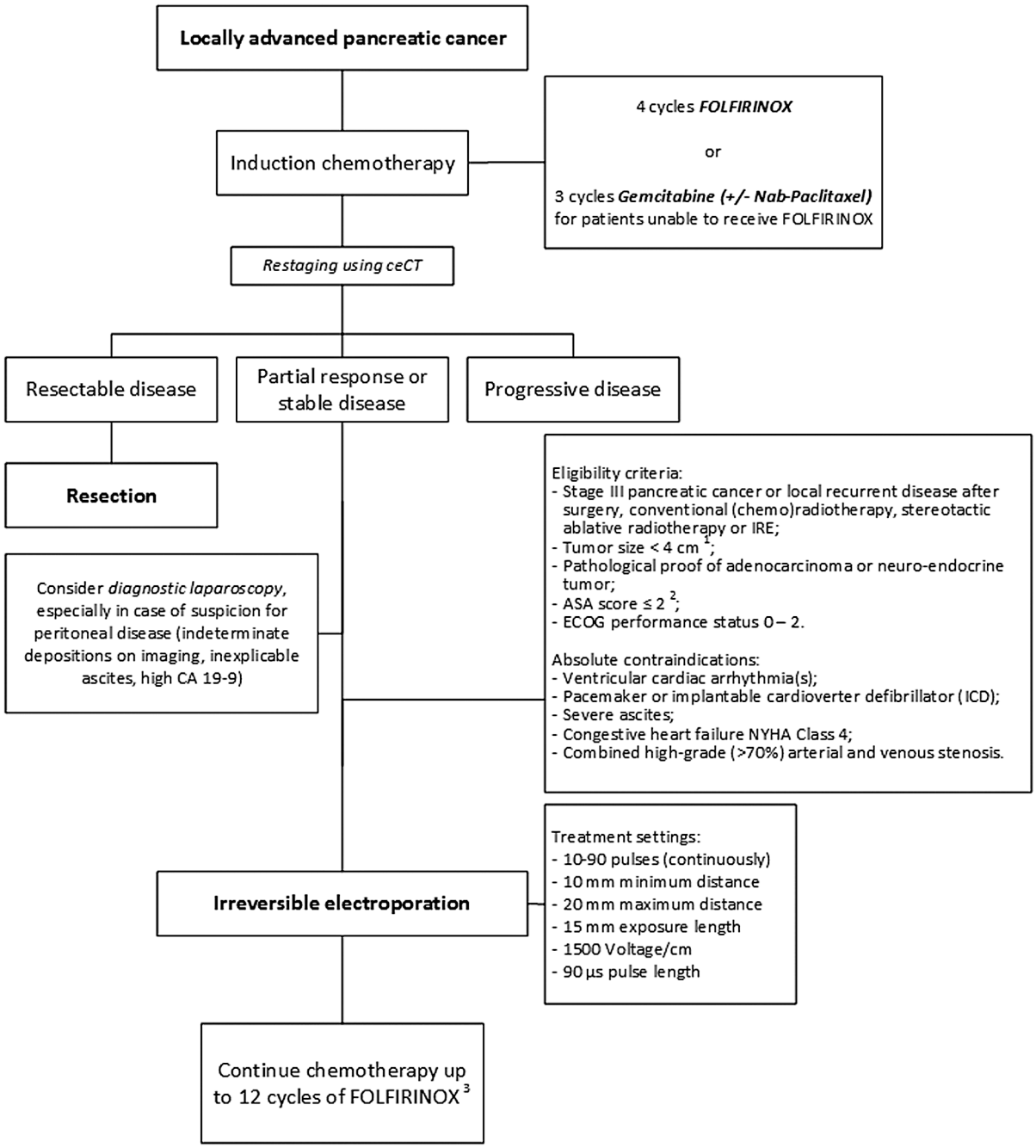

Fig. 2 Flowchart for patients with locally advanced pancreatic cancer. ceCT, contrast-enhanced computed tomography; IRE, irreversible electroporation; ASA, American Society of Anesthesiology; ECOG, Eastern Cooperative Oncology Group; ICD, implantable cardioversion defibrillator; NYHA, New York Heart Association.

guided tumor ablation (i.e., having performed and/or supervised > 100 ablation procedures) and preferably require proctor-initiated certification before performing IRE.

