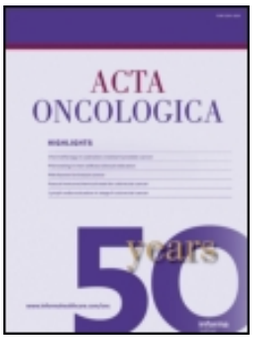

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ORIGINAL ARTICLE

Capecitabine based postoperative accelerated chemoradiation of pancreatic carcinoma. A dose-escalation study

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Abstract

The objective of this study was to evaluate the safety of escalating up to 55 Gy within five weeks, the dose of external beam radiotherapy to the previous tumor site concurrently with a fixed daily dose of capecitabine, in patients with resected pancreatic cancer. *Material and methods.* Patients with resected pancreatic carcinoma were eligible for this study. Capecitabine was administered at a daily dose of 1600 mg/m^2. Regional lymph nodes received a total radiation dose of 45 Gy with 1.8 Gy per fractions. The starting radiation dose to the tumor bed was 50.0 Gy (2.0 Gy/fraction, 25 fractions). Escalation was achieved up to a total dose of 55.0 Gy by increasing the fraction size by 0.2 Gy (2.2 Gy /fraction), while keeping the duration of radiotherapy to five weeks (25 fractions). A concomitant boost technique was used. Dose limiting toxicity (DLT) was defined as any grade>3 hematologic toxicity, grade>2 liver, renal, neurologic, gastrointestinal, or skin toxicity, by RTOG criteria, or any toxicity producing prolonged (> 10 days) radiotherapy interruption. *Results and discussion.* Twelve patients entered the study (median age: 64 years). In the first cohort (six patients), no patient experienced DLT. Similarly in the second cohort, no DLT occurred. All 12 patients completed the planned regimen of therapy. Nine patients experienced grade 1-2 nausea and/or vomiting. Grade 2 hematological toxicity occurred in four patients. The results of our study indicate that a total radiation dose up to 55.0 Gy/5 weeks can be safely administered to the tumor bed, concurrently with capecitabine (1600 mg/m^2) in patients with resected pancreatic carcinoma.

Approximately 10 new cases of pancreatic cancer are diagnosed per 100 000 persons-years in western countries [1]. Even if pancreatic cancer is discovered at a resectable stage, only one or two of 10 patients are expected to survive for more than five years after curative resection [2,3]. Death usually results from hepatic failure caused by biliary obstruction by local tumor extension or hepatic replacement by metastases [4]. Local recurrence occurs in 50–86% of patients [5–7].

In an effort to improve patient outcomes, adjuvant strategies employing chemotherapy and/or radiotherapy have been investigated in prospective randomized trials [8–10]. The results of these trials seem to indicate the relative ineffectiveness of adjuvant chemoradiation in patients with surgically treated pancreatic carcinoma. In fact, even if survival was improved with adjuvant chemo-radiation in the GITSG trial, local recurrence rate was as high in patients undergoing

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surgery alone (33%) as in those receiving adjuvant therapy (49%). Local tumor recurrence was also identified as a component of the first site of failure in 53% of patients enrolled in the EORTC trial and 62% of patients enrolled in the ESPAC-1 trial.

However these data are exceedingly difficult to interpret due to several factors such as lack of protocol compliance, inadequate statistical power and lack of control of surgical quality. Among these limitations, some criticism has attracted the type of radiotherapy used. In fact, in all these trials, radiotherapy was planned without the aid of a computed tomography (CT) based planning for more accurate tumor localization and was delivered up to total dose of only 40 Gy, in a split course fashion.

It can be hypothesized that higher doses of adjuvant radiotherapy can further decrease the incidence of local recurrence. For instance, we have observed a remarkably low rate of local recurrence (19.2%) in a long follow-up series receiving external beam radiotherapy (EBRT) plus intraoperative radiotherapy (IORT) up to a total dose of approximately 60 Gy [11]. Instead of IORT, which is not available in all radiotherapy units, other techniques for dose intensification, such as concomitant boost strategies, could be tested.

The primary objective of this study was to evaluate the safety of escalating up to 55 Gy within five weeks the dose of EBRT to the previous tumour site concurrently with a fixed daily dose of capecitabine, in patient with resected pancreatic cancer.

