



The addition of deep hyperthermia to gemcitabine-based chemoradiation may achieve enhanced survival in unresectable locally advanced adenocarcinoma of the pancreas



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ABSTRACT

Introduction: Driven by the current unsatisfactory outcomes for patients with locally advanced pancreatic cancer (LAPC), a biologically intensified clinical protocol was developed to explore the feasibility and efficacy of FOLFORINOX chemotherapy followed by deep hyperthermia concomitant with chemoradiation and subsequent FOLFORINOX chemotherapy in patients with LAPC.

Methods: Nine patients with LAPC were treated according to the HEATPAC Phase II trial protocol which consists of 4 cycles of FOLFORINOX chemotherapy followed by gemcitabine-based chemoradiation to 56 Gy combined with weekly deep hyperthermia and then a further 8 cycles of FOLFORINOX chemotherapy.

Results: One grade three related toxicity was reported and two tumours became resectable. The median overall survival was 24 months and 1 year overall survival was 100%.

Conclusions: Intensification of chemoradiation with deep hyperthermia was feasible in nine consecutive patients with LAPC.

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1. Introduction

The incidence and mortality of pancreatic ductal adenocarcinoma (PDAC) are similar and this highly fatal disease has a 5 year survival rate of only 5% [1]. 50% of patients have metastatic disease at diagnosis and 30% present with locally advanced non-metastatic but inoperable pancreatic cancer (LAPC) [2] which has a median overall survival (OS) of 15 months [3]. At presentation, 10–20% of cases qualify for surgical resection, which is the only curative treatment option. The high percentage of patients presenting with LAPC and the frequent microscopic incomplete resections provide a strong rationale for clinical research into increasing the efficacy of non-surgical therapies. In 2013, a comprehensive review and meta-analysis regarding neoadjuvant therapies in LAPC summarised the limited evidence that combination chemotherapy

(CT) might induce resectability in up to 30%–40% of patients with LAPC [4]. Gemcitabine has long been the chemotherapeutic agent of choice [5] and chemoradiation (CRT) is the standard modality after induction chemotherapy in LAPC.

Clinical hyperthermia is a unique multifaceted, therapeutic modality that achieves cytotoxicity and radio- and chemosensitisation and is also an immunomodulator akin to *in situ* tumour vaccination [6]. Meta-analyses and network meta-analyses have confirmed the greater efficacy of thermoradiotherapy over radiotherapy and the lack of significant additional toxicity in various tumour entities [7–10]. Gemcitabine is a proven radiosensitiser due to reduced radiotherapy-induced DNA repair, S phase cell cycle arrest and the triggering of apoptosis [11]. Furthermore, HT has been shown to sensitise the effects of gemcitabine at 43 °C. This has been best observed if gemcitabine is given 24 h after HT [12]. Hyperthermia increases the cytotoxicity of gemcitabine in human pancreatic cancer cell lines [12,13] and thus a combination of HT, RT and gemcitabine would lead to triple sensitisation: thermal sensitisation of RT, thermal sensitisation of gemcitabine [14]

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and radiosensitisation by gemcitabine. A concurrent approach of gemcitabine, RT and HT (HTCRT) merits evaluation in LAPC and has been previously explored in a prospective single arm study reporting a median OS of 15 months and a 1 year OS of 67% [15].

Driven by the current unsatisfactory outcomes for patients with LAPC, a biologically intensified clinical protocol was developed to explore the feasibility and efficacy of FOLFIRINOX chemotherapy followed by HTRC with gemcitabine and additional FOLFIRINOX chemotherapy in patients with LAPC.

