Dosimetric Study between Helical Tomotherapy, Rapidarc and Fixed Field Intensity Modulated Radiation Therapy for Pancreatic Cancer Cases

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Abstract

Objective: The aim of this present study was to investigate the potential clinical role of a novel treatment technique Rapid-Arc, Helical Tomotherapy (HT) and Conventional IMRT for post-operated pancreatic cancer. Material and Method: Five patients with post operated pancreatic cancer were selected for the dosimetric study. A convenient prescription (2Gy/fraction) was considered: 45 Gy for PTV and 55 Gy for SIBV according to RTOG protocol. For each patient three optimized plans were generated. Constraints to maximum and minimum dose to the PTV were also applied during dose optimization. Results: No statistical significance was observed between RA and HT independently from the MLC resolution meaning that for such small targets, although the resolution matters, the modulation capability of the optimization process is dominant. Concerning organs at risk, all techniques achieved largely the planning objectives described in the methods and proved to have the same degree of inter-patient variability.

Keywords: Rapid Arc, Helical Tomotherapy, Intensity modulated radiotherapy

I. INTRODUCTION

The present study investigate the potential clinical role of a novel treatment technique Rapid-Arc, Helical Tomotherapy (HT) and Conventional IMRT for post-operated pancreatic cancer. Both helical tomotherapy and rapidarc (RA) are rotational radiotherapy modalities that use continuous gantry rotation with dynamic multileaf collimator (MLC). HT delivers intensity-modulated fan beams using binary MLC in a helical rotational pattern about the patient by translating the patient through rotational gantry (TomoTherapy Hi-Art II system) (1-3). Rapidarc, by contrast, uses a conventional linear accelerator (Linac) to deliver radiation in a cone beam geometry using dynamic MLC within one gantry rotation, with no couch translation during the treatment (4-6). The 'conventional' intensity modulation approach with fixed gantry and intensity modulated beams delivering the dose by means of the sliding window approach. The main drawback of IMRT are the more complex and time consuming treatment planning process and the need for more extensive physics quality assurance. In addition, IMRT uses a large number of static beams and monitor units (MUs) (5), which increase radiation delivery times up to 20min and also patient exposure to low –dose radiation.

In general, an increase in the number of IMRT beams increases the degree of freedom (6), making intensity modulation arc therapy a logical next step in IMRT delivery. Several optimization methods for arc therapy based on direct aperture optimization have been described (7-9). A recently described novel approach for volumetric modulated arc therapy enables IMRT like dose distributions to be delivered using a single rotation of the gantry (10).This concept has been clinically implemented in the Eclipse treatment planning software (Varian Medical systems, Palo Alto, CA) under the name Rapid Arc (RA). In RA, the gantry speed, dynamic MLC movement and dose rate vary continuously during delivery. In addition, there is a full leaf interdigitation, allowing multiple small islands of dose to be delivered to the planning target volume (PTV) at each gantry position. Clinical introduction of such new treatment techniques should be preceded by detailed validation of a range of plans (11,12). Extensive studies on treatment planning or dosimetric validation and comparision of RA dose distribution with those obtained by existing IMRT techniques have not yet been reported.

Pioneered by Mackie et al.(1,2), HT was made commercially available by TomoTherapy Inc., and it has been used for a wide variety of applications in clinical radiation oncology(7-9). Each gantry rotation consists of 51 equally spaced beam projections and 64 binary MLC leaves in each projection. Each MLC leaf is individually controlled and allows intensity modulation within a full

range (0-100%) of each projection. Projection time is limited by the gantry rotation speed (15-60sec). The degree of intensity modulation is determined by the modulation factor, which is the maximum leaf open time divided by the average leaf open time. Similar to helical computed tomotherapy (CT), the degree of fan-beam overlapping in HT is determined by the pitch factor, which is the ratio of couch translation per rotation to the jaw width. In the current released version (version 3.1.4) the jaw width options are 1.0, 2.5, and 5.0cm.