Material and methods

Eligibility

Patients with resected pancreatic adenocarcinoma were eligible for this trial. Eligibility criteria for adjuvant radiotherapy included nonmetastatic pancreatic adenocarcinoma, age younger than 75 years, 0–2 Eastern Cooperative Oncology Group performance score, granulocyte count greater than 3 000 granulocytes/ml, platelet count greater than 100 000 platelets/ml, and hemoglobin level greater than 10 g/dl. Before starting chemoradiotherapy, the following tests were performed in all patients: physical examination, complete blood count, blood chemistry, chest radiography. Abdominal computed tomography (CT) with intravenous contrast medium was always performed after surgery. Cancer staging was performed according to the Union Internationale Contre le Cancer 1997 classification [12]. Patients with a history of prior upper abdominal radiotherapy were ineligible for this trial. Prior chemotherapy administration was allowed. This trial was a prospective dose escalation study approved by the Institutional Review Board. All patients provided a written informed consent before therapy initiation.

Treatment

Oral capecitabine was administered at a dose of 800 mg/m^2 twice daily (total daily dose 1600 mg/m^2) on Monday through Friday for the duration of radiotherapy.

Computed tomography (CT) image-based three-dimensional treatment planning was utilized to optimize EBRT treatment planning. At the time of CT scanning, the patient was placed in supine position with both arm raised. A vac-loc bag was used to ensure set-up reproducibility. Contiguous 5-mm CT axial images were obtained from the upper border of T11 to the lower border of L3. CT simulation was performed with oral contrast material to assist in localizing the stomach and intestines. The CT scans were transferred to a treatment planning workstation (Plato Sunrise, Nucletron B.V., Veeuendaal, Netherlands) for definition of target volumes and critical structures and for treatment planning. The clinical target volume (CTV) was designed to adequately cover: the tumor bed (with a least a 2-cm margin) defined according to pre-resection CT primary tumor volumes, or operative clip placement (CTV1), plus the pancreatic remnant and the primary lymphatic drainage (CTV2). In case of tumor of the pancreatic head, the primary lymphatic drainage comprised the hilar and hepatic artery, celiac, peripancreatic, superior mesenteric and para-aortic area nodes at the T12–L2 level. In case of tumor of the pancreatic body or tail, the primary lymphatic drainage also included the splenic hilus and splenic artery nodes, while excluding the hilar and hepatic artery nodes. The planning target volume (PTV) was defined by adding 1 cm to the anteroposterior and lateral margin and 2 cm to the cephalocaudal margin. Kidneys, liver, stomach, and intestines were contoured for dose-volume histogram (DVH) analysis.

External beam radiation was delivered using a four-field technique (anteroposterior/posteroanterior and two opposed lateral wedged fields) with the requirement that at least 95% of the PTV receives 95% of the prescribed dose. All the patients were treated with 6–15 MV photons from Elekta Precise accelerators (Elekta Oncology Systems, Crawley, UK) equipped with multileaf collimators with 1 cm leaf width at the isocenter. Single-exposure portal images were acquired daily for set-up verification, by using the initial eight monitor units delivered of each treatment field. Translational deviations of isocenter position larger than 5 mm were immediately corrected.

During radiotherapy and for at least six months thereafter proton pump inhibitors were prescribed to all patients. Antiemetic prophylaxis with 5-HT3 antagonists was prescribed before starting chemoradiation. In patients with grade$\geq$3 toxicity treatment was discontinued until grade 2 toxicity was resumed.

Table I. Dose cohorts.

Dose level		Dose escalation *Radiation total dose/fraction size*		*Capecitabine*
No. of planned patients	Level	PTV2	PTV1	
6	1	45 Gy/1.8 Gy	50.0 Gy/2.0 Gy	1600 mg/m^2 per os daily
6	2	45 Gy/1.8 Gy	55.0 Gy/2.2 Gy	1600 mg/m^2 per os daily

Sequential adjuvant chemotherapy with different schedules was administered at the discretion of the oncologist of reference.

