Ablative Techniques in Advanced Pancreatic Cancer: Do They Affect The Quality of Life? – Review

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ABSTRACT
In advanced cases of pancreatic cancer chemotherapy is a standard treatment method without significant benefits for the overall survival rates. Over the past 15 years, the technological advances in medicine led to the development of various ablative techniques. The purpose of this review was to look through the literature to find out if quality of life was investigated in patients with advanced disease after ablation. Poor quality of life, severe pain and the use of opioid analgesics with many side effects are essential problems which could be solved by a suitable method for local tumor destruction.

INTRODUCTION
Pancreatic adenocarcinoma is worldwide the forth most common cause of cancer-related death [1]. Nowadays, it remains one of the most challenging malignant diseases in many ways. About 80-90% of patients are already locally and systemically advanced at the time of diagnosis with median survival of 3-4 months without treatment. Even with some improvements in treatment in the last 40 years, however, there has been an insignificant increase from 2% to 5-6% in 5-year survival rates. Surgical resection remains the only option for possibly curative treatment but only 5%-22% are amenable to surgery at presentation, still the 5-year survival remains less than 30% [1- 3]. The standard treatment of advanced cases includes chemotherapy or chemoradiation. The benefits in terms of improving survival (only a marginal survival benefit of 2–3 months reported) and providing palliative care (toxicity leading to side effects and complications) remain controversial and require good patient selection [1].

Pancreatic cancer (PC) patients present with systemic and gastrointestinal symptoms severely impairing their quality of life (QoL) [3]. Abdominal pain is probably the most common and distressing symptom along with weight loss and fatigue, causing anxiety and depression in most of the patients. In the course of the disease, biliary and intestinal obstruction or pancreatic insufficiency with diarrhea and vomiting complete the clinical presentation. Pain relief with opioids is often inadequate, has temporary results and many side effects. According to literature, nerve block procedures and thoracoscopic splanchnicectomy can lead to significant but very limited reduction of pain and do not improve either quality of life or survival so their value is questionable and their used as additives to opioids is advised [4, 5].

Apart from the cancer itself, different interventions during treatment also affect patients’ QoL in terms of general condition, physical, emotional and social functioning. This is why considering patients’ personal needs and durability is important. For this reason, information about the health-related quality of life (HQOL) must be taken into account apart from the routinely used objective data such as survival, remission and recurrence time, complications, respond to treatment, tumor markers etc. [3,6,7].

In inoperable advanced PC cases, providing local disease control, better survival and symptom relief can be achieved by physical destruction of the tumor with different ablation techniques. Such ablative therapies are high-intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), irreversible electroporation (IRE), iodine-125, iodine-125-cryosurgery, photodynamic therapy (PDT) and microwave ablation [8].

AIM
The aim of our review was to search through the literature if the quality of life of patients with advanced pancreatic cancer was investigated after different ablation techniques.

METHODOLOGY
A non-systematic literature search was performed through...
the PubMed, Scopus, EMBASE databases and the Cochrane Library to identify studies published before 1st April 2015, related to quality of life after ablative techniques, introduced in PC treatment. The search also included relevant information in the literature about validated instruments for evaluation of the quality of life. The ablation techniques included in the search were high-intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), irreversible electroporation (IRE), photodynamic therapy (PDT), cryoablation, and microwave. Only materials in English describing ablation in unresectable PC were selected. Review articles, original manuscripts, abstracts and clinical guidelines were included. References were also screened for any relevant studies.

**Quality of Life Evaluation**

For an aggressive disease such as PC, the treatment must not only be clinically effective, but must cause as little harm as possible [6, 10]. This is why using patients’ self-assessment and QoL evaluation as an additional criterion for patient stratification and treatment choice should be well developed. Many studies have already provided satisfactory results about baseline and treatment QoL as a prognostic factor both for survival and respond to therapy [6, 11, 12, 13]. As important as QoL is, the instruments used to evaluate it must be relevant and feasible. They range from visual analogue scales to generic and disease-specific questionnaires.

The pain response is usually measured by a numeric rating scale (0-10). Performance status in oncology is a measure for patients’ general condition or well-being and daily routine, used to determine the curative or palliative treatment necessary. In some trials it is used to try to evaluate the quality of life. The Karnofsky performance status (KPS) score is often used for evaluation of the oncology patient’s health status. In the Karnofsky score 100 is “perfect” health and 0 means death [14]. The Eastern Cooperative Oncology Group (ECOG) score is similar to the Karnofsky scale but ranges from 0 to 5 (here 0 stands for “perfect” health; 5—for “death”) [15]. The Edmonton Symptom Assessment System (ESAS) is another simple method for the assessment of palliative care patients [16].

