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Phase II trial

Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma

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Abstract

***Background and purpose*: The majority of patients with pancreatic cancer have advanced disease at the time of diagnosis and are not amenable for surgery. Stereotactic radiotherapy (SRT) may be an alternative treatment for patients with locally advanced disease. The effect of SRT was investigated in the present phase-II trial.**

***Patients and methods*: Twenty-two patients with locally advanced and surgically non-resectable, histological proven pancreatic carcinoma were included into the trial. The patients were immobilized by the Elekta stereotactic body frame (SBF) or a custom made body frame. SRT was given on standard LINAC with standard multi-leaf collimator. Central dose was 15 Gy×3 within 5–10 days.**

***Results*: Evaluation of response was found to be very difficult due to radiation and tumour related tissue reaction. Only two patients (9%) were found to have a partial response (PR), the remaining had no change (NC) or progression (PD) after treatment. Six patients had local tumour progression, but only one patient had an isolated local failure without simultaneous distant metastasis. Median time to local or distant progression was 4.8 months. Median survival time was 5.7 months and only 5% were alive 1 year after treatment. Acute toxicity reported 14 days after treatment was pronounced. There was a significant deterioration of performance status ($P=0.008$), more nausea ($P=0.001$) and more pain ($P=0.008$) after 14 days compared with base-line. However, 8 of 12 patients (66%) improved in performance status, scored less nausea, pain, or needed less analgesic drugs at 3 months after treatment. Four patients suffered from severe mucositis or ulceration of the stomach or duodenum and one of the patients had a non-fatal ulcer perforation of the stomach.**

***Conclusions*: SRT was associated with poor outcome, unacceptable toxicity and questionable palliative effect and cannot be recommended for patients with advanced pancreatic carcinoma.**

Keywords: Pancreatic cancer; Stereotactic radiotherapy; Phase-II study

Pancreatic cancer represents a major challenge. It ranks one of the leading causes of cancer deaths in most countries around the world. One of the important problems in the treatment of pancreatic cancer is the late diagnosis of the disease. Even though imaging technologies such as laparoscopic or endoscopic ultrasound have resulted in better patient selection [1], the outcome after traditional treatment is still poor. Only few tumours are resectable at the time of diagnosis and surgical resection of operable cases leads to long-term survival in only approximately 10% in the resectable patients [2–5]. Radiotherapy alone or in combination with chemotherapy in the treatment of inoperable cases is currently under development in many centres [6–10]. However, studies on radiotherapy are at this time either immature or have shown a poor outcome. There is therefore a great need for development of new treatment possibilities for patients with pancreatic cancer.

Stereotactic radiotherapy (SRT) allows escalation of radiation dose to a small target defined as the radiological defined tumour volume with a small margin. The treatment is given in one or a few fractions sparing the surrounding normal tissue by optimal utilization of the geometry by multiple non-coplanar field arrangement. SRT of malignant extracranial tumours (ESRT) was introduced in 1992 [11–13]. However, the available data on this subject is still sparse. The effect of high dose precision radiotherapy of non-resectable pancreatic cancer was investigated in a Danish

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joint phase-II study at Aarhus and Copenhagen University Hospitals.

Methods and materials

Patient selection

Patients entered the study from January 2000 to July 2001 based on the following criteria: histological or cytological proven adenocarcinoma of the pancreas, inoperable judged by the surgeon, the radiologist and the oncologist, UICC stage T1-3 N0 M0 (=AJCC stages I–II)[14], no more than 6 cm in largest diameter, tumour visualized on CT-scan, WHO/ECOG performance status 0–2, and informed consent by the patient. All patients underwent CT-scan, 14 patients went through endoscopic ultrasonography and 12 patients had laparoscopic ultrasonography or explorative laparotomy before ESRT.