Radiation dose escalation

Regional lymph nodes received a total dose of 45 Gy with 1.8 Gy per fraction; dose escalation was delivered to tumor bed only. Being 50.4 Gy of standard fractionated 3D-conformal radiotherapy well tolerated when given concurrently with 1600 mg/m^2/day of capecitabine [13], this radiation dose was selected as the starting level for this dose escalation trial. A total dose of 50.0 was delivered to the tumor bed, with 2.0 Gy per fraction. As shown in Table I, escalation was achieved up to a total dose of 55.0 Gy by increasing the fraction size by 0.2 Gy (2.2 Gy per daily fraction), while keeping EBRT duration to five weeks (25 fractions). This radiation dose corresponds to an equivalent dose of 57.2 Gy in 2 Gy fraction for late effect (α/β ratio: 3) [14] and to a biologically effective dose of 60.7 Gy [15]. We decided to stop the dose escalation at this level because of the adjuvant intention of the treatment and the high risk of severe gastrointestinal complication with radiation doses higher than 55 Gy [16].

Each enrolled subject was sequentially assigned to a particular dose level (Table I). EBRT dose escalation was primarily based on acute and subacute toxicity as late toxicity can occur months or years later. Acute-subacute toxicities were defined as those that occurred within three months from the end of EBRT. Toxicities that developed at least three months after radiation were defined as late toxicities. All adverse events were monitored continuously during treatment and for six weeks after the end of treatment, and every three months thereafter. Cell blood count and lab test were performed weekly during chemoradiation.

Study design and end points

The primary objective of this study was to evaluate the safety of escalating up to 55 Gy within five weeks the dose of EBRT to the previous tumour site concurrently with a fixed daily dose of capecitabine, in patient with resected pancreatic cancer. Six patients were assigned to each dose level. The treatment was considered unsafe if dose limiting toxicity (DLT) occurred in greater than two patients of the six-patient cohort. DLT was defined as any grade$>$3 hematologic toxicity, grade$>$2 liver, renal, neurologic, gastrointestinal, or skin toxicity, by RTOG criteria [17], or any toxicity producing prolonged ($>$10 days) radiotherapy interruption.

Statistical methods

All patients who started the treatment were included in the analysis. Toxicity was classified by type, grade, and probable relationship with the study treatment. Progression free survival (PFS) was described using the Kaplan-Meier method. Time to progression was measured from surgical resection until disease progression.

Results

Patient population

Twelve patients were enrolled, six patients per each dose level. Patient characteristics are detailed in Table II. All patients were in good general conditions (ECOG performance status 0-1). Ten of 12 patients

Table II. Patient and tumor characteristics.

Characteristics	No. of patients
Patients enrolled	12
Sex	
Female	5
Male	7
Age, years	
Median	64.5
Range	50–83
Surgery	
Duodenocefalopancreasectomy	10
Other	2
Surgical margin status	
Negative	8
Microscopic infiltration	2
Unknown	2
Lymph nodal status	
Negative	4
Positive	8
Prior chemotherapy	
Gemcitabine	6
Gemcitabine plus 5-Fluorouracil	4
None	2

Table III. Nonhematologic toxicity during chemoradiation.

		Dose level	
Toxicity	Grade	*50.0 Gy*	*55.0 Gy*
Nausea	0	2	2
	1	4	3
	2	0	1
	3–4	0	0
Vomiting	0	3	2
	1	3	3
	2	0	1
	3–4	0	0
Diarrhea	0	6	5
	1	0	1
	2	0	0
	3–4	0	0

were treated after duodeno-cephalo-pancreatectomy. Six Whipple and two Traverso-Longmire interventions had been performed. Two patients had been treated with a modified cephalo-pancreatectomy because of previous partial gastroresection. Two other patients underwent distal pancreatectomy and splenectomy. Most patients (83%) had received two cycles of gemcitabine-based chemotherapy before chemo-radiation. The median follow-up time was 15 months for all patients (range: 6–33 months).

Toxicity

No patient showed DLT. Nonhematologic adverse events are shown in Table III. Upper gastrointestinal toxicity was the most frequently observed nonhematologic toxicity. Overall 9/12 (75.0%) patients showed grade 1–2 nausea and/or vomiting, (first cohort: 4; second cohort 5). Only one patient, in the second cohort, experienced grade 2 nausea and vomiting. Grade 2 diarrhea did not occur in any patient. Hematological toxicity was mild. Grade 2 anemia was observed in two patients. One patient experienced grade 2 neutropenia. Platelet count decreased below 75000/ml in one patient. No patients required treatment interruption and all patients completed the treatment protocol. To date, no late toxicity has been observed.