Different instruments for QoL assessment are the Functional Assessment of Cancer Therapy (FACT) questionnaires (FACT-G and FACT-Hep) as well as the ones validated by the European Organization of Research and Treatment of Cancer (EORTC QLQ-C30 and QLQ Pan26) [13, 17, 18]. Other questionnaires are under investigation - the NIH PROMIS, the pancreatic cancer disease impact (PACADI) score and Gastrointestinal Symptom Rating Scale (GSRS) - a validated questionnaire to assess GI symptoms [19].

**High-Intensity Focused Ultrasound (HIFU)**

HIFU is a new therapeutic for the treatment of locally advanced, unresectable and systematically advanced, metastatic PC patients with no surgical excision and no blood-loss during procedure. An extracorporeal device is used to focus high-intensity ultrasound beam into a target zone of the tumor and causes local destruction with high level of precision, preserving the surrounding tissues. HIFU causes a rapid local rise in temperature over 70 degrees which leads to coagulative necrosis. HIFU also induces apoptosis at a lower dose of hyperthermia than necrosis [20, 21]. Most of the complications of HIFU reported in literature are minor and could be avoided by careful preoperative patient selection and preparation, HIFU parameter calculation and target localization as well as intraoperative monitoring [22]. Complications observed include superficial skin burns or edema, fever, insignificant gastrointestinal dysfunction and mild abdominal pain in the treated area, duodeno-pancreatic fistulas, asymptomatic vertebral body or subcutaneous fat necrosis with no need for further treatment. A major concern about HIFU is pancreatitis, caused by the physical destruction of cells [20, 21, 22]. Up to present, no deformation or occlusion after HIFU treatment is reported. Only one patient had portal vein thrombosis after HIFU [23]. Large studies in China and smaller researches in Europe have confirmed HIFU as a safe and feasible treatment option for advanced PC patients [22-31].

Significant pain relief, increased KPS, prolonged survival and restricted tumor growth are reported in almost all studies [22-33]. The median survival reported is 8-11 months in stage III and 5-6 mo in stage IV patients. All researchers report pain relief after HIFU treatment in about 80%-100% of patients [22-32]. A study showed that the average pain scores (according to VAS) on the day before treatment was 5.80±2.14, and those at 7th day after HIFU were 2.45±2.4 [32]. A significant correlation is reported between HIFU treatment and the average quantity of morphine needs. A study reported decrease of 16.8±39.7 mg for each person every day [32]. Also, common symptoms such as fatigue and loss of appetite were improved after HIFU exposure, increasing the QoL.

According to literature, a combination multimodality treatment with HIFU, chemotherapeutics, chemoradiation and immunotherapeutics could have better therapeutic outcomes such as higher level of pain relief and longer survival [33, 34, 35]. A recent study on combination treatment of gemcitabine with HIFU in locally advanced PC showed that overall survival was 12.6 mo and the estimates of overall survival at 12 and 24 months were 50.6% and 17.1% respectively. Pain was relieved in 78.6% [34]. Dimitrov et al reported pain relief from 7 to 2 out of 10 according to VAS in a patient after HIFU; combined with neoadjuvant and adjuvant chemotherapy. The authors introduced the EORTC instruments for evaluation of the QoL of PC patients. In their case report QoL assessed with the validated instruments was improved significantly. The patient survival after HIFU at the time of case report was 24 months [33]. The literature data about HIFU treatment was presented concisely in Table 1.