Radiotherapy

Two different patient immobilization systems were used. At Aarhus University Hospital, patients were immobilized by the stereotactic body frame® (SBF) produced by Elekta AB, Sweden. The SBF contained an external reference system that was visible on CT and it can be used for set-up at the LINAC. Precise positioning of the patient was secured using a large vacuum pillow in the SBF and laser-guided skin marks. A diaphragm control applying a constant pressure on the upper abdomen assuring maximal respiratory amplitude of the diaphragm movement of 5 mm, was used to reduce the internal movement of the target [11]. At Copenhagen University Hospital, patients were immobilized by a custom made vacuum pillow and skin marks. CT-scan was performed for treatment planning, and in 15 cases an additional CT-scan was carried out to confirm the position of the isocenter. Spiral CT-scan was performed with intravenous contrast with 5 mm slice thickness (8 mm/s) reconstructed with 4 mm inter-slice distance. Treatment planning was carried out on a Helax, TMS (Aarhus) or CadPlan Plus/Eclipse, Varian (Copenhagen) treatment planning systems. Delineation of the gross tumour volume (GTV) and the clinical target volume defined as the tumour and surrounding oedema (CTV) was always performed by the radiotherapist and the radiologist in union. An isotropic margin around the CTV of 5 mm in the transversal and 10 mm in the cranio-caudal direction was added to form the planned target volume (PTV). The CTV was encompassed by the 95% isodose, and the PTV by the 67% isodose surface (Fig. 1). A planned dose of 45 Gy was delivered in three fractions (3 fractions/week) to the ICRU reference point. ESRT was performed on a Siemens Primus (Aarhus) or a Varian Clinac 2100/2300 (Copenhagen) using 5–8 static coplanar or non-coplanar beams formed by multi-leaf collimator with leaf width of 5-10 mm at the isocenter. If only one CT-scan was performed, the position of the patient (vertebral spine) was checked by portal film or electronic portal imaging prior to each treatment (PVI, Varian). In case of deviation, the isocenter was adjusted. All patients had prophylactic ondansetron 16 mg during the treatment period and pantoprazol 20-40 mg daily for at least 4 weeks.

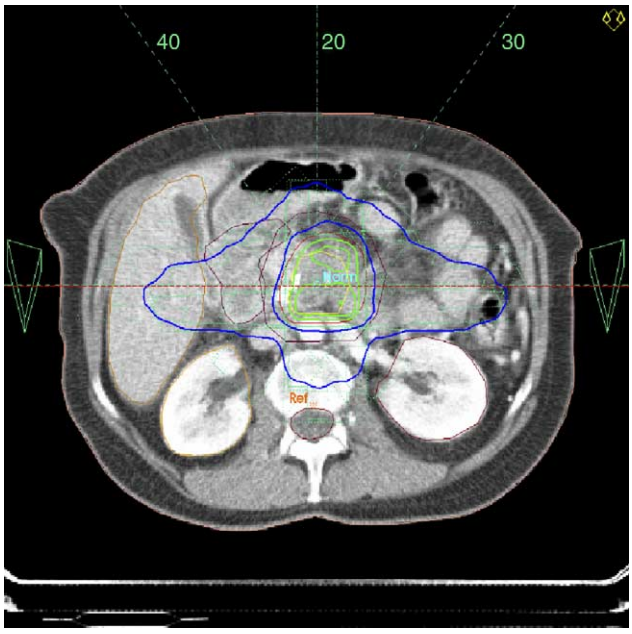

Fig. 1. Treatment plan for a patient with pancreatic carcinoma treated with ESRT.

The Ethics Committee of Aarhus County approved the study, and informed consent was obtained from all patients.

Follow-up

Evaluation of toxicity was performed at base-line and ½, 2, 3, 6, 9, 12, 18, and 24 months after treatment. CT-scans were performed at base-line and 3, 6, 9, 12, 18, and 24 months after treatment. The WHO performance status and toxicity grading system was used for evaluation of side effects. Base-line toxicity was evaluated at the day of the first treatment. Tumour response was evaluated according to the WHO criteria. In case of radiological changes that could represent a recurrence, the radiologist was instructed to take a biopsy. If the fine needle aspiration contained tumour cells, the patient was considered to be in progression.

Statistics

Survival tables and plots were performed by the Kaplan-Meier method. A Wilcoxon test was used to test the differences between performance status and grade of toxicity before and after treatment. The significance level was set to 5%. Time to progression and death was measured from time of first treatment until the endpoint was reached.

