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Triple approach strategy for patients with locally advanced pancreatic carcinoma

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Abstract

Background: Radiofrequency ablation (RFA) is a relatively new technique, applied to metastatic solid tumours which, in recent studies, has been shown to be feasible and safe on locally advanced pancreatic carcinoma (LAPC). RFA can be combined with radio-chemotherapy (RCT) and intra-arterial plus systemic chemotherapy (IASC). The aim of this study was to investigate the impact on the prognosis of a multimodal approach to LAPC and define the best timing of RFA.

Methods: This is a retrospective observational study of patients who have consecutively undergone RFA associated with multiple adjuvant approaches.

Results: Between February 2007 and December 2011, 168 consecutive patients were treated by RFA, of which 107 were eligible for at least 18 months of follow-up. Forty-seven patients (group 1) underwent RFA as an up-front treatment and 60 patients as second treatment (group 2) depending on clinician choice. The median overall survival (OS) of the whole series was 25.6 months: 14.7 months in the group 1 and 25.6 months in the group 2 ($P = 0.004$). Those patients who received the multimodal treatment (RFA, RCT and IASC-triple approach strategy) had an OS of 34.0 months.

Conclusions: The multimodal approach seems to be feasible and associated with an improved longer survival rate.

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Introduction

Pancreatic cancer is usually associated with an unfavourable outcome in spite of multiple approaches. Its poor prognosis is related to an aggressive biological behaviour and to the high rate of metastatic stage at diagnosis.

Surgery with radical intent can be applied in 20% of patients with pancreatic cancer whereas the remainder are usually considered for palliative adjuvant therapy. The addition of chemotherapy has achieved only a modest survival benefit leading to the evaluation of novel interventions.[1–6] The evidence of an unexpected high rate of recurrence after resection even for early stage disease suggests that pancreatic adenocarcinoma is a systemic disease from the outset.[7] Locally advanced pancreatic carcinoma associated with vascular involvement, is still a matter of debate in terms of definition and better therapeutic approaches. Many therapeutic options have been suggested: extended radical surgery with vascular grafts, aggressive chemo and/or radiotherapy and ablative therapies but a definitive protocol has not yet been approved.

RFA is a relatively new technology, which is usually applied to unresectable solid tumours for palliation. RFA applied to locally advanced pancreatic carcinoma has shown to be feasible and safe.[8,9] Up until now, systemic chemotherapy followed by radiotherapy represents the gold standard treatment.[10] Radio-chemotherapy (RCT) can increase local control of the disease and intra-arterial chemotherapy has been considered to reduce progression in the

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liver.[11–14] The primary aim of the study was to test different treatments associated with RFA in locally advanced pancreatic cancer patients to determine whether this is an effective multimodal approach. The secondary aim was to investigate the role of intra-arterial and systemic chemotherapy (IASC) combined with ablative debulking by RFA.

Patients and methods

All consecutive patients affected by a histologically proven locally advanced pancreatic cancer presenting to the Pancreatic Unit, Pederzoli Clinic, Peschiera del Garda (VR) were enrolled for RFA from 1st February 2007 to 31st December 2011. Application of RFA in this context was approved by the Ethical Committee of Verona University and a local committee. Written informed consent was obtained from all patients. Information on all patients was recorded on the unit database.

Patients were included with the following criteria: age between 18 and 80 years, pre-operative staging [ultrasonography (US), abdominal computed tomography (CT) or magnetic resonance imaging] diagnostic for an unresectable non-metastatic pancreatic solid mass, pre-treatment cytology positive for pancreatic carcinoma on expert pathologist opinion, the absence of distant metastases and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria were: contraindications to surgery and the presence of multiple pancreatic lesions, and metastatic disease. Pre-treatment evaluation included medical history, physical examination, body weight, complete blood cell count, biochemical profile, a carbohydrate antigen 19-9 (CA 19-9) value and electrocardiogram. Follow-up, including clinical examination, body weight, complete blood cell count, biochemical profile, CA 19-9 level, abdominal US and CT, was planned after 30 days and every 3 months thereafter.

Treatments

The RFA procedure has been widely described in a previous paper.[8] During a laparotomy, exploration of the peritoneal cavity is performed to detect misdiagnosed metastatic malignancies and intra-operative US is utilized to confirm unresectability and to exclude liver metastases. A biliary and/or gastric bypass was performed for jaundice and/or duodenal obstruction when required. A soft abdominal drain was left near the site of RFA probe insertion to detect pancreatic fistulae. After the procedure, patients were assessed daily for evidence of acute pancreatitis, bleeding, pancreatic fistulae and infection.

