Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Individually optimized stereotactic radiotherapy for pancreatic head tumors: A planning feasibility study

Milly Buwenge[a,1], *Savino Cilla*[b,*,1], *Alessandra Guido*[a], *Lucia Giaccherini*[a], *Gabriella Macchia*[c], *Francesco Deodato*[c], *Silvia Cammelli*[a], *Francesco Cellini*[d], *Gian C. Mattiucci*[d], *Vincenzo Valentini*[d], *Markus Stock*[e,1], *Alessio G. Morganti*[a,1]

[a] *Radiation Oncology Center, Department of Experimental, Diagnostic and Specialty Medicine – DIMES, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy*
[b] *Medical Physic Unit, Fondazione "Giovanni Paolo II", Catholic University of Sacred Heart, Campobasso, Italy*
[c] *Radiotherapy Unit, Fondazione "Giovanni Paolo II", Catholic University of Sacred Heart, Campobasso, Italy*
[d] *Radiation Oncology Department, Università Cattolica del Sacro Cuore, Rome, Italy*
[e] *EBG MedAustron, Wiener Neustadt, Austria*

ARTICLE INFO

Article history:
Received 7 March 2016
Received in revised form
10 June 2016
Accepted 1 September 2016
Available online 28 September 2016

Keywords:
Pancreatic neoplasms
IMRT
Stereotactic body radiotherapy
Simultaneous integrated boost

ABSTRACT

Aim: Aim of this study was to perform a planning feasibility analysis of a 3-level dose prescription using an IMRT-SIB technique.
Background: Radiation therapy of locally advanced pancreatic cancer should administer a minimum dose to the duodenum and a very high dose to the vascular infiltration areas to improve the possibility of a radical resection.
Materials and methods: Fifteen patients with pancreatic head adenocarcinoma and vascular involvement were included. The duodenal PTV (PTVd) was defined as the GTV overlapping the duodenal PRV. Vascular CTV (CTVv) was defined as the surface of contact or infiltration between the tumor and vessel plus a 5 mm margin. Vascular PTV (PTVv) was considered as the CTVv plus an anisotropic margin. The tumor PTV (PTVt) was defined as the GTV plus a margin including the PTVv and excluding the PTVd. The following doses were prescribed: 30 Gy (6 Gy/fraction) to PTVd, 37.5 Gy (7.5 Gy/fraction) to PTVt, and 45 Gy (9 Gy/fraction) to PTVv, respectively. Treatment was planned with an IMRT technique.
Results: The primary end-point (PTVv $D_{mean} > 90\%$) was achieved in all patients. PTVv $D_{98\%} > 90\%$ was achieved in 6 patients (40%). OARs constraints were achieved in all patients.
Conclusions: Although the PTVv $D_{95\%} > 95\%$ objective was achieved only in 40% of patients, the study showed that in 100% of patients it was possible to administer a strongly differentiated

* *Corresponding author at*: Medical Physics Unit, Fondazione di ricerca e cura "Giovanni Paolo II", Università Cattolica del Sacro Cuore, Largo Gemelli 1, Campobasso, Italy.
E-mail address: savinocilla@gmail.com (S. Cilla).
[1] These authors contributed equally to this work.
http://dx.doi.org/10.1016/j.rpor.2016.09.003

mean/median dose. Prospective trials based on clinical application of this strategy seem to be justified in selected patients without overlap between PTVd and PTVv.

1. Introduction

Pancreatic carcinoma is one of the neoplastic diseases with the worst prognosis. Radiation therapy has been used both as adjuvant and curative treatment. However, the ability to use effective doses is limited by the presence of the surrounding radiosensitive organs (kidney, intestine, stomach, liver, spinal cord). Hence, it is difficult to administer to the tumor a high dose of radiation. This is probably one of the reasons for the disappointing clinical results, with a median survival around 10–12 months in patients with advanced disease[1,2] and around 20–24 months in patients with resectable disease.[3]

Recently, it has been proposed by some authors to use stereotactic body radiation therapy (SBRT) for the treatment of these tumors.[4–18] The use of stereotactic techniques is theoretically useful to administer high doses of radiation to the tumor with optimum sparing of organs at risk (OARs). Furthermore, SBRT treatment has other advantages and particularly its brevity. This enables an easy integration with chemotherapy and the improvement of patients quality of life. Three recent reviews of the literature,[19–21] focused on the few experiences available in the scientific literature, highlighted that (1) treatment with radiosurgery of pancreatic tumors produces survival results similar to those recorded in series based on prolonged chemoradiation; (2) the main limitation of this technique is the high incidence of duodenal complications (bleeding, ulceration, perforation).