2. Methods

Patients were treated according to the previously published ethics-approved protocol (HEATPAC Phase II trial, ClinicalTrials.gov: NCT02439593) [16] after the tumour was deemed inoperable [17] at a multidisciplinary tumour board. Between 06/2015 and 01/2019, nine patients with LAPC were identified and treated according to protocol. 7 of the 9 patients could not be included in the HEATPAC study as they either (a) were treated before the start of the HEATPAC study to check feasibility and logistics ($n = 2$), or (b) had been already started on pre-HTCRT chemotherapy with FOLFIRINOX at other centres ($n = 5$) or (c) they did not fulfil the inclusion criterion of M0 disease ($n = 2$) due to suspicion of low volume metastases. Patients were commenced on 4 cycles of FOLFIRINOX chemotherapy on a two weekly schedule [18]. CT, MRI or PETCT imaging was repeated four weeks after completion of chemotherapy and the resectability of the tumour was re-evaluated. In the event of persisting inoperability, patients received photon radiotherapy with 28×1.8 Gray (Gy) = 50.4 Gy to the clinical target volume, with a simultaneous integrated boost to the gross tumour volume and any involved regional lymph nodes to 56 Gy, delivered daily over 5.5 weeks with a VMAT technique combined with gemcitabine chemotherapy 400 mg/m² weekly [16].

HT was delivered at Kantonsspital Aarau, Switzerland and regular quality assurance was carried out in accordance with European Society of Hyperthermia Oncology (ESHO) guidelines for clinical studies in regional deep HT [19,20]. Deep HT was delivered with the BSD 2000 unit with the Sigma-60 or Sigma-Eye phased array applicator (M/s Pyrexar Medical, Salt Lake City, Utah, USA). To define the HT treatment volume, a planning CT was carried out in the HT treatment position on the HT planning support (hammock) adapted for CT. The tumor and the adjacent normal structures were contoured on these scans. The HT treatment planning target volume was based on the radiotherapy PTV/CTV and planned using the HT treatment planning Sigma HYPERPLAN software (M/s Dr. Sennewald Medizintechnik GmbH, Munich, Germany) by segmentation and creation of a grid model of the various body tissues according to their dielectric properties (e.g. tumor, intestine, abdominal organs, muscle, bone, fat) followed by simulation of the electric fields. Suitable power and steering parameters were used to generate a specific absorption rate distribution in the target volume using finite element modeling. A warm-up heating phase of 30 min followed by 60 min of HT treatment were applied.

Prior to each hyperthermia session, a multisensor (8 sensors) thermometric probe (FISO, FISO Technologies Inc. Quebec, Canada) was placed endoscopically in the C-loop of the duodenum. The position of the probes was checked under fluoroscopy and with a CT scan to ensure correct placement adjacent to the primary tumor. Direct intratumoral temperature measurements were not possible without undue risk to the patients, thus the temperatures recorded approximated those achieved in the tumor. Maximum power, ranging between 650 and 750 W (median: 700 W), was delivered according to the tolerance of the patient and

temperature was continuously recorded during the heating session. Eight cycles of two weekly FOLFIRINOX chemotherapy [18] were commenced four weeks later and imaging was performed three months after completion of therapy.

Response assessment: Response was assessed by comparing the pre-treatment tumor volume and metabolic activity with measurements taken 4 weeks after completion of radiotherapy.

Therapeutic response was assessed by PET-CT and MRI and contrast-enhanced CT in addition if available. Radiological response was evaluated as per the revised Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1) [21] and the metabolic response according to the PERCIST criteria [22].

Statistical analysis: Survival analysis was performed using Kaplan-Meier statistics. All survival estimates were computed from the first day of FOLFIRINOX chemotherapy. Progression-free survival represented the length of time during and after the treatment of disease, during which the patient had either complete, partial or stable response as defined in the “response assessment”. Progressive disease and death due to any cause irrespective of the disease status were considered as events for calculation of PFS. The overall survival period was computed from the first day of FOLFIRINOX until last follow-up or death. Death due to any cause was considered as an event for overall survival.

3. Results

Follow-up data were available for all nine patients and are summarised in Table 1. Seven patients received the planned four cycles of neoadjuvant FOLFIRINOX, one received five and one received nine. All tumours were subsequently restaged and remained inoperable according to radiological criteria and discussion at a multidisciplinary team meeting. Nine patients received subsequent RT (eight to 56 Gy and one patient to 50.4 Gy) combined with gemcitabine and hyperthermia. The median temperature recorded on the endoscopic duodenal probe during delivery of hyperthermia was 39.9 °C (39.1–40.8 °C). The RT boost was omitted in one patient due to grade 3 nausea and vomiting. Another patient received only 2 cycles of gemcitabine and 2 sessions of hyperthermia due to rapidly increasing ascites of uncertain origin which resolved completely.