There are already clinical studies reporting enhanced antitumor immunity after HIFU. The immune response can be stimulated by large amount of tumor antigens in
<table>
<thead>
<tr>
<th>Ablation Method</th>
<th>PC Patients Treated</th>
<th>Complications</th>
<th>Ablation Technique</th>
<th>Ablation Apparatus</th>
<th>QoL-Assessment Tool</th>
<th>Improvement of the QoL</th>
<th>Combination with chemotherapy/ QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIFU</td>
<td>• Locally advanced</td>
<td>Mainly minor complications</td>
<td>Extra-corporeal</td>
<td>US transducer</td>
<td>EORTC, VAS, Karnofsky PS</td>
<td>• pain relief</td>
<td>• improved QoL</td>
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<td></td>
<td>• Metastatic</td>
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<td>• decreased opioid intake</td>
<td>• relieved pain</td>
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<td>• better survival</td>
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<td>• better tumor response</td>
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<tr>
<td>RFA</td>
<td>• Locally advanced</td>
<td>High morbidity in the first studies; Lower morbidity later</td>
<td>Intraoperative/ Percutaneous + palliative surgery</td>
<td>Electrode needles inside the tumor</td>
<td>NONE described</td>
<td>• pain relief</td>
<td>• better survival</td>
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<td>• better pain score</td>
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<td>• better tumor response</td>
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<tr>
<td>IRE</td>
<td>• Locally advanced</td>
<td>Moderate rate, but few reports</td>
<td>Intraoperative/ Percutaneous + general anaesthesia + neuromuscular block + cardiac synchronisation + palliative surgery</td>
<td>Electrode needles inside the tumor</td>
<td>VAS</td>
<td>• pain relief</td>
<td>• better survival</td>
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<td>• better survival</td>
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<tr>
<td>PDT</td>
<td>• Locally advanced</td>
<td>Mainly minor complications</td>
<td>Percutaneous</td>
<td>Optic fibers + photosensitizer</td>
<td>No data found</td>
<td>No data found</td>
<td>No data found</td>
</tr>
<tr>
<td>Cryo-ablation</td>
<td>• Locally advanced</td>
<td>Low rates of significant complications</td>
<td>Intraoperative/ Percutaneous + palliative surgery</td>
<td>Electrode needles inside the tumor</td>
<td>No data found</td>
<td>Few patients with pain relief</td>
<td>No data found</td>
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<tr>
<td></td>
<td>• Metastatic</td>
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<tr>
<td>Micro-wave ablation</td>
<td>Locally advanced</td>
<td>Considered mild but few reports</td>
<td>Intraoperative/ Percutaneous + palliative surgery</td>
<td>Electrode needles inside the tumor</td>
<td>No data found</td>
<td>One patient with 22m. survival</td>
<td>No data found</td>
</tr>
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</table>

HIFU high intensity focused ultrasound; RFA radiofrequency ablation; IRE irreversible electroporation; PDT photodynamic therapy; PC pancreatic cancer; US ultrasound; EORTC European organization of research and treatment of cancer; VAS visual analog scale; QoL quality of life; PS – performance status
the necrotic tissue, protein Ag determinants and heat shock protein activation by hyperthermia, local aseptic inflammation due to necrosis [36, 37].

Radiofrequency Ablation (RFA)

RFA is an ablative method for local radiofrequency-induced thermal coagulation of solid tumors under ultrasound (US) guidance during open surgery by needles with expandable electrodes, placed in the tumor. RFA has been used successfully for hepatic tumors. Recent studies have come with tentative results for unresectable locally advanced, non-metastatic PC ablation [8, 9, 38, 39, 40]. However, the number of patients treated with RFA was small in most reports.

RFA for PC was combined with palliative bypass surgery and drainage in most studies [38, 39, 40, 41, 45]. The local temperature reached up to 105 degrees as in the liver tumor ablation. The early applications of RFA in the pancreas were associated with very high rates of morbidity related to RFA (4-37%), overall morbidity (10%-40%) and mortality (0%-25%) [38, 39, 40]. Median survival after RFA was 3-33 months, in most studies around 16 months [38, 39, 40, 41]. Frequent complications were fluid collection, pancreatic fistula, duodenal perforation and vascular damage, digestive or abdominal bleeding, infections or abscesses [38, 39, 40, 41, 42]. Severe acute pancreatitis was a rare complication. In a study with 20 cases, two patients died from severe complications - septic shock and gastrointestinal bleeding [42]. In later RFA applications the temperature goal was decreased to <90 °C at the RFA probe tip and sufficient distances between the probe and surrounding structures as well as local cooling was ensured [43, 44]. While some studies reported a significant decrease in morbidity, others still had some tentative results.

In all studies RFA led to tumour necrosis and tumor cytoreduction [38-44]. Authors observed promising results in pain relief (in 50% of cases in one study, and in 68% according to another) and decreased analgesia requirements [38-43].

Some studies came out with survival of those who received chemotherapy after RFA reaching 25.6 months. These results are suggestive of better outcomes of combined local control and systemic treatment but further research is needed [53]. RFA combined with 125Iodine seed implantation for unresectable pancreatic tumors was reported as a feasible and safe option with better tumor responses, significantly decreased tumor marker levels and pain score. In this study, the median survival time of 32 patients was 17.5 months, and 20months for the group receiving chemotherapy against 16months for the group with no chemotherapy [54]. Some authors suggested RFA as an alternative to the conventional phenol and alcohol neurolytic splanchic nerve block methods thanks to the well-known neuroanatomy and accurate needle placement [55]. There was no QoL instrument implemented in the RFA studies (Table 1).