Treatment failures

One year disease free survival was 72.9%. Three patients developed liver metastases at 11, 12, and 27 months respectively after surgery. To date, no cases of local recurrence has been observed.

Discussion

In this study it was shown that 55 Gy/5 weeks (biologically effective dose: 60.7 Gy) fractions can be safely administered concurrently with capecitabine (1600 mg/m^2/day), in patients with resected bilio-pancreatic carcinoma.

To our knowledge, this is the first prospective trial of concurrent chemoradiotherapy with capecitabine in patients with resected bilio-pancreatic cancer. In a phase II study, Saif and coworkers, investigated the feasibility of concurrent capecitabine and 50.4 Gy of conventionally fractionated radiotherapy, in patients with locally advanced pancreatic cancer. This regimen was both tolerable and effective with only 5% of patients experiencing severe gastrointestinal toxicity [13]. However, the tolerability can be quite different in a post-operative setting. It can be reduced due to the previously administered treatment. Anatomic variations such as the different arrangement of the jejunum and ileum due to the restoration of intestinal continuity, and the removal of organ at risk such as the duodenum and gastric antrum, can also variably affect the patient tolerance to chemoradiation.

While dose escalation in locally advanced unresected pancreatic cancer has been extensively evaluated [18,19], only a few dose escalation trials have been performed in post-operative setting. In a phase I trial Allen and coworkers, determined the maximal tolerated dose of radiation delivered to the primary tumor bed, in combination with full-dose gemcitabine (1000 mg/m^2 weekly $\times$ 3), after resection of pancreatic cancer [20]. The maximal tolerated radiation dose, administered using conformal techniques targeted to the tumor bed only, was 39 Gy in 2.6 Gy fractions. The DLT was nausea. Also in our experience nausea and vomiting were the side effect most frequently observed. However emesis was mild and no DLT occurred up to a total dose of 55 Gy to the tumor bed, despite 45 Gy were also administered to a larger volume comprising the regional lymph node areas. This finding is probably due to the different schedule of concomitant regimen of chemotherapy used. Furthermore, because of the moderate emetogenic potential reported for upper abdomen irradiation [21], antiemetic drugs were routinely prescribed to our patients before starting chemoradiation.

One of the major drawbacks of this trial is the heterogeneity of chemotherapy schedules administered before chemoradiation. Two patients did not receive any chemotherapy. However, since the majority of patients (83%) had received two cycles of gemcitabine-containing regimen before starting chemoradiation, we can argue that this regimen may be tolerable even in patients treated without chemotherapy.

Adjuvant chemotherapy with gemcitabine has been proven to improve survival over observation alone in an adjuvant setting (CONKO-001 trial) [22]. With a median follow-up of 53 months recurrent disease developed in 133 of 179 eligible patients (74.3%)

in the gemcitabine group and 161 of 175 patients (92.0%) in the control group. Even if the majority of relapses occurred at distant sites, local recurrence with or without distant metastasis occurred in 34% of patients, who relapsed in the gemcitabine group.

The addition of gemcitabine to 50.4 Gy of adjuvant fluorouracil-based chemoradiation in patients with pancreatic head tumors was associated with a survival benefit in the RTOG 9704 trial. However, toxicity in both treatment groups of the RTOG trial was substantial. In the gemcitabine group, grade 3 or 4 hematologic toxicity occurred in 58% of the patients and approximately 80% of the patients experienced grade 3 or 4 toxicity. The most common grade 3 or higher nonhematologic toxicity was diarrhea, which affected 19% of the patients in the fluorouracil group and 15% of the patients in the gemcitabine group. Other common grade 3 or higher toxic effects were mucous membrane or stomatitis (fluorouracil group, 15%; gemcitabine group, 10%), nausea and vomiting (fluorouracil group, 11%; gemcitabine group, 10%) [23].

Since there is no consensus on what constitutes "standard" adjuvant therapy, patients with resected pancreatic cancer should be enrolled in controlled clinical trial. As it seems to be well tolerated, even after gemcitabine-based adjuvant chemotherapy, 3D conformal radiotherapy delivering 55 Gy to the tumor bed with concurrent administration of capecitabine could be tested in a phase II clinical trial.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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