More recently, the possibility of administering SBRT treatments with intensity-modulated techniques (IMRT) based on the use of a Simultaneous Integrated Boost (SIB) has been proposed.[20] This method allows to simultaneously administer different doses of radiation within the target. Therefore, the use of this technique may allow the administration of a high radiation dose to the target, while delivering a reduced dose to the Planning Target Volume (PTV) subvolume overlapping the duodenal wall.[22,23]

Furthermore, several authors proposed the use of radiotherapy as preoperative treatment.[24–26] The reason is that most patients have a locally advanced and, therefore, unresectable tumor at diagnosis. Typically, the reason for unresectability is the infiltration of the blood vessels close to the pancreas (mainly the superior mesenteric artery and vein and the celiac trunk). Some studies on the use of preoperative radiotherapy and chemoradiation showed the possibility to achieve a radical resection even in patients with initially unresectable disease. However, the success rate is still low (about 25–30%)[27] because of the limits in the radiation dose that can be safely administered in this anatomical region.

In view of this problem, some authors proposed once again the use of IMRT-SIB, because of the opportunity to administer a safe dose to the PTV and a higher dose to the tumor region invading the blood vessels.[28] This technique has the potential to achieve a greater regression in this critical area of the tumor.

Both these strategies (sparing the duodenum and increasing the dose to the vessels) seem reasonable and promising. Therefore, it would be interesting to combine both of them. In fact, a combination of these dose modulations into a 3 level dose prescription can be hypothesized, with a lower dose to PTV overlapping the duodenum, a high dose to vascular invasion and an intermediate dose in the remaining PTV. However, the mean diameter of locally advanced pancreatic carcinoma being around 40–45 mm,[29] the possibility to vary the dose in such a small volume had never been hypothesized and tested in these patients.

Therefore, the aim of this study was to perform a planning feasibility analysis of a dose prescription in 3 levels within a pancreatic tumor treated by SBRT. More specifically, using the IMRT-SIB technique with 3 markedly different doses (in 5 fractions) was tested and evaluated.

2. Material and methods

2.1. Study design

A planning study was performed on a sample of 15 patients with a histologically proven pancreatic head adenocarcinoma deemed unresectable due to vascular involvement.

2.2. End-points

The primary end-point of the study was the rate of patients in whom, respecting all OARs constraints and the constraint PTVv $D_{2\%} < 115\%$, the constraint $D_{mean} > 90\%$ of the prescribed dose was achieved for the 3 different PTVs. Secondary end-points were the percentage of patients in whom, respecting all OARs constraints and the constraint PTVv $D_{2\%} < 115\%$, a PTVv near minimum dose ($D_{98\%}$) > 90%, a PTVv $D_{95\%} > 95\%$, and a median dose ($D_{50\%}$) > 95% were achieved.

2.3. Treatment simulation

The stereotactic body frame (SBF, Elekta, Crawley, UK) was used for patients immobilization. It is an immobilization device that defines a stereotactic system of coordinates for the target position instead of basing on the anatomical landmarks such as bony structures or skin markers.[30,31] To reduce involuntary abdominal movements due to respiration, an abdominal compressor is attached to the SBF by a rigid arc, aiming at minimizing the mobility of targets close to the diaphragm by mechanically pressing the patients epigastrium. Organ motion due to residual respiratory movements, resulting in target displacement, was measured by performing 30 axial CT scans on the same slice during free breathing.

Acquisition of axial images necessary for stereotactic localization and plan optimization were taken by 3-mm scans CT-simulation using the spiral technique. For small bowel visualization, 2 cc of oral Gastrografin, diluted in ½ liter of water were given to each patient, 30 min before CT scans acquisition.

2.4. Volumes of interest definition and delineation

The following definitions for target volumes were used (Fig. 1). A duodenal PTV (PTVd) was defined as the GTV overlapping the duodenal PRV plus an anisotropic margin (5 mm craniocaudal direction and 3 mm in the other directions). A vascular CTV (CTVv) was defined as the surface of contact or infiltration between tumor and vessel plus 5 mm margin around the vessel (including the whole circumference of the vessel). The vascular PTV (PTVv) was considered as the CTVv plus an anisotropic margin (5 mm craniocaudal direction and 3 mm in the other directions). The tumor PTV (PTVt) was defined as the GTV plus an anisotropic margin (5 mm craniocaudal direction and 3 mm in the other directions) including the PTVv and excluding the PTVd. Target and OARs contouring was performed by a radiation oncologist with the aid of a radiologist using a CT-simulation performed in the arterial phase. Practically, target delineation was performed as follows. As the first step, the GTV was contoured. Then, the duodenum was delineated from the pylorus to the duodenojejunal junction. Then, the duodenum-PRV was defined by adding 5 mm in craniocaudal direction and 3 mm in the other directions. After identification of the overlap between GTV and duodenum-PRV, the same margins (3–5 mm) were added to this volume and the volume defined in this way was considered as PTVd. Then, the site of vascular infiltration was identified and the involved vessel was contoured, with a circumferential margin of 5 mm, for the whole craniocaudal extension of infiltration or contact between GTV and vessel (or vessels, in case of the involvement of more than one vascular structure). This volume was defined as CTVv. Adding the same margins (3–5 mm), the resulting volume was defined as PTVv. Finally, the remaining GTV, plus the margins indicated above, was defined as PTVt including all the PTVv and excluding the PTVd. The organs at risk were delineated as indicated in the RTOG atlas. More specifically, the kidneys (the two entire volumes, separately) and the liver (including the entire volume) were considered and contoured. Stomach, small bowel, colon and spinal cord were also outlined from 20 cm above the GTV cranial margin to 20 cm below the caudal GTV margin. PRVs of these OARs were defined by adding an isotropic margin of 5 mm.

2.5. Dose levels and dose-volume constraints

The following doses were prescribed as the median dose (to a total of 5 fractions to be delivered within a week) to the different PTVs: 30 Gy (6 Gy/fraction) to PTVd, 37.5 Gy (7.5 Gy/fraction) to PTVt and 45 Gy (9 Gy/fraction) to PTVv, respectively. In order to facilitate a comparison with RT treatments performed with conventional fractionation (2 Gy/fraction), these doses were recalculated in terms of "Equivalent Dose in 2-Gy fractions" (EQD2), using the formula:

$$\mathrm{EQD2} = D\left[\frac{d+\frac{\alpha}{\beta}}{2+\frac{\alpha}{\beta}}\right]$$

with α/β ratio of 10. The EQD2 to PTVd, PTVt, and PTVv were equal to 40 Gy, 54.7 Gy, and 71.2 Gy, respectively. The dose-volume constraints were based on the AAPM TG101 recommendations: D_{max} of $PRV_{duodenum} < 32.0$ Gy, D_{max} of $PRV_{spinal\ cord} < 30.0$ Gy, D_{max} of $PRV_{stomach} < 32.0$ Gy, $D_{700cc\ liver} < 21.0$ Gy, $D_{200cc\ kidneys} < 17.5$ Gy.

Table 1 – Patient characteristics.

	No.	%
Gender		
M	7	46.7
F	8	53.3
Age, median (range)	65 (48–73)	
Involved vessel		
Celiac trunk	5	33.3
Superior mesenteric artery	8	53.3
Portal vein	2	13.3
Superior mesenteric vein	4	26.7
Tmor stage		
T3	3	20.0
T4	12	80.0
Nodal stage		
N0	9	60.0
N1	6	40.0
Tumor diameter, median (range), cm	3.8 (2.4–5.2)	

2.6. Planning technique

Treatment for each patient was planned with a step and shot IMRT technique, based on the class solution proposed by Bouchard and colleagues.[32] Briefly, a six-beams orientation technique was used, with gantry angles for five coplanar incidence at 90°, 150°, 225°, 310°, and 350° with couch at 0°, while a gantry angle of 330° was with couch at 90°. This last beam arrangement has the potential to decrease bilateral kidney dose, a useful choice for patients with risk factors for treatment related kidney dysfunction. Treatment planning calculation was based on the following setting: maximum number of segments/plan: 60, minimum segment area: 3 cm^2, minimum number of monitor units/segment: 2. All treatments were planned for delivery using 6 MV photons produced by an Elekta Precise linear accelerator equipped with a MLCi multileaf collimator (1 cm leaf projected thickness at isocenter) and capable of on board kilovoltage orthogonal planar imaging. All plans were generated with Oncentra Masterplan treatment planning system (Elekta, Crawley, UK). Dose specification and nomenclature were according to the ICRU report 83.[36] Dose calculation was performed using the pencil beam algorithm with inhomogeneity correction and a dose grid resolution of 0.2 cm. An example of treatment planning with dose distribution and DVH is shown in Fig. 1a and b.

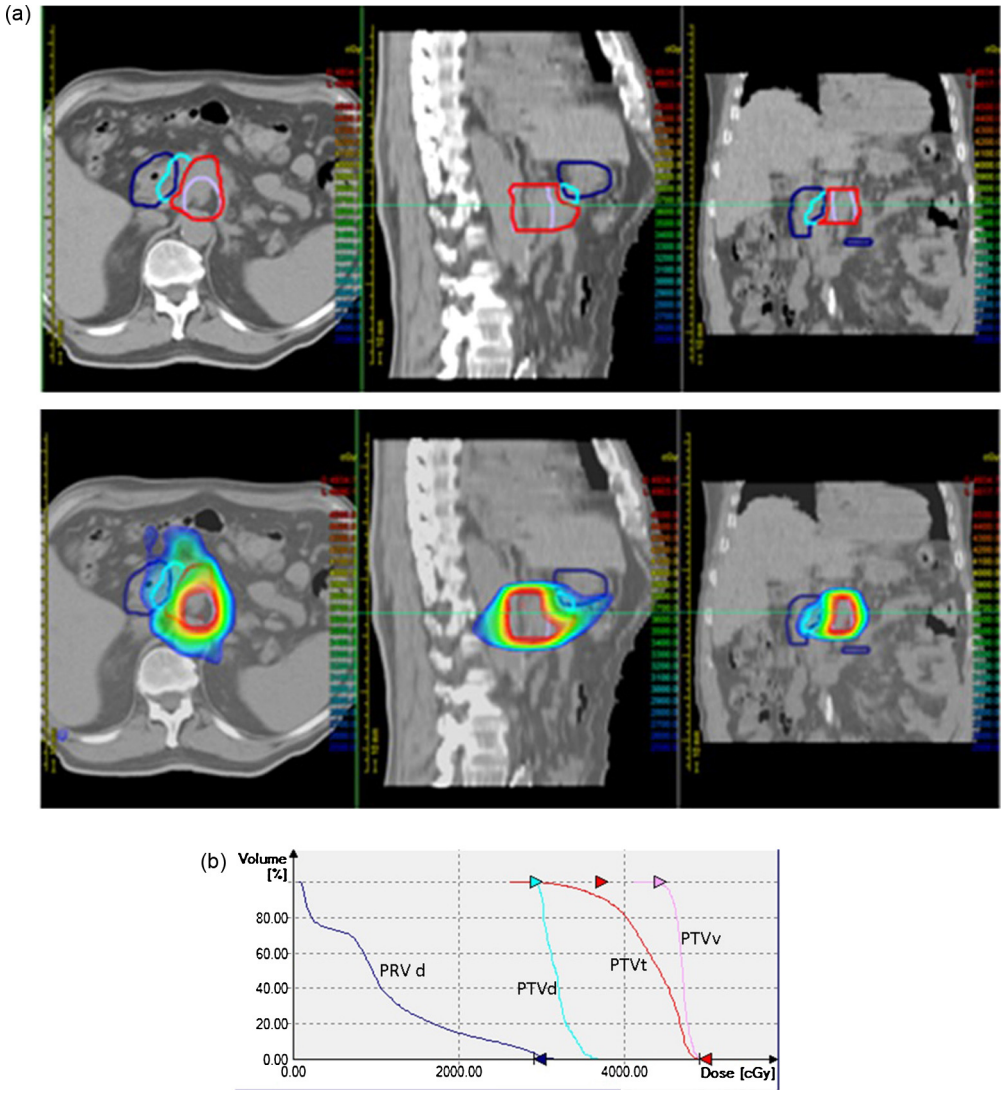

Fig. 1 – (a) Axial, sagittal and coronal slice isodose distribution of SBRT (IMRT-SIB) respecting all constraints (OARs, PTVv $D_{2\%}$, and D_{mean}). The following volumes are shown: Duodenum (blue), PTVd (clear blue), PTVt (red) and PTVv (violet). (b) Dose–volume histogram for PRVd, PTVd, PTVt, PTVv of the same patient respecting all constraints (OARs, PTVv $D_{2\%}$, D_{mean}).

2.7. *Plan evaluation and statistical analysis*

Dosimetric parameters of the PTVs (PTVd, PTVv, PTVt) and PRVs (duodenum, spinal cord, stomach, liver and kidneys) were evaluated using data from tabular cumulative dose-volume histograms (DVHs). Results are reported as a mean value and ranges of each dosimetric parameter.

3. Results

3.1. *Patients characteristics*

Fifteen patients with pancreatic head carcinoma, unresectable due to vascular infiltration, were included in this study. Patient characteristics are shown in Table 1. In all patients the target motion, measured as previously described, was <5 mm in the cranio-caudal direction and <3 mm in the other directions.