Single arc refers that continuously delivers dose throughout one gantry rotation (6,15,16), as opposed to delivering several discrete intensity patterns with multiple gantry rotations. Dose distributions, comparable to a conventional IMRT technique, can be delivered to a conventional IMRT technique, can be delivered in 2 to 4 minutes. Several single arc products are commercially available for clinical implementation, such as Varian's Rapidarc (RA) (Varian Medical System, Palo Alto, CA) adopted from the work of Otto (6). RA delivers radiation in a continuous gantry sweep with dynamic variation of MLC positions, dose rate and gantry speed. A RA MLC sequence consists of a series of aperture shapes and weights for the individual beam angles within the rotational arc. In single arc, only one aperture shape is assigned to each beam angle without intensity modulation in each aperture. The present study comparison was limited to two commercial solutions in addition to RapidArc. In the area of modulated arcs, we selected the Helical Tomotherapy (HT) approach, characterised as the RapidArc shown here, by a purely coplanar beam incidence. To benchmark results against consolidated solutions, we selected the rotational fan beam Helical tomotherapy approach.

Table – 1
Summary of Patient selection and prescription characteristics

Patient	*Targets*	*Volume (cc)*	*Prescription (Gy)*
P1	*PTV*	*599.96*	*45.0*
	SIBV	*287.86*	*57.5*
P2	*PTV*	*399.25*	*45.0*
	SIBV	*175.82*	*57.0*
P3	*PTV*	*235.70*	*45.0*
	SIBV	*076.73*	*57.0*
P4	*PTV*	*700.00*	*45.0*
	SIBV	*357.00*	*57.0*
P5	*PTV*	*437.90*	*45.0*
	SIBV	*168.70*	*57.0*

The existing plan comparison studies were conducted by our institution .Therefore, the conclusions reached may be affected by that institution's relative experience in the techniques of interests, in addition to patient case selection. A recent study has conducted a comparison and shown that rapidarc technique was able to provide shorter treatment time, with a reduction of approximately 40% and plan quality comparable to that of HT (22). The goal of the present study was to perform an unbiased comparison between HT and RA and conventional "fixed field" IMRT by eliminating the aforementioned shortcomings.

II. METHODS AND MATERIALS

A. Patient Selection and Contouring

Five patients with post operated pancreatic cancer were selected for the dosimetric study (Table 1). These patients were randomly selected from the list of patients with pancreas cancer history. Anatomical data were acquired on computed tomography (CT) with adjacent slices 3mm thick. All structures were contoured in Eclipse planning system (Version 8.6.14). All patients were prescribed doses to planning target volume (PTV) and simultaneously integrated boost volume (SIBV). The mean volume for PTV was 474.56 cm^3, minimum 235.7 cm^3 and maximum 700 cm^3. The mean volume for SIBV was 213.11 cm^3, minimum 76.73 cm^3 and maximum 357 cm^3.

B. Treatment Planning

A convenient prescription (2Gy/fraction) was considered: 45 Gy for PTV and 55 Gy for SIBV according to RTOG protocol. Normalisation for all plans was set to the mean dose to the PTV and SIBV. For PTV the planning objectives were to cover at least 95% of the PTV with the 95% prescribed dose, minimum PTV dose > 90% prescribed dose and maximum dose < 107% prescribed dose. For OARs, the tolerance levels for maximum were spinal cord 45Gy, for kidney's mean dose, V_{20}, for liver V_{30} < 66% normal liver volume, for duodenum maximum dose, V_{45}, V_{50}, V_{55} evaluated.

For each patient three optimized plans were generated. Constraints to maximum and minimum dose to the PTV were also applied during dose optimization. The goal of planning was to give the least possible amount of dose to all OARs while not exceeding these dose constraints or degrading tumour coverage. Plans were reviewed and accepted by our physician before being locked and swapped for analysis.