Patients were considered for different adjuvant approaches depending on clinician choice and general conditions. Radiotherapy was delivered as an external beam radiation at a dose of 54.0–59.4 Gy. Chemotherapy involved the use of gemcitabine administered weekly on Tuesdays and Fridays at a daily dose of 40 mg/m^2 through the entire course of radiotherapy. Gemcitabine was suspended for haematological toxicity greater than grade 1 until haematological recovery occurred.

Intra-arterial chemotherapy combined with systemic chemotherapy consisted of: day 1, epirubicin 35 mg/m^2 and cisplatin 42 mg/m^2 via the coeliac axis by bolus injection through a catheter inserted in the femoral artery. Gemcitabine was administered on day 2 of each cycle at a dose of 1000 mg/m^2 (intravenously, over 30 min). Capecitabine was given orally at the dose of 650 mg/m^2 twice a day, on days 2–15. Cycles were repeated every 28 days until progression of disease, unacceptable toxicity or withdrawal of patient consent. Gemcitabine and capecitabine doses were reduced by 25% if either grade 2 neutropenia or thrombocytopenia occurred. Treatment was delayed for a maximum of 2 weeks if neutropenia, thrombocytopenia, anaemia or non-haematological toxicity of grade 3 or more was present. In the case of grade 4 neutropenia and/or thrombocytopenia, the doses of gemcitabine and capecitabine were reduced by 25% in subsequent cycles. Toxicity assessment and the measurement of haematological function were performed weekly. Renal and hepatic function was checked before each cycle. Systemic chemotherapy consisted of gemcitabine alone (1000 mg/m^2) given on a weekly basis or combined with cisplatin (75 mg/m^2 every 3 weeks) or oxaliplatin (100 mg/m^2 on day 2 every 14 days).

Patients were divided into two groups: group 1 included those submitted to RFA as up-front treatment and group 2 included those who received RFA as a secondary treatment.

Statistics

Overall survival (OS) was calculated from the date of the diagnosis to death from any cause using Kaplan–Meier survival analysis. The median survival value and 95% confidence interval was calculated. Uni- and multivariable variable analyses, using log-rank[15] and logistic regression[16] methods, were performed to identify factors related to survival. Statistical analysis was performed using the statistical package SPSS for Windows, version 13.0 (SPSS Inc., Chicago, IL, USA). *P*-values of less than 0.05 were considered statistically significant.

Results

Between February 2007 and December 2011, 168 consecutive eligible patients with locally advanced pancreatic adenocarcinoma underwent RFA. In total, 107 patients were eligible for at least 18 months of follow-up. Patients were divided into two groups (Fig. 1): group 1 (47 patients) included those referred for RFA as a primary treatment; and group 2 (60 patients) those who underwent RFA after other treatments. Post-operative treatments of group 1 were: chemo-radiotherapy (25 patients), chemotherapy (15 patients), chemo-radiotherapy + IASC (3 patients) and IASC alone (1 patient). Pre-operative treatments of group 2 were: chemotherapy (47 patients), chemo-radiotherapy (7 patients), chemo-radiotherapy + IASC (4 patients), chemotherapy + IASC (1 patient) and IASC (1 patient). Post-operative treatments after RFA were: chemo-radiotherapy (20 patients), chemotherapy (18 patients), chemo-radiotherapy + IASC (11 patients) and IASC (11 patients).