A PETCT scan was scheduled after completion of first line FOLFIRINOX chemotherapy and after completion of HTRC to assess response and resectability according to the PERCIST criteria [22]. Paired scans were available in 8 of 9 patients. The PET scans after FOLFIRINOX chemotherapy showed a metabolic partial remission (PR) in 6/8 patients and stable disease (SD) in 2/8 patients. A PETCT scan repeated 3 months after completion of HTRC showed that 4/8 patients achieved a metabolic complete response (CR), 1/8 a PR and 3/8 SD when compared with the post chemotherapy PETCT scan. Two tumours became resectable and the postoperative stages were ypT0 ypN0 (pCR) and ypT2 ypN0 (pPR). Five patients received between 1 and 12 cycles of additional FOLFIRINOX chemotherapy and two patients subsequently received palliative gemcitabine chemotherapy at disease progression. As of 20th September 2020, two patients are alive and seven have died.

All nine patients (100%) were alive 1 year after commencing induction chemotherapy and five of nine patients (56%) were alive 2 years from the same time point. The median OS was 24 months (95% CI 21.2–26.8 mths) (Fig. 1a), which remained unchanged when the two patients with resected tumours were excluded. One of the two patients with a complete pathological response and a R0 resected tumour is still alive with no evidence of disease 34 months from start of induction chemotherapy, despite M1 disease (a solitary liver metastasis, later resected) at diagnosis. The second patient with M1 disease survived 1 year. Median

Table 1
Patient demographics.

Gender	Age	TNM	No. of cycles FOLFORINOX pre HTCTRT	Total RT dose (Gy)	Total no. of hyperthermia sessions	Maximum Recorded endogastric hyperthermia (°C)	Toxicity CTC AE v5.0	No. of cycles FOLFORINOX post HTCTRT	Further therapy	PFS from start of neoadj. chemo (mths)	OS from start of neoadj. chemo (mths)
M	68	T3N1M0	4	56	2	39.9	Abdominal pain Gr 2	0	SBRT of lung metastases	4	34
M	77	T4N1M0	5	56	6	40.0	Nausea Gr 1 Diarrhoea Gr 1	4	Nab-Paclitaxel/ Gemcitabine	12	17
M	81	T4N0M0	4	56	4	40.5	Abdominal pain Gr 1	8		21	24
M	44	T3N1M1	4	56	6	38.7	Vomiting Gr 1	2	Pancreatico-duodenectomy	29	30
F	58	T2N1M1	4	56	5	39.1	Abdominal pain Gr 1 Nausea Gr 1	8	Gemcitabine	11	13
F	56	T4N1M0	4	56	6	40.8	Nausea Gr 2 Diarrhoea Gr 1	1	Pancreatico-duodenectomy	11	22
M	70	T3N1M0	4	56	4	39.8	Vomiting Gr 2	0		16	18
M	79	T3N1M0	4	56	6	39.2	Abdominal pain Gr 1 Gastric ulceration Gr 2	4		29	29
F	60	T4N1M0	9	50.4	5	39.9	Nausea Gr 3	0	Nab-Paclitaxel/ Gemcitabine	15	24

radiological progression-free survival was 15 months (95% CI 6.2–23.7 mths) (Fig. 1b) and 1 year PFS was 64.8%. Most patients reported transient Grade 1–2 nausea and abdominal discomfort during HTCTRT and one patient required antiemetics and hydration for grade 3 nausea (Table 1). The ascites in the above-mentioned patient disappeared within months after completion of treatment.

4. Discussion

We report the results of nine consecutive patients treated with an intensified HTCTRT regimen designed for optimal biological interaction between all three therapeutic modalities. The median overall survival of 24 months reported here appears superior when compared with recent trials of photon-based chemoradiation.