Results

A total number of 22 patients with pancreatic cancer were included in the study. Of these, 19 had an inoperable primary pancreatic cancer and three had a recurrence after a Whipple resection, two with a local recurrence and one with a lymph node metastasis. Patient characteristics are given in Table 1. All patients had non-resectable tumours due to invasion of vessels or other adjacent structures. Twelve females and 10 males were included. Median age was

Table 1
Patients characteristics, radiation dose, response and survival

Patient	Gender (m/f)	Age (years)	Perform-ance status (WHO)	Tumour size[a] (cm)	Radiation dose (Gy/f.)	Local response[b]	Site of failure[c]	Survival (months)
1	F	71	2	2.5	45/3	NA	NA	0.7[d]
2	F	68	0	2.0	45/3	PD	L+D	8.1[d]
3	M	68	2	5.0	45/3	NC	D	4.3[d]
4	M	56	0	5.1	45/3	PR		18.1
5	F	61	2	3.0	45/3	NA	NA	10.5[d]
6	M	51	0	2.8	45/3	NA	NA	2.6[d]
7	F	51	1	6.1	45/3	NA	D	0.7[d]
8	F	61	1	3.8	45/3	NC	D	8.8[d]
9	F	53	1	3.4	45/3	NC	D	3.9[d]
10	M	61	1	4.9	30/3	NC	D	5.1[d]
11	F	76	1	5.7	45/3	NC	NA	6.4[d]
12	M	64	0	3.2	45/3	PD	L+D	9.7[d]
13	F	61	1	4.9	45/3	NA	NA	6.3[d]
14	M	50	1	3.8	45/3	PD	L+D	5.7[d]
15	F	55	1	3.8	45/3	PR	D	4.9[d]
16	M	69	1	4.2	45/3	NC	NA	4.4[d]
17	M	63	1	5.4	45/3	PD	L+D	4.0[d]
18	F	59	1	4.2	45/6	NC	D	9.8[d]
19	M	44	0	3.8	45/3	PD	L+D	9.8[d]
20	F	63	1	2.6	45/3	PD	L	8.2[d]
21	F	54	0	4.0	45/3	NA	D	7.4[d]
22	M	43	2	3.5	45/3	NA	NA	2.5[d]

[a] Largest diameter in transversal plane.
[b] PR, partial response; NC, no change; PD, progressive disease; NA, data not available.
[c] L, local; D, distant; NA, data not available.
[d] Dead.

61 (43–76) years. At the time of inclusion, all patients had performance status of 0–2.

Radiotherapy data

Even though the median tumour diameter was only 3.8 (range 2.0–6.1) cm corresponding to a GTV of 32 (range 7–102) cm, the volume receiving above 67% of the prescribed dose was relatively large with a median value of 136 (range 38–376) ccm. The discrepancy between the relatively small tumour size and large treated volumes was caused by diagnostic uncertainty in delineation of the CTV due to tissue reaction and oedema of adjacent tissue. One patient was treated with a smaller dose of 10 Gy×3, and in another case a dose of 7.5 Gy×6 was prescribed. Both patients were included in the analysis.

Set-up accuracy of the patient was checked by a second CT-scan in 15 patients with match of the vertebral spine before start of treatment. The deviation in the three planes was always less than 5 mm and no correction of the isocenter was necessary. In Copenhagen, patients were aligned by use of portal imaging and a 'surrogate isocenter' defined by the vertebral spine. The isocenter was always adjusted if any deviation was observed on portal imaging.

Tumour response

All CT-scans at time of inclusion and at follow-up were reviewed by two radiologists.

Comparing CT-scans before and after treatment, two patients (9%) had a partial remission (PR). One of these progressed locally later, the other was still without progression at the time of analysis (Table 1). In six patients, the tumour failed locally, however, five of these failed outside the irradiated volume at the same time. Only one patient had an isolated local failure, which was confirmed by cytology. With five local failures within 6 months after treatment, the actuarial local control rate was 57%. Six patients had chemotherapy with gemcitabine at relapse.