Discussion

In this article, a multidisciplinary panel with IRE experts, consisting of surgeons and interventional radiologists, provided a guideline for IRE treatment of pancreatic malignancies using a three-step modified Delphi method, with recommendations regarding (contra)indications, patient selection, pretreatment assessment, procedural parameters, and follow-up. After having reached a 100% response rate in the first round, the response rates decreased to 64% in the second and third rounds. Regardless of the relatively small number of experts in the panel, consensus was reached on 147/158 items (93%).

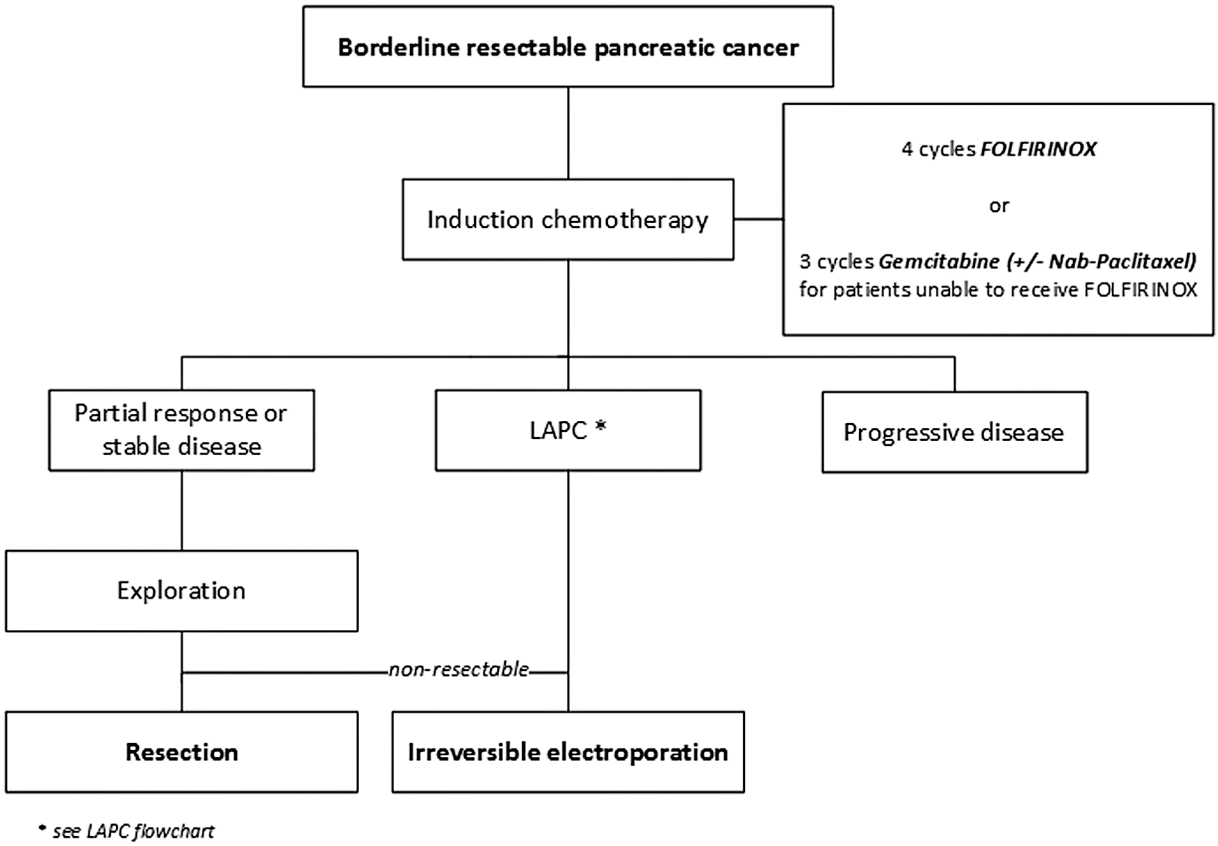

Fig. 3 Flowchart for patients with borderline resectable disease. LAPC, locally advance pancreatic cancer.