3.2. *Planning results*

The planning results are shown in Table 2, while Fig. 1a shows an example of contouring and isodose distribution in one patient and Fig. 1b shows the DVH of the same patient, whereas Fig. 2 illustrates the overall planning results graphically. Overall, the primary end-point (PTVv $D_{mean} > 90\%$) was achieved in all patients. Both PTVv $D_{98\%} > 90\%$ and PTVv $D_{95\%} > 95\%$ were achieved in 6 patients (40%). OARs D_{max} constraints were achieved in all patients. Also volume-constraints for parallel OARs were well within objectives: for the liver mean D_{700cc} was 0.9 Gy (range: 0.0–2.3 Gy) and for kidney mean D_{200cc} was 3.0 Gy (range: 0.3–7.6 Gy). PTVv $D_{2\%}$ was <115% in all patients. Finally, in all patients $D_{50\%}$ was >95% of the prescribed dose for the 3 different PTVs. The mean number of segments per plan was 58 (range: 54–60). Mean number of monitor units was 1732 (range: 1335–1995).

Table 2 – Planning results (Gy).

	Objectives	Mean (range)
PTVv (45.0 Gy)		
D_{mean}	45.0	45.9 (41.5–48.0)
$D_{98\%}$	≥40.5	36.9 (28.4–44.9)
$D_{95\%}$	≥42.7	38.7 (29.7–45.3)
$D_{50\%}$	45.0	46.5 (42.8–48.6)
$D_{2\%}$	<49.5	49.7 (48.8–51.1)
PTVt (37.5 Gy)		
D_{mean}	37.5	42.5 (38.8–45.2)
$D_{98\%}$	≥33.8	31.4 (27.5–33.5)
$D_{95\%}$	≥35.6	33.1 (28.1–35.7)
$D_{50\%}$	37.5	42.6 (37.8–46.5)
PTVd (30.0 Gy)		
D_{mean}	30.0	30.4 (29.0–32.1)
$D_{98\%}$	≥27.0	28.0 (24.8–30.2)
$D_{95\%}$	≥28.5	28.5 (26.5–30.4)
$D_{50\%}$	30.0	30.1 (28.5–31.9)
Duodenum (PRV)		
D_{max}	<32.0	31.6 (30.2–32.0)
$D_{2\%}$		29.5 (28.0–30.3)
Spinal cord (PRV)		
D_{max}	<30.0	14.5 (6.2–29.6)
$D_{2\%}$	<30.0	13.8 (5.2–29.0)
Stomach (PRV)		
D_{max}	<32.0	23.4 (1.6–31.8)
$D_{2\%}$	<30.0	19.2 (0.9–27.8)
Liver		
D_{700cc}	<21.0	0.9 (0.0–2.3)
D_{mean}	Minimize	3.1 (1.0–5.6)
Kidneys		
D_{200cc}	<17.5	3.0 (0.3–7.6)
D_{mean}	Minimize	5.5 (3.4–8.2)

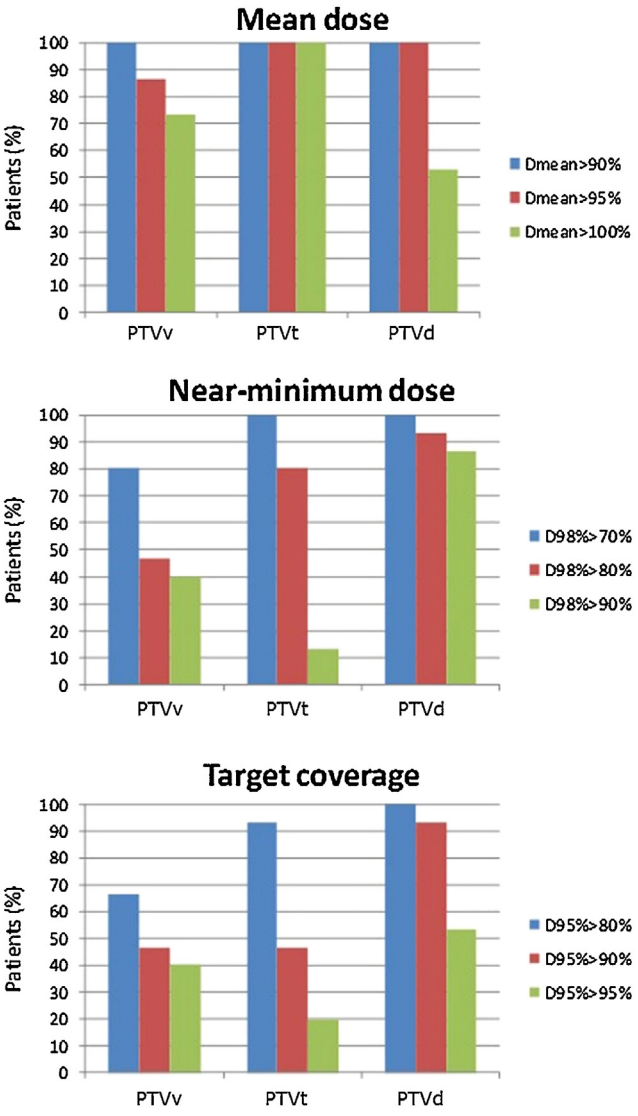

Fig. 2 – Graphical illustration of the overall planning results.

4. Discussion

Locally advanced pancreatic carcinomas represent a difficult therapeutic challenge. In these patients, RT has been used both for symptomatic relief and to increase the probability of radical surgical resection. SBRT is an emerging RT technique for pancreatic tumors, based on high dose irradiation in few fractions on the primary tumor alone, unlike traditional techniques including prophylactic nodal irradiation. The omission of nodal irradiation could be considered as a negative issue, given the high incidence of nodal metastases in pancreatic carcinoma. However, this choice may be acceptable assuming that: (1) RT to advanced pancreatic tumors has usually a palliative purpose; (2) lymph node metastases rarely cause symptoms.

As explained before, in some cases treatment may have a neoadjuvant purpose, with the aim to promote tumor downstaging, especially in cases of vascular infiltration. In fact, vessels involvement is usually the reason for unresectability, unlike nodal metastases. Moreover, it has to be considered that in case of surgery, lymph node metastases are generally removed. Most importantly, even if clinical experience of SBRT is still preliminary, the survival results seem similar to those of standard concurrent chemoradiation.[19]

Therefore, there are two different aims in RT of advanced pancreatic cancer: treatment either for palliative or neoadjuvant purposes. The different intentions obviously lead to varying RT prescriptions. In palliative treatments, a moderate dose should be prescribed to avoid radiation induced toxicity since the goal of therapy is to improve the quality of life. In neoadjuvant treatments, it is preferable to use a high dose, since the risk of duodenal toxicity is avoided by surgical removal of the duodenum. The choice of treatment aim in some cases is quite obvious. For example, in a patient with a complete inclusion of the celiac trunk, it is difficult to expect a downstaging effect able to allow radical surgery. However, in many other cases, the choice is not that obvious. In fact, only after the response evaluation it is possible to know whether the achieved RT effect was only palliative or able to achieve a radical surgical resection. Therefore, in clinical practice, the choice of the treatment goal cannot always be clearly defined.

Our study question originated from these practical clinical considerations. Is a treatment feasible which simultaneously guarantees to most patients a palliative effect without serious toxic effects, with the highest possibility to undergo

radical resection? Therefore, an original scenario based on the combination of two strategies (more dose to the vascular involvement and less dose to the duodenum) was hypothesized. To achieve this result a strongly inhomogeneous dose distribution was accepted and actually pursued. If SBRT, unlike standard RT, is based on a higher dose to the target center to improve the dose gradient at target periphery, in this specific study an extreme dose inhomogeneity had the supplementary goal to achieve two different but contemporary clinical objectives.

The study was based on the use of a dose of 45 Gy in 5 fractions for PTVv, and 30 Gy in 5 fractions for PTVd. This choice was based on several considerations. A dose of 45 Gy in 9 Gy fractions corresponds to an equivalent dose in 2 Gy (EQD2) of 71.2 Gy for acute responders tissues as the tumor (α/β ratio: 10). This is a dose markedly higher compared to preoperative RT studies and, therefore, potentially more effective than standard regimens. The dose of 30 Gy to PTVd corresponds to a EQD_2 for the late effects of 54 Gy, using an α/β ratio of 3. In this case it is a dose lower (even if close) to the maximum tolerable dose for the duodenum (55 Gy). At the same time, it corresponds to an EQD_2 of 40 Gy for acute responders tissues (as the tumor) using an α/β ratio of 10. This dose can be considered sufficient to achieve a palliative effect. In fact, in our previous pilot study, a dose of 30 Gy in 10 fractions (3 Gy/fraction; EQD_2: 32.5 Gy) produced a complete response of pain in 50% of patients with a partial response in a further 25% of patients.[27] Finally, the administration of a higher dose (37.5 Gy, 7.5 Gy/fraction, EQD_2: 54.7 Gy with α/β ratio of 10) to part of the tumor could increase the palliative effect.

In this study, from GTV to PTV margins, for planning purpose in all patients a radial margin of 3 mm and a cranio-caudal margin of 5 mm were used. Although in previous studies of stereotactic radiation therapy lower margins (2–4 mm) were used,[4,14,16] we considered that these larger margins were more reasonable and prudent, with the aim of avoiding marginal misses. In fact, based on the results of a study on organ motion in patients with locally advanced adenocarcinoma of the pancreas, margins of GTV to 10 mm, 7 mm, and 6 mm in the cranio-caudal, anterior-posterior and medial-lateral direction were recommended, respectively.[33] Furthermore, in a study on the effect of abdominal compression, it was observed that with the use of this technique, a cranio-caudal margin of 5 mm is sufficient in 93% of cases.[34]

Furthermore, in this study we defined the vascular CTV by using a 5 mm margin around the infiltrated vessels. Vascular infiltration by pancreatic adenocarcinoma derives from the invasion of perivascular lymphatic vessels and from perineural extension around the vascular wall.[35] In order to obtain an adequate plan for surgical resection we considered as reasonable the delivery of an ablative dose to a 5 mm thick tissues surrounding the vascular wall.

We must admit that the choice of the D_{mean} as the primary objective of the study is not totally conventional. In fact, the ICRU report 83 recommends the use of multiple dose-volume constraints (D_{mean}, $D_{98\%}$, $D_{95\%}$, $D_{2\%}$).[36] However, in the same report it was stated that the desired absorbed dose might be difficult to achieve, particularly in case of overlapping volumes (between PTV and PRV) and conflicting absorbed-dose objectives. In these cases, the ICRU 83 report suggests the use of two different methods. One is represented by dividing the PTV in different segments, some of which contain the overlapping volumes. In the other strategy "the absorbed-dose objectives for planning are relaxed for one or more of the contoured volumes that exhibit overlap regions".[36] In some way, by contemporarily using different PTV and prioritizing the objective of the mean target dose, we tried to achieve "a controlled underdosage of a volume inside the PTV".[36]

We believe that this choice may be clinically acceptable, considering that the proposed treatment does not have the aim of an exclusive therapy but a palliative and/or neoadjuvant purpose. Moreover, it should be emphasized that the achievement of the D_{mean} and $D_{50\%}$ objectives was not obtained at the expense of an extreme overdosing in PTV subvolumes. In fact, in all patients the constraint PTVv $D_{2\%} < 115\%$ was respected.

Furthermore, it can be observed that our dosimetric results were recorded using widely available MLCs (10 mm leaf thickness) and commonly used setting parameters (segment/plan ≤ 60). These results could have been improved by using 5 mm leaf thickness and a larger number of segments.

In conclusion, even if the objective of PTVv $D_{95\%} > 95\%$ was achieved only in 40% of patients, the study showed that in 100% of patients it was possible to administer a strongly differentiated mean and median dose, and in particular a low dose to the overlap region between the target and duodenum, a high dose to the site of vascular infiltration, and an intermediate dose to the remaining target volume. Finally, it should be stressed that median dose ($D_{50\%}$) to PTVv was 42.8–48.6 Gy in 5 fractions, corresponding to an EQD_2 of 66.2–79.9 Gy (median: 71.2 Gy). This equivalent dose is probably underestimated since it does not take into account that treatment is performed in a shorter time compared to standard treatments. Furthermore, this dose is definitely higher compared to standard preoperative treatment of locally advanced pancreatic tumors (median: 50.2 Gy, range: 45–55.8 Gy).[27]

Based on these results, prospective trials based on a clinical application of this strategy seem to be justified, at least in selected patients without overlapping between PTVd and PTVv, to evaluate the clinical efficacy of this technique in the setting of locally advanced pancreatic carcinoma.

Conflict of interests

None declared.

Financial disclosure

None declared.

REFERENCES

1. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008;**19**:1592–9.