C. Helical Tomotherapy (HT) Plans

The HT planning software used for this study at our institute (Tata memorial hospital) was Hi-Art II version 3.1.4.32. The CT images were taken on GE 4DCT with slice thickness 3mm. CT images were exported to the eclipse planning system for contouring the structures and planning purpose. The contoured CT structured set was exported to HT planning system for purpose of HT planning. The convolution-superposition algorithm based on the collapsed cone approach (23,24) was used for dose calculation in

HT planning system. Details on the HT optimisation process can be found in (3,13,14) and references therein. In this study, a jaw width of 2.5cm and a pitch factor of 0.3 were used for all the cases. The MLC is equipped with 64 leaves with a 0.625cm width at Isocentre. The modulation factor was set to be 2.5 for pancreas cases. A typical dose calculation grid (3.76X3.76X3 mm^3) was used for all the cases. The HT machine commissioned for this planning study is calibrated to 880 cGy/min at a depth of 1.5 cm with 85 cm source-surface distance (SSD) setup.

D. Intensity Modulated Radiotherapy (IMRT) Plans

IMRT plans were optimized according to the 'conventional' intensity modulation approach with fixed gantry and intensity modulated beams delivering the dose by means of the sliding window approach. In Eclipse, the optimization engine of IMRT computes optimal fluence maps from dose volume constraints derived from the general planning objectives. Optimal fluence maps are then converted by a leaf motion calculator into actual fluence maps which are deliverable using a dynamic multileaf collimator according to the sliding window segmentation algorithm. Plans were individually optimized using five coplanar fields in axial plane. Optimizations and dose calculations were done with Eclipse version 8.6.14 (Varian medical systems). Beam geometry optimization was performed by means of the automatic tool implemented in Eclipse as part of the IMRT process. Plans were optimized using the High Definition MLC 120 (HD-MLC). This is characterized by a spatial resolution of 2.5mm at isocentre for the central 8cm and of 5mm in the outer 2x7 cm, a maximum leaf speed of 2.5cm/sec and a leaf transmission of 1%. Dose calculation was performed by means of the AAA algorithm with a spatial resolution of 2.5mm.

E. RapidArc (RA) Plans

At planning level, RapidArc consists of optimising a dose distribution from dose-volume objectives including the optimization from dose-volume objectives including the optimization of the main features of the linac head (e.g. head scatter) and of the MLC (e.g. speed, transmission , round leaf tip and tongue and groove design). To achieve the desired level of modulation required , the optimization is enabled to vary also the instantaneous dose rate from 0 to the maximum (600 or 1000 MU/min depending on the linac type), as well as the gantry rotational speed (from a maximum of 5.5^0/s). To minimize the contribution of tongue and groove effect during the arc rotation and to benefit from the leaves trajectories non coplanar with respect to patient's axis, the collimator rotation in RapidArc is set to values different from zero. In this study collimator was rotated to 45^0.The entire gantry rotation is described in the optimisation process by a sequence of 177 control points (i.e. one control point (CP) every roughly 2^0). A dedicated Progressive Resolution Optimisation (PRO) algorithm (Version 8.6.14) is used by RapidArc. With PRO the total 360^0 arc is initially represented by a small number of 10 control points (elementary beams) with a quite coarse resolution. During optimisation, the dose distribution is computed with a fast Multi-Resolution Dose Calculation Algorithm (MRDC). When dose is calculated for a particular control point, the MLC motion and dose rate are converted into a temporary fluence that models the linac head scattering, and the MLC leakage, rounded leaf ends, tongue and groove design as well as the leaf motion between neighbour control points. MRDC is based on the convolution superposition principle, and it used 3D convolution scatter computation. The PRO algorithm is highly interactive allowing users to adapt dose-volume constraints during the process as well as to go forward or backward in the multi resolution levels to speed up the process or to change optimisation strategy according to user's philosophