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Pancreatic cancer

Dosimetric and clinical predictors of toxicity following combined chemotherapy and moderately hypofractionated rotational radiotherapy of locally advanced pancreatic adenocarcinoma

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ABSTRACT

Background and purpose: Hypofractionated radiotherapy (RT) of pancreatic adenocarcinoma is limited by the tolerance of adjacent normal tissues. A better understanding of the influence of dosimetric variables on the rate of toxicity after RT must be considered an important goal.

Methods and materials: Sixty-one patients with histologically proven locally advanced disease (LAPD) were analyzed. The therapeutic strategy consisted of induction chemotherapy (ChT) followed by concurrent chemoradiotherapy (CRT). In 39 out of 61 patients the target volume was based on a four-dimensional CT (4D-CT) procedure. Delivered dose was 44.25 Gy in 15 fractions to PTV_2, which consisted of pancreatic tumor and regional lymph nodes considered radiologically involved; 23 out of 61 patients received a simultaneous integrated boost (SIB) to a tumor sub-volume infiltrating the great abdominal vessels (PTV_1) with dose in the range of 48–58 Gy. RT was delivered with Helical Tomotherapy. Dose–volume histograms (DVHs) of target volumes and organs at risk (OARs) were collected for analysis. The predictive value of clinical/dosimetric parameters was tested by univariate/multivariate analyses.

Results: The crude incidence of acute gastrointestinal (GI) grade 2 toxicity was 33%. The 12-month actuarial rate of "anatomical" (gastro-duodenal mucosa damage) toxicity was 13% (95% CI: 4–22%). On univariate analysis, several stomach and duodenum DVH endpoints are predictive of toxicity after moderately hypofractionated radiotherapy. Multivariate analysis confirmed that baseline performance status and the stomach V_{20}[%] were strong independent predictors of acute GI grade $\geqslant 2$ toxicity. The high-dose region of duodenum DVH (V_{45}[%]; V_{40}[%]) was strongly correlated with grade $\geqslant 2$ "anatomical" toxicity; the best V_{40}[%] and V_{45}[%] cut-off values were 16% and 2.6% respectively.

Conclusion: Regarding dosimetric indices, stomach V_{20}[%] correlates with a higher rate of acute toxicity; more severe acute and late anatomical toxicities are related to the high dose region of duodenum DVH.
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Pancreatic cancer is one of the leading causes of cancer deaths worldwide. The majority of pancreatic cancer patients have locally advanced (LAPD) or metastatic disease [1]. The optimal therapeutic strategy for LAPD is still a matter of debate [2–6]. For instance, phase III trials comparing chemoradiotherapy and chemotherapy alone have provided inconsistent data [2].

Considering the frequent metastatic progression of the disease many authors from numerous Institutions have decided to use chemotherapy (ChT) alone as initial treatment, followed by concurrent chemoradiation (CRT) in patients without distant progression [7–10].

The involvement of regional lymph nodes as first site of relapse has been reported to be negligible in two studies in which only the primary tumor and enlarged lymph-nodes were irradiated [8,11].

Attempts have been made to escalate the radiation dose in order to improve local control; radiation dose escalation has been attempted through the use of intraoperative radiotherapy [6], stereotactic radiotherapy [12–15], and intensity modulated RT (IMRT). There have been few published reports using IMRT to treat pancreatic cancer [16–18]; IMRT reduced the mean dose to all OARs, and toxicity profiles compared favorably with similar ChT regimens with conventional 3-dimensional techniques [19,20].

The good sparing offered by IMRT combined with a moderately hypofractionated regime could be a premise for better local control without increasing adverse effects. In a recent paper by Ben-Josef et al. [21], the radiation dose ranged from 50 Gy to 60 Gy with treatment fixed over five weeks (2.0–2.4 Gy/fraction); the

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encouraging data suggested that outcome may be improved through the intensification of local therapy.

Given the availability in our department of the respiratory-gated four dimensional computed tomography (4D-CT), IMRT and Image Guided RT (IGRT) technologies, a phase I study was defined to treat LAPD using a moderately hypofractionated irradiation regime (44.25 Gy, 15 fractions) with concomitant chemotherapy and simultaneous integrated boost (SIB) to tumor sub-volume infiltrating the vessels with escalating doses from 48 Gy to 58 Gy. A second group of patients was treated with the same dose prescription (44.25 Gy, 15 fractions) to the tumor volume and involved lymph nodes in an observational study.

The present study investigated the relation between toxicity and dose/volume parameters in the case of LAPD, having as its primary endpoint the definition of DVH related predictors of acute and late toxicities; all patients received induction ChT followed by a moderately hypofractionated RT with concomitant chemotherapy (CRT).

Methods and materials

Patient population

In our Institute, patients with stage III/IV without distant disease progression after induction ChT were treated with consolidation chemoradiation (CRT). The target volume consisted of the identified or suspected tumor and regional lymph nodes considered radiologically involved or PET/positive; no prophylactic nodal irradiation was performed [9,22].

In this paper, 61 patients with histologically proven pancreatic adenocarcinoma treated in our hospital with hypofractionated RT concomitant with chemotherapy (ChT) in the period of 2005–2010 are considered. Induction ChT consisted of four to six months of four-drug combinations of cisplatin, epirubicin, gemcitabine, 5-fluorouracil or capecitabine (Acronyms: PEFG of PEXG, respectively) in 45 out of 61 patients [23]. The other 16 patients were treated with gemcitabine alone (seven patients), capecitabine alone (seven patients), and cisplatin plus gemcitabine (two patients). Patients without systemic failure at the end of induction ChT were submitted to concomitant chemoradiation with oral capecitabine, 1250 mg/m^2/day (55 patients; 90%), or 5-FU 250 mg/m^2/day (five patients; 8%). Two patients did not receive concomitant ChT (persistent elevated level of bilirubin for one patient; refusal due to grade 3 diarrhea during induction with capecitabine for the other patient).

Twenty-three patients were enrolled in a phase I study approved by the Ethics Committee (Group_1), and 38 patients in an observational study related to our standard procedure in LAPD cases (Group_2); all patients provided written informed consent before the start of the treatment.

The main eligibility criteria of the two chemoradiation protocols included histologically proven adenocarcinoma, clinical stage III or IV [24] with metastatic disease in complete or partial response over a period of at least four months after the completion of induction ChT, age 18–75 years, Karnofsky performance status (KPS) $\geqslant$70, adequate bone marrow, renal and hepatic function. No previous radiation therapy to the pancreas was admitted.

The time interval between the end of induction ChT and the start of CRT was between two and four weeks in stage III patients. All patients received pump inhibitors as mucosal protective support.

Treatment technique

The treatment method and the planning procedure have already been published in detail elsewhere [18]. Enrolled patients were positioned on a Wing Board® and a Comby-Fix® device; after induction ChT a simulation contrast-enhanced four-dimensional CT (4D-CT) and FDG-PET/CT was performed for all phase I patients and whenever possible for the other patients. Due to the limited number of 4D-CT procedures available for RT planning, 16 patients enrolled in the observational study underwent a standard simulation contrast-enhanced CT and FDG-PET/CT. The contrast-enhanced 4D-CT procedure and its use in pancreatic tumor delineation have been previously described and discussed [25,26].

Primary tumor and enlarged lymph nodes visible on the contrast enhanced CT or 4D-CT images were defined as GTV. When a standard CT was performed, PTV_2 was defined as GTV plus a margin of 10/10/15 mm (Left–right, anterior–posterior, superio–inferior directions). In the case of 4D-CT, GTV was contoured on at least four phases. An ITV is obtained by the convolution of fours GTVs; a further margin of 5/5/7 mm was added to create PTV_2. In the phase I group, a PTV_1 was defined following the same procedure but considering only the area of the tumor one cm around the infiltrated vessels. A dose of 44.25 Gy in 15 fractions was prescribed as the median dose to the PTV_2; the SIB dose to the PTV_1 was in the range of 48–58 Gy. In case of overlap between PTV_2 and stomach–duodenum, an overlap structure (OVL_PTV_2) receiving reduced total doses was defined according to its volume: 44.25, 43.25 and 42.25 Gy for $OVL\_PTV_2 < 15$, <30 and <50 cm^3 respectively.

Assuming an α/β equal to 10 Gy (for tumor/early responding tissue) and 4 Gy (for late complications of the bowel, [27]), a total dose of 44.25 Gy in 15 fractions can be converted in 2 Gy equivalent dose (EQD_2) equal to 47.75 Gy and 51.26 Gy respectively. Considering a conventional dose of 54 Gy in 30 fractions the two fractionation regimes could be considered equivalent for late responding tissues; the slight difference in the case of early responding tissues could be even less considering the longer overall treatment time with conventional approach (six weeks compared with three weeks in our moderately hypofractionated approach), for certain tumors some authors estimated a dose loss per day due to repopulation of around 0.4 Gy [28,29].

Plans were developed with the primary aim of achieving good target coverage (delivery of $\geqslant$95% of the prescribed dose to $\geqslant$95% of the volume); the volume of irradiated normal tissue was reduced to as great a degree as possible during the iterative optimization process while maintaining tumor coverage as the highest priority; constraints used during HT plan optimization have been previously reported [18].

The following healthy structures were delineated: duodenum, stomach, kidney, spinal cord and liver; dose volume histograms (DVHs) of PTV_1, PTV_2, and OARs were compiled for each patient. The duodenum was contoured from the pylorus to the ligament of Treitz; for each patient, stomach and duodenum volumes (including their lumen) were delineated/reviewed by an expert radiation oncologist (PP). A composite structure Sto_Duo containing both the stomach and duodenum was also generated; it was suggested that it played a key role in a more accurate prediction of gastrointestinal bleeding [30].

For all patients a daily on-line correction using MVCT scans was applied by means of a two-step registration strategy already detailed elsewhere [18]: briefly, after automatic matching on bony anatomy between MVCT and simulation CT, the physician completed the positioning by means of direct visualization of the anatomical details considered as further reference points for positioning adjustment.

Toxicity

During the treatment patients were examined once a week by radiation and medical oncologists. During the follow up, complete