2. Morganti AG, Valentini V, Macchia G, et al. 5-Fluorouracil-based chemoradiation in unresectable pancreatic carcinoma: phase I-II dose-escalation study. *Int J Radiat Oncol Biol Phys* 2004;**59**:1454–60.
3. Wolff RA, Varadhachary GR, Evans DB. Adjuvant therapy for adenocarcinoma of the pancreas: analysis of reported trials and recommendations for future progress. *Ann Surg Oncol* 2008;**15**:2773–86.
4. Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J Gastrointest Surg* 2010;**14**:1547–59.
5. Goyal K, Einstein D, Ibarra RA, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *J Surg Res* 2012;**174**:319–25.
6. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol* 2005;**76**:48–53.
7. Koong AC, Christofferson E, Le QT, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**:320–3.
8. Koong AC, Le QT, Ho A, et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2004;**58**:1017–21.
9. Lominska CE, Unger K, Nasr NM, Haddad N, Gagnon G. Stereotactic body radiation therapy for reirradiation of localized adenocarcinoma of the pancreas. *Radiat Oncol* 2012;**7**:74–80.
10. Macchia G, Morganti AG, Cilla S, et al. Quality of life and toxicity of stereotactic radiotherapy in pancreatic tumors: a case series. *Cancer Invest* 2012;**30**:149–55.
11. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;**78**:735–42.
12. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**:e615–22.
13. Rwigema JC, Heron DE, Parikh SD, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer* 2012;**43**:70–6.
14. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2008;**72**:678–86.
15. Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**:181–8.
16. Seo Y, Kim MS, Yoo S, et al. Stereotactic body radiation therapy boost in locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2009;**75**:1456–61.
17. Shen ZT, Wu XH, Li B, Wang L, Zhu XX. Preliminary efficacy of CyberKnife radiosurgery for locally advanced pancreatic cancer. *Chin J Cancer* 2010;**29**:802–9.
18. Gurka MK, Collins SP, Slack R, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. *Radiat Oncol* 2013;**8**:44–53.
19. Buwenge M, Cellini F, Silvestris N, et al. Robotic radiosurgery in pancreatic cancer: a systematic review. *Word J Gastroenterol* 2015;**21**:9420–9.
20. Hajj C, Goodman KA. Pancreatic cancer and SBRT: a new potential option? *Rep Pract Oncol Radiother* 2015;**20**:377–84.
21. Brunner TB, Nestle U, Grosu AL, Partridge M. SBRT in pancreatic cancer: what is the therapeutic window? *Radioth Oncol* 2015;**114**:109–16.
22. Kumar R, Wild AT, Ziegler MA, et al. Stereotactic body radiation therapy planning with duodenal sparing using volumetric-modulated arc therapy vs intensity-modulated radiation therapy in locally advanced pancreatic cancer: a dosimetric analysis. *Med Dosim* 2013;**38**:243–50.
23. Murphy JD, Christman-Skieller C, Kim J, Dieterich S, Chang DT, Koong AC. A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;**78**:1420–6.
24. Adhoute X, Smith D, Vendrely V, et al. Subsequent resection of locally advanced pancreatic carcinoma after chemoradiotherapy. *Gastroenterol Clin Biol* 2006;**30**: 224–30.
25. Aristu J, Canon R, Pardo F, et al. Surgical resection after preoperative chemoradiotherapy benefits selected patients with unresectable pancreatic cancer. *Am J Clin Oncol* 2003;**26**:30–6.
26. Polistina F, Costantin G, Casamassima F, et al. Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. *Ann Surg Oncol* 2010;**17**:2092–101.
27. Morganti AG, Massaccesi M, La Torre G, et al. A systematic review of resectability and survival after concurrent chemoradiation in primarily unresectable pancreatic cancer. *Ann Surg Oncol* 2010;**17**:194–205.
28. Yang W, Reznik R, Fraas BA, et al. Dosimetric evaluation of simultaneous integrated boost during stereotactic body radiation therapy for pancreatic cancer. *Med Dos* 2015;**40**:47–52.
29. Morganti AG, Trodella L, Valentini V, et al. Pain relief with short-term irradiation in locally advanced carcinoma of the pancreas. *J Palliat Care* 2003;**19**:258–62.
30. Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. *Acta Oncol* 1994;**33**: 677–83.
31. Blomgren H, Lax I, Näslund I, Svanström R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 1995;**34**:861–70.
32. Bouchard M, Amos RA, Briere TM, Beddar S, Crance CH. Dose escalation with proton radiation treatment for pancreatic cancer. *Radiother Oncol* 2009;**92**:238–43.
33. Goldstein SD, Ford EC, lDuhon, Mchutt T, Wong J, Herman JM. Use of respiratory-correlated four-dimensional computed tomography to determine acceptable treatment margins for locally advanced pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2010;**76**:59–62.
34. Lovelock DM, Zatcky J, Goodman K, Yamada Y. The effectiveness of a pneumatic compression belt in reducing respiratory motion of abdominal tumors in patients undergoing stereotactic body radiation. *Technol Cancer Res Treat* 2004;**13**:259–67.
35. Noto M, Miwa K, Kitagawa H, et al. Pancreas head carcinoma: frequency of invasion to soft tissue adherent to the superior mesenteric artery. *Am J Surg Pathol* 2005;**29**:1056–61.
36. International Commission on Radiation Unit and measurement. Journal of the ICRU 2010; 10, report 83. Oxford University Press, Chap. 5, p. 55–59.