Progression free- and overall survival

Median time to local and/or distant progression was 4.8 months (Fig. 2). The progression free survival after 1 year was 9% (0–24%) and only one patient was without progression 18 months after treatment. Median survival time was 5.4 months and overall survival after 1 year was 5% (95% CI: 0–12%) (Fig. 2).

Toxicity

A number of patients were lost to follow-up due to deterioration or death. Even without sign of progression, three patients entered a hospice programme and discontinued follow-up (CT-scan and toxicity registration). All patients were evaluated for toxicity at base-line, but only 18 patients were evaluated after 14 days, 14 after 2 months, 12 after 3 months, four after 6 months, and one patient 9, 12, and 18 months after treatment. One patient deteriorated within the short period of time between inclusion and first treatment and thus had a WHO performance status (PS) of 3 at start of treatment. At base-line, 14 patients (64%) were

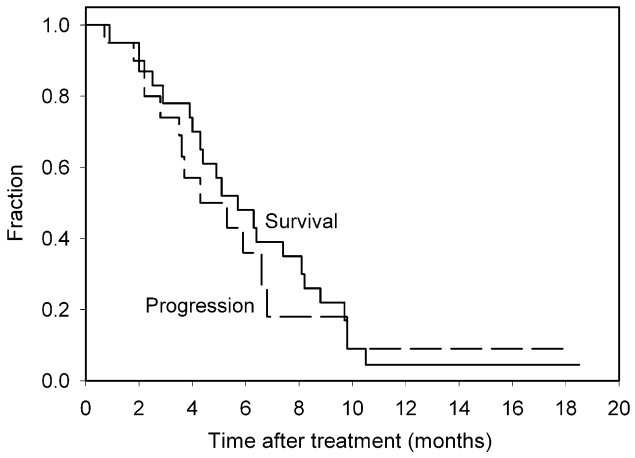

Fig. 2. Progression free and overall survival of 22 patients with locally advanced pancreatic carcinoma treated with ESRT.

evaluated as having one or more toxicity scores ≥ 2. This was due to nausea (2), diarrhoea (2), constipation (1), pain (14), or consumption of analgesics (12).

Table 2 summarizes acute toxicity for 18 patients at base-line and 14 days after treatment. There was a marked deterioration in performance status ($P=0.008$) and increased nausea ($P=0.001$), increased pain (0.008) and a trend for increased use of analgesics ($P=0.08$). Progression to toxicity grade 2 or higher was observed in 79% of the patients. Actuarial analysis showed that at 14 days after treatment, the fraction of patients with PS$\geq$2 and nausea$\geq$grade 2 increased by 100% compared to base-line (Table 2). The fraction of patients experiencing pain grade ≥ 2 also significantly increased and at 3 months after treatment 94% of patients had pain grade ≥ 2 and 80% received morphine. Some patients had a transient improvement later on. Of 12 patients evaluated for toxicity 3 months after treatment, eight patients improved in one or more toxicity scores as an indication of a possible palliative effect. Two patients (17%) improved in performance status, three patients (25%) experienced less nausea, six patients (50%) had less pain and one patient (9%) reduced consumption of analgesic. However, these patients also received intensive supportive care. All patients with nausea and pain received acid blockers and analgesics, and most patients used anti-emetics.

In four patients, severe mucositis ($n=2$) or ulceration ($n=2$) of the stomach or duodenum was observed by endoscopy. A fifth patient was operated for an ulcus-perforation of the stomach. In these cases, part of the stomach or duodenum received a dose of at least 67% of the prescribed dose.

Discussion

Extracranial stereotactic radiotherapy (ESRT) based on the SBF was introduced at Karolinska Hospital, Stockholm in the early 1990s [12]. A large number of SBF's have been distributed around Europe, North America, and Asia, and a large number of patients have undergone ESRT based on principles of the SBF or other custom made systems. Even though the number of patients treated with ESRT is high, only limited scientific evidence supports the treatment. So far, only few prospective and few retrospective studies have been published. In a German phase I/II dose-escalating study including 35 patients with 60 liver tumours, primarily metastases, it was demonstrated that 14–20 Gy in a single fraction and relatively small margins resulted in poor local control whereas doses of 22–26 Gy resulted in a 80% local control rate [15]. A paper from the same group showed similar dose relationship for small cell lung cancer [16]. A retrospective analysis of 50 patients treated for a variety of different tumour types with tumours of the lung, liver, and abdomen has been published by the Swedish group [12]. As a promising finding in that study, 80% of tumours were controlled locally (defined as no evidence of progression). The study is based on a heterogeneous patient population and a broad variety of radiation dose schedules. A high local control rates is also found by retrospective Japanese studies on ESRT in limited stage non-small cell lung cancer [17,18]. These studies—most of them retrospective—conclude that only minimal toxicity is related to the treatment.