Irreversible Electroporation (IRE)

Irreversible electroporation (IRE) is a non-thermal ablation technique using short electrical pulses between needles around the tumor, placed after laparotomy or through the skin under US guidance [56]. It is performed under general anesthesia with neuromuscular blockade to avoid muscle contractions. IRE has been performed in locally advanced, surgically unresectable, non-metastatic cases. One of the main concerns and now a patient exclusion criterion is a metal stent in the bile duct. A case report described severe complications including bowel perforation and bleeding from a branch of the superior mesenteric artery leading to death after IRE in the head of the pancreas close to a metal stent [57]. A review of 4 studies with 74 patients in total reported morbidity from 0 to 33% and significant survival benefit: overall survival in matched IRE group - 20months, and non-IRE group - 11 months. A moderate rate of complications from IRE is reported up to present but the studies are still few with a small number of patients [8, 9, 56]. A study of 27 patients (with IRE; IRE+ resection; IRE+ palliative surgery) demonstrated 90 days after treatment some palliation of pain, assessed by VAS (pain score from 5 to 3) and reduction of narcotic use (from median 75 mcg to 25 mcg fentanyl per day) [57]. There is still no specific data about quality of life, affected by IRE (Table 1).

Microwave Ablation

Microwave ablation is a local thermal ablative method, used safely in liver tumors. Studies for its use in locally advanced, non-metastatic PC cases are few. It is based on microwave currents from antennae percutaneously or most often intraoperatively inserted into the tumour during palliative bypass surgery under imaging guidance [8, 9, 58, 59]. The largest study up to present included 15 patients and there were minor complications were reported in 40%, namely asymptomatic pancreatitis, ascites and minor bleeding. One patient had a survival of 22 months [59]. Quality of life, including pain relief was not assessed with a validated tool (Table 1).

Cryoablation

Cryotherapy is a technique for argon-gas-based freezing of unresectable pancreatic lesions to -160 °C by probes placed in the pancreas intra-operatively or percutaneously under US guidance. Safety margins and simultaneous palliative bypass procedures are brought to attention here too. Studies report prolonged survival with low rates of significant complications [8, 9, 61, 62, 63] A study revealed median overall survival in a combined cryoimmunotherapy group of 13months compared to chemotherapy group - 3.5 months [64]. Pain control is assessed in few patients with some positive results for alleviating the pain symptoms [62-63]. The effects on Qol. have not been described yet (Table 1).

Photodynamic Therapy (PDT)

Photodynamic therapy causes predictable destruction of tumor cells, photosensitized with special substances and
exposed to light from optic fibers, placed percutaneously under image guidance. A study of 16 patients reported median survival of 9.5 months. In two cases bleeding from the gastrointestinal tract was observed. Photosensitiveness and danger of skin necrosis was a major concern in the first clinical trials, nowadays successfully avoided by new generations of photosensitzers [8, 9, 65, 66].

**DISCUSSION**

Based on the review data, we can outline several problems. Firstly, there is no standardized method for dynamically evaluating the QoL of PC patients, treated with ablative techniques. The development of a method improving the QoL would lead to a positive change in the really grim statistics for this type of cancer, so establishing a trustworthy instrument for evaluation is important. Another problem which was also a major discussion topic during the American Society of Clinical Oncology (ASCO) annual meeting 2013 was whether quantity or quality of life must be the treatment goal in patients with advanced PC. It was underlined that clinical response to chemotherapy does not automatically correlate with improved QoL of patients. Also poor quality of life is associated with a low response to chemotherapy [6]. The literature review shows that technological progress is now capable of successfully combining chemotherapy with local ablation of the tumor in the pancreas. The combination of physical destruction with chemotherapy could not only lead to prolonged survival but also to improved QoL. This beneficial effect may be associated with decreased pain, reduced dose of morphine derivatives, increased total immunity and some antibodies, etc. Last, but not least it is a discouraging fact for patients to know that they are left on palliative chemotherapy without a real opportunity for treatment. Considering the up-to-date studies, it can be concluded that for an ablative method to achieve its goal to increase QoL, it should cause possibly the most minimal trauma and/or to be non-invasive; have minimal complications; should lead to pain relief after treatment; achieve tumor necrosis; provide accuracy and precision as well as image-guided control. It should be borne in mind that most ablation techniques have restrictions in the treatment indications and cannot be used in all cases with advanced PC. Most authors carry out a serious patient selection for successful implementation of the techniques into the clinical practice [8, 9, 20, 27, 38, 39, 56]. Ablative therapies in patients with advanced pancreatic cancer seem to be feasible and safe [8, 9]. Quality of life assessment is still a secondary goal in most researches.

**CONCLUSION**

None of the ablative techniques is a standardized method for pancreatic malignancies yet, but studies have proved them safe and feasible with different rates of complications. Survival outcomes as well as benefits for quality of life need further investigation. There is not yet a standardized method for QoL evaluation in ablative treatment. Multimodality treatment with chemotherapy and ablation methods should seem to better outcomes in advanced PC cases.

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**Conflict of interest**

Authors have no conflicts of interest

**References**


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