Although no consensus was reached concerning the maximum longest tumor diameter, 71% agreed that 4 cm should be the upper limit. Hence, the expert panel settled to consider 4 to 5 cm tumors as a *relative* and >5 cm tumors as an *absolute* contraindication for pancreatic IRE. Controversial results on routinely prescribed pain medication after pancreatic IRE may be explained by the approach used (i.e., open laparotomy or percutaneously). Several experts stated to routinely prescribe opiates, while others routinely prescribe acetaminophen.

All proposed criteria (RECIST, mRECIST, PERCIST, Choi, and AMREC) for the detection of disease progression were dismissed by the experts as adequate criteria for tumor progression after pancreatic IRE. RECIST considers tumor shrinkage as measure of tumor activity; so, it can mislead in the assessment of treatment response after IRE as this often leaves scar tissue that is approximately the same size as the

Table 2 Laboratory tests

Cancer antigen 19–9
Hemoglobin
Hematocrit
Platelets
White blood cells
C-reactive protein
Aspartate transaminase
Alanine transaminase
Gamma-glutamyltransferase
Alkaline phosphatase
Bilirubin
Albumin
Amylase
Lipase
Creatinine
Sodium
Potassium

Table 3 Procedure parameters

Parameter	Recommendation
Test pulses	10
Treatment pulses	90
Pulse delivery	Continuously (10–90)
Minimum distance	10 mm
Maximum distance	20 mm
Exposure length	15 mm
Voltage	1,500 V/cm
Pulse length	90 µs

initial tumor lesion.[19] Choi and mRECIST criteria could overcome the limitations of RECIST by measuring the tumor enhancement.[20,21] However, this two-dimensional tumor assessment method may be unable to effectively identify tumor apoptosis induced by IRE, since tumors do not expand or reduce symmetrically and undergo heterogeneous changes which would affect the reliability of Choi and mRECIST.[22] The limitations of current response evaluation criteria mandate the development of reliable and reproducible criteria, specifically applicable for tumor response after local ablative therapies.

The strength, but also the limitation, of this study lies in the design of the modified Delphi method. One major advantage is that the questionnaires were completed anonymously by the experts, which reduces the effects of dominant individuals.[23] Since both specialties, interventional radiologists and surgeons, that perform percutaneous and open pancreatic IRE, respectively, were represented in the expert panel, the recommendations in this study are generalizable and valid. The rather low number of panelists in the expert panel was a potential limitation. However, a higher level of agreement is necessary to obtain consensus in a smaller group, which indicates unanimity on the recommendations made in this study. Although these guidelines provide a recommendation regarding the number of preoperative cycles FOLFIRINOX, preferably four cycles, this matter is still subject to further study. In the era of shared decision-making, the treatment decisions should be personalized to every single patient. Hence, the abovementioned recommendations should merely be considered a quality improvement guideline for clinical practice, allowing deviations in specific cases. Furthermore, the recommendations are based on expert opinions, which does not automatically guarantee that the proposed inclusion and exclusion criteria and technical considerations represent the optimal parameters, making it level V evidence as defined by the Centre for Evidence-based Medicine.[24] Nonetheless, the clinical implications of the recommendations are of great importance. In literature, the evidence on which to base guidelines for IRE treatment is still scarce, apart from the manufacturer's guidelines. These manufacturer's guidelines are prepared with the greatest safety precautions, leading to exclusion of patients who may have been suitable for treatment with IRE. For example, patients with unretrievable metal Wallstents and patients with a history of cardiac disease or epilepsy should no longer automatically be deprived from receiving pancreatic IRE. However, a study from Hogenes et al showed a reduction in electrical field strength when a metal stent lies in proximity of the IRE electrodes.[25] Therefore, clinicians should be aware of the possible ineffective tumor ablation when a metal stent lies within the ablation zone, which could potentially be counteracted by increasing the number of pulses.

In conclusion, these guidelines provide expert recommendations, created by a modified Delphi consensus study, regarding (contra)indications, patient selection, pretreatment assessment, procedure, and follow-up of IRE treatment for pancreatic malignancies. Based on the recommendations, a uniform standardized protocol has been provided as clinical guideline for IRE treatment of pancreatic cancer, to obtain the necessary basis for scientific progress and to optimize oncological outcome.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study informed consent is not required. For this type of study consent for publication is not required.

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Appendix 1 List of experts and affiliations

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Appendix 2 Items and level of agreement of the first questionnaire