One of the major indications for ESRT is claimed to be inoperable pancreatic cancer. However, only one previous study has been published on this subject. In a prospective dose-escalating study by Koing et al. [19] in patients with locally advanced pancreatic cancer, single dose ESRT was found to be safe with limited toxicity and local control in 6 out of 6 patients receiving the highest dose level of 25 Gy to the periphery (90% isodose) in a single fraction. Median survival for all patients was 11 months and 8 months for patients receiving the highest dose level. All patients in the study had either a systemic or a local failure.

Table 2
Performance status (PS) and toxicity grade at base-line and 14 days after treatment

	Base-line PS and grade					14 days after treatment PS and grade				
	0	1	2	3	4	0	1	2	3	4
Performance status[a]	6	12	3	1	0	3	5	8	2	0
Nausea[a]	15	5	2	0	0	4	3	7	4	0
Diarrhoea	15	5	0	2	0	12	3	1	2	0
Pain[a]	7	3	9	3	0	2	3	4	8	0
Analgesic consumption	8	0	2	3	9	2	2	1	5	8

[a] $P<0.05$, Wilcoxon test.

In the present phase-II study, we have found a very poor effect of ESRT. In an actuarial analysis, local control was only achieved in 57% at 6 months and all but two patients suffered from metastatic disease shortly after treatment. One of these patients is without recurrence at time of analysis and the other died with an isolated local failure. Also, the survival in the present study is not better than what is expected from patients receiving chemotherapy or supportive care only [20]. Even though no patients in this study had evidence of distant metastasis at time of treatment, the median survival was as short as 5.4 months.

The toxicity of the treatment reported in this study was pronounced. Since this patient group deteriorates within a relatively short period of time due to disease progression, this study is not able to demonstrate the complete profile of toxicity after ESRT. However, there is a significant worsening of performance status, increase of emesis, increase of pain, and a trend for increase in consumption of analgesics between base-line and 14 days after treatment. Some patients experienced a transient improvement at follow-up later on. In 12 patients at risk 3 months after treatment, six patients (50%) felt less pain whereas only one patient managed with a lower analgesic score. This clinical improvement may in some patients be due to a palliative effect of the treatment, whereas others may have improved due to effects of analgesics and other types of supportive care. Overall, the study demonstrates a marked toxicity of the procedure. In addition, a large proportion of the patients suffered from severe duodenitis, gastritis, or ulceration of the bowel. Severe gastric or duodenal ulceration or mucositis was observed in five patients, and this number is expected to be higher if more patients were examined by endoscopy.

Definition of local control may be important in interpretation of these differences in results of studies. In this study, even minor radiological changes led to a biopsy which often discovered a recurrence and evaluation of follow-up CT-scans was performed by two experienced radiologists in union. There are no firm criteria for response and local recurrence after ESRT, and particularly in the treatment of pancreatic cancer this represents a major problem. The high frequency of local failure in the present study may partly be explained by high frequency of biopsy sampling. Predefined criteria for these factors is therefore of high value.

Evaluation of toxicity is also problematic in pancreatic carcinoma. The progression of toxicity scores within 14 days after treatment as observed in the present study can only be explained as being related with the treatment. However, later on it is difficult to distinguish between symptoms related with progression of disease or toxicity related with the treatment. In the present study, it was decided to register any change in score regardless of its possible relation to disease or treatment.

In the study by Koing [19], a similar technique was used. The biological effect of a single dose of 25 Gy (peripheral) to early as well as late reacting tissues as calculated by the linear–quadratic model is higher if we compare to 45 Gy in three fractions (10 Gy peripheral) [21]. However, the toxicity reported in the study was lower as compared to the present study.