Pancreatic cancer is notable for its resistance to photon radiotherapy, chemotherapy and targeted therapies. Chemoradiation has long been used in locally advanced pancreatic cancer in attempt to render tumours operable or achieve local control. The LAP07 study has called the radiation component into question however, as overall survival with gemcitabine-based chemoradiation to 54 Gy (15.2 months) was not superior to that observed with gemcitabine chemotherapy alone (16.5 months) [23]. A similar median OS of 15 months has recently been reported in the interim analysis of the CONKO-007 randomised trial of chemotherapy versus chemoradiotherapy in inoperable pancreatic cancer [3]. One clinical trial of photon chemoradiation compared with chemoradiation and hyperthermia has been published previously. Maluta et al. reported a comparative cohort trial of 68 patients treated with 3-D radiotherapy between 30 Gy in 10 fractions and 66 Gy in 33 fractions combined with gemcitabine alone or with oxaliplatin, cisplatin or 5-fluorouracil, with or without twice-weekly deep hyperthermia. The overall survival in the first group was 11 months and was 15 months in the hyperthermia group ($p = 0.025$) without additional toxicity, demonstrating feasibility

and suggesting a modest but significant overall survival benefit from hyperthermia [15]. Of note, some of the patients received only a palliative dose of radiotherapy. Two small trials of gemcitabine and regional hyperthermia have been reported. In patients with LAPC and metastatic pancreatic cancer, median survival was 17.7 months in 6 patients with M0 disease [24] and 15 months was following sequential gemcitabine and cisplatin combined with hyperthermia [14].

The present study used intraduodenal temperature instead of intratumoral thermometric measurements. This pragmatic thermometric assessment was chosen to be safe and acceptable to the patients during the 6 weeks of treatment. A multisensor probe with 8 sensors (at 2 cm intervals) was placed in the C-loop of the duodenum prior to each weekly hyperthermia session. This provided information regarding the locoregional temperature in the heated volume. Invasive thermometry for intratumoral measurement would have been limited to one or few thermal sensors and would only represent the temperature adjacent to the tip of the probe. Our centre presently has no facilities for non-invasive thermometry using MRI. Moreover, non-invasive thermometry has challenges associated with pancreatic motion [6].

Investigations into alternative forms of irradiation with protons and carbon ions in LAPC have been recently published. 42 patients received proton beam irradiation combined with gemcitabine chemotherapy, 32 of whom also received hyperthermia. OS from the initial treatment was 84.5% at 1 year and 58.7% at 2 years with a median OS of 27.5 months and 2 patients (4%) became resectable [25]. In a trial of carbon ion therapy in 72 patients with LAPC, the majority received induction and concurrent gemcitabine chemotherapy, and OS rates were 73% at 1 year, and 46% at 2 years with a median OS of 21.5 months [26]. Both series report superior outcomes to photon CRT and the median OS are very similar to the HEATPAC series. Indeed it has been suggested that hyperthermia could modify the radiobiological properties of photons to resemble