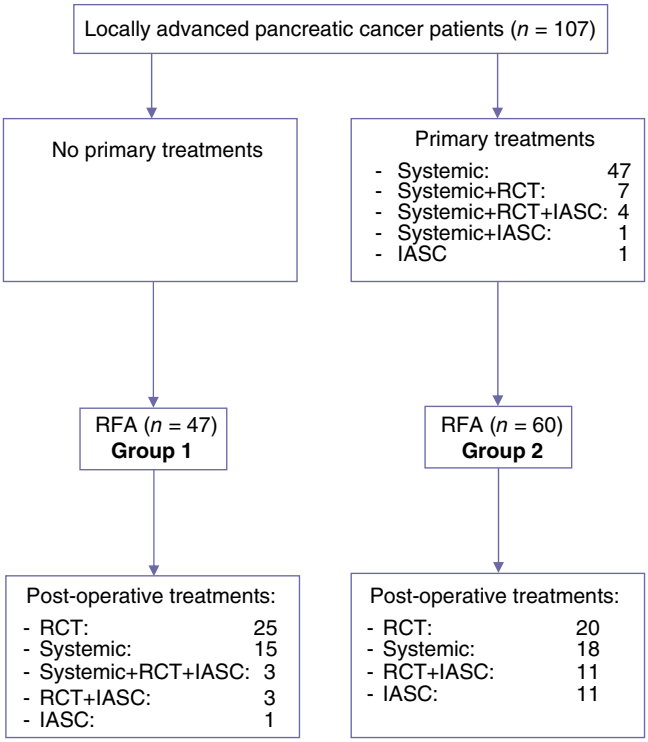

Figure 1 Flow diagram. RFA, radiofrequency ablation; RCT, radiochemotherapy; IASC, intra-arterial chemotherapy combined with systemic chemotherapy

Patient characteristics are summarized in Table 1. RFA-related complications are summarized in Table 2. The overall post-operative mortality rate was 1.8%: one death from hepatic failure after a long course of chemotherapy and one death from sepsis after a duodenal perforation. The post-operative course was uneventful in 75.0% of patients. The overall morbidity rate was 28.0% of which the abdominal complications rate was 26.1%. Among these, 17.7% were considered RFA-related complications caused by thermal injuries. Specific morbidity related to surgery was 8.4%. Four patients (3.7%) developed multiple complications and in two of these patients a re-laparotomy was necessary because of intra-abdominal bleeding.

Neoadjuvant therapies did not affect the complication rate ($P = 0.2$). A temperature >90°C applied to the tumour was found to be the only independent factor related to complications. No differences in terms of the number of applications, type of needle and time of procedure were found to be relevant.

Among patients receiving RCT, 1/73 (1.3%) developed grade 3 haematological toxicity requiring a 1-week rest period, 10/73 (13.6%) developed grade 2 haematological toxicity and 14/73 (19.1%) grade 2 gastrointestinal toxicity. One patient (1.3%) developed grade 3 gastrointestinal toxicity.

Of the IASC patients, haematological toxicity was the most common complication that developed in 25/35patients (71.4%), with 8/35 (22.8%) of grade 3–4 neutropenia without febrile complications; grade 3–4 thrombocytopenia in 6/35 (17.1%) without bleeding; and grade 3 anaemia in 2 patients (5.7%).

Among the non-haematological toxicities, 4/35 (11.4%) developed grade 2 mucositis, 4/35 (11.4%) grade 2 nausea and vomiting, 3/35 (8.6%) grade 2 hand and foot syndrome and mild cisplatin-related peripheral sensory neurotoxicity in 4/35 (11.4%). No toxicity related to the angiographic procedure was observed.

The median OS was 25.6 months (19.3–31.9). Fifty-three patients had an OS greater than 20 months. Four patients were resected after the new multimodal protocol: 2 patients died from disease at 28 months, one is currently progression free after 47 months and one is disease free after 51 months. Patients in group 1 presented with a median survival of 14.7 months (11.3–18.1) compared with 25.6 months (16.1–35.1) in group 2. The 32 patients undergoing the triple approach strategy had a median survival of 34.0 months (29.1–38.9), compared with an OS rate of 18.4 months (13.3–23.5) in all other patients.

Discussion

Pancreatic cancer has been found to be one of the most aggressive tumours with a very high rate of early progression(s). Locally advanced stages have been treated so far with multiple approaches such as aggressive surgery with vascular grafts and multiple chemo-radiotherapy schemes but prognosis still remains very poor.

In spite of all the disheartening results, OS should be the primary end point of clinical trials, especially in series of poor prognosis patients, as in pancreatic cancer. Both Evaluation Criteria in Solid Tumours (RECIST) and WHO criteria, which consider volume reduction as a positive response, are inadequate for pancreatic cancer and they are not related to effective prognosis. Furthermore, progression-free survival, although very important in the definition of the best chemotherapy approach, can introduce additional bias related to the wide variability in terms of time to diagnosis. With such a large number of variables, a single-arm study can usually be conducted and in keeping with the data from the literature as a control arm.[1,17]