Different factors may contribute to the negative results of the study. First, pancreatic cancer is an aggressive malignant disease with a high potential for metastasis. This is underlined by the finding in the present study where 20 of 21 patients (95%) developed metastases at time of recurrence. This is also the findings in any other studies on localized pancreatic cancer treated by radiotherapy alone or in combination with chemotherapy [19,22–25]. Secondly, this tumour type is considered resistant to therapy, including radiotherapy. Thirdly, precise determination of the target which is evidently important in radiotherapy is very difficult. The pancreatic tumours may be difficult to delineate due to its poor definition on CT-scan and due to oedema adjacent to the tumour and respiration associated internal target movement also contributes to the uncertainties in dose delivery to the tumour.

Very tight margins are used in ESRT. The Stockholm group have shown that margins of 5–10 mm to account for reposition accuracy and internal movement are sufficient [11]. Similar small margins were used by Koing et al. who also introduced a breath holding technique [19]. In the present study, patients were carefully instructed to breath still and steadily and a diaphragm control was used to minimize the movement of the target. The body frame assures an accurate reproducibility of the patient positioning and in 15 cases where repeated CT-scans were performed, reposition accuracy was within 5 mm. The small margins are therefore considered sufficient and at least this uncertainty is much smaller than the uncertainty introduced in delineation of the tumour volume.

Conventional fractionated radiotherapy has been used for patients with locally advanced pancreatic carcinoma. In retrospective studies, response rates after 54–59 Gy were 23–43% [8,9]. These response rates are higher than the 9% of the present study, but evaluation of tumour response is problematic in pancreatic tumours. In a Dutch phase-II study, 44 patients were treated with 3D conformal radiotherapy and 2 Gy fractions to a total dose of 70–72 Gy [6]. In that study, no objective response was observed. The median survival time was 11 months. Acute grade II toxicity was observed in 57% of the patients, mainly consisting of fatigue and/or nausea and emesis, but only one patient (2%) suffered from grade 3 or higher toxicity. Upper gastric bleeding, stomach ulceration or duodenal ulceration was observed in eight of 40 patients at risk 6 months or later after radiotherapy. Sixty-eight percent of the patients experienced pain relief. Even though we should be careful comparing the Dutch study with the present, the Dutch study seem to be superior concerning survival whereas toxicity may be comparable.

The effect of combined chemo-radiotherapy was investigated in a randomized trial by Moertel et al. [10] back in 1981. Radiotherapy was given as simple opposing fields and thus to a rather large volume. The study showed that patients treated with 5-FU combined with 40 or 60 Gy had better survival compared with patients treated with 60 Gy without chemotherapy. Most patients only experienced mild toxicity, but two patients had severe gastrointestinal bleeding. Based on the study by Moertel, concomitant chemo-radiotherapy is widely used as routine or in clinical trials. Adjuvant chemo-radiation before or after surgical resection is also widely used [22–25]. Results from studies in this strategy are promising compared to surgical resection

alone. However, chemo-radiation is also related with relatively high toxicity and the strategy has never been proven to be superior to surgery alone in a randomized trial.

Chemotherapy in the treatment of inoperable patients may have effect on disease related symptoms and survival. In a study by Burris et al. [20], patients were randomized between gemcitabine and 5-FU. This study demonstrated a palliative effect on cancer related symptoms of 24% in gemcitabine treated patients compared with 5% in 5-FU treated patients. Patients treated with gemcitabine also had superior survival with 18% being alive after 12 months compared with 2% of patients treated with 5-FU. Gemcitabine—together with best supportive care—is therefore by many considered to be the standard treatment of patients with non-resectable pancreatic cancer.

In conclusion, the present study finds no benefit from hypofractionation high dose radiotherapy guided by stereotactic principles. Based on the survival data of the 22 patients entering the present study, there is no indication of a survival benefit of the treatment. In addition, the palliative effect was questionable and the toxicity was substantial. Results of the present study emphasize the need to introduce new treatment strategies in prospective clinical trials.

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