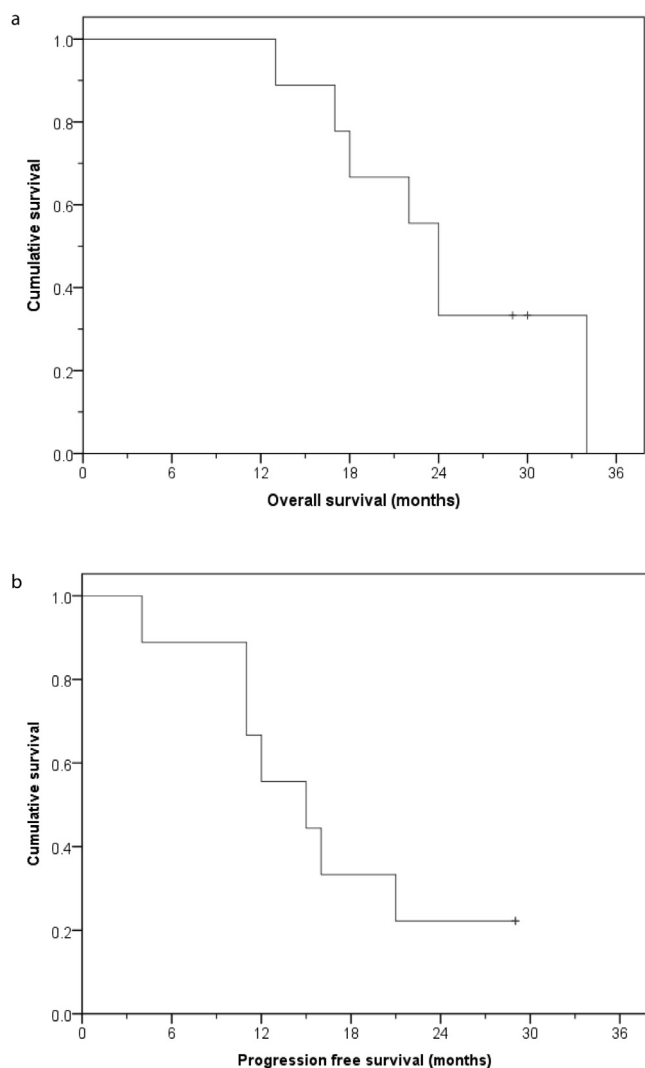


Fig. 1. According to the Kaplan-Meier curves, median overall survival was 24 months (95% CI 21.2–26.8 mths) (Fig. 1a) and median progression-free survival was 15 months (95% CI 6.2–23.7 mths) (Fig. 1a).

those of neutrons without additional toxicity [27] and that proton irradiation hyperthermia combined with would have the properties of high LET carbon ions [28].

When designing the HEATPAC protocol, multi-agent FOLFIRINOX was chosen as the induction and additive chemotherapy due to the increased efficacy over gemcitabine in the palliative setting reported by Conroy et al. [18]. All nine tumours remained inoperable after neoadjuvant chemotherapy however and the chemoradiation with hyperthermia is the most therapeutically active component of the protocol. A Phase II trial with similar design recently reported a 60% R0 resection rate in patients with LAPC using 8 cycles of FOLFIRINOX/losartan followed by 5×5 Gy proton therapy with capecitabine or 55.8 Gy photon radiotherapy with concurrent 5-fluorouracil or capecitabine. In the interim analysis of the CONKO-007 trial, median OS was significantly better (26.5 months) in patients with an R0 resection after neoadjuvant treatment than in non-operated patients (16.5 months) [3]. Patients in the non-surgical HEATPAC cohort had a similar median OS (24 months) to patients achieving an R0 resection in CONKO-007 and these data highlight the potential role of HTCRT as part of 'total neoadjuvant therapy' [29].

Immunotherapy is recognised as the fourth pillar of cancer therapy. Modulation of the tumor immune microenvironment, along

with the other mechanistic effects of hyperthermia, make it a compelling area of active research in therapy-refractory tumours such as PDAC. A current European phase III trial (HEAT) will compare overall survival and progression-free survival following the addition of hyperthermia to gemcitabine or gemcitabine and cisplatin as adjuvant therapy following a R0 or R1 resection in patients with resectable pancreatic cancer.

The clinical outcomes of this selected patient cohort are provocative as the median OS of 24 months with HTCRT far exceeds the median OS of 15.2 months (95% CI, 13.9–17.3 months) with CRT reported in LAP07, and this despite two patients having M1 disease. This multimodality approach of triple sensitisation to achieve biological intensification of therapy has yielded very encouraging data but accrual to the HEATPAC protocol has unfortunately been limited by the low incidence of eligible cases in a small population and there only being one deep hyperthermia unit in Switzerland. Multicentre international cooperation is urgently required for adequate recruitment to the HEATPAC randomised trial to draw conclusions regarding efficacy.

5. Conclusions

Triple sensitisation with HTCRT was associated with promising feasibility, toxicity and efficacy in this small cohort of patients. Median overall and progression free survival exceeded those currently seen with gemcitabine-based CRT in LAPC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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