The OS of the whole group of 25.6 months was encouraging but patients treated with RFA as an up-front treatment had a poorer OS compared those who received RFA as second-line treatment. Pre-operative chemotherapy allows the identification and exclusion of patients with an early progression of disease and who most likely represent a non-responder category to treatment and inappropriate candidates for invasive treatments. This does not necessarily imply that chemotherapy before RFA adds a statistical bias of selection but, instead, given that 30% of patients with LAPC have occult metastases at diagnosis, chemotherapy could actually represent the best option.[10]

The morbidity rate related to associated surgery was 8.4% in keeping with the literature related to surgical palliation of pancreatic cancer.[18] RFA-related complications do not differ between

Table 1 Patients characteristics

	RFA up-front (Group 1: *n* = 47)	RFA secondary treatment (Group 2: *n* = 60)
Median age (years)	68.9 (53.0–83.0)	60.3 (44.7–77.5)
Gender ratio (M : F)	26:21	34:26
Tumour site		
Head	31	43
Body-tail	16	17
Median tumour size (mm)	40.0 (15.0–65.0)	35.0 (15.0–70.0)
Baseline CA 19-9 (u/ml)	186 (4–3540)	132 (1–2555)

RFA, radiofrequency ablation; CA 19-9, carbohydrate antigen 19-9.

Table 2 RFA complications

	n patients
Abdominal complications	
RFA related	
Pancreatic fistula	6 (5.6%)
Acute pancreatitis	3 (2.8%)
Portal vein thrombosis	5 (4.7%)
Duodenal injury	3 (2.8%)
Other	2 (1.9%)
Surgery-related	
Biliary fistula	4 (3.7%)
Haemoperitoneum	2 (1.9%)
Other	3 (2.8%)
Systemic complications	
Liver failure	1 (0.9%)
Psychosis	1 (0.9%)

RFA, radiofrequency ablation.

those who underwent RFA as an up-front or secondary treatment. No other factors were found to be relevant in predicting complications. The temperature applied to the tumour seems to be the only important consideration (90 °C instead of 105 °C, as normally applied to liver metastasis).[8] Cumulative toxicity was not found to be related to the multiple associations of drugs and therapies.

Chemo-radiotherapy has been shown to be effective in local disease control.[19] Conceptually, the presence of a viable tumoural residue at the periphery of the treated area represents a peculiar aspect of the procedure, in which ablation must respect a 'security edge' to avoid thermal injury to nearby organs and vessels.[9] Radiotherapy is proposed to treat, in particular, the viable residue. Another important factor to take into account is that RFA, by destroying the tumour using thermal coagulation and protein denaturation, leads to apoptosis which enhances the immune response by recruiting immune cells and releasing tumour antigens.[20,21] It has been found that thermal ablation of solid tumours triggers an anti-tumour-specific immunity response which can be very effective in a primary tumour and in metastasis control. Based on this evidence, RFA could hypothetically act as an enhancer of additional therapies.

The pharmacological rational for regional drug delivery is to increase drug concentrations at tumour sites and reduce complications owing to systemic drug exposure.[22] In a phase III study, an intra-arterial four-drug regimen (5-fluorouracil, folic acid, epirubicin and carboplatin) improved the OS in patients with LAPC compared with systemic gemcitabine.[23] A similar four-drug approach (intra-arterial epirubicin and cisplatin plus systemic gemcitabine and capecitabine) has also shown to be well tolerated as a second-line treatment.[24–26]

The triple approach strategy (RFA plus RCT plus IASC) is a new multi-step therapeutic approach with a good overall median survival of 34 months and represents one of the longest survival rates for LAPC reported in literature. In the past 20 years, a large number of patients have been treated in several randomized-controlled phase III trials, even although the real benefit in term of survival still remains very poor, with a median OS ranging from 8 to 13 months.[1,27]

The decision to give systemic chemotherapy rather than IASC was based on the clinician's choice, and may have added further bias thereby limiting the conclusions that can be made. Further studies are planned to confirm the feasibility and efficacy of this triple approach as well as basic science investigation of the hypothetical immunity reactions.

In conclusion, systemic chemotherapy plays an important role as an up-front treatment of locally advanced pancreatic carcinoma. RFA has to be applied in all patients with stable disease after a short neoadjuvant treatment. Conceptually, radiotherapy is mandatory to complete the destruction of the whole tumour or, at least, to keep under control the viable safety residue. All patients with good response need to be addressed to IASC after the previous steps.

A randomized controlled trial is planned to define the real impact of RFA on prognosis compared with traditional approaches.

Conflicts of interest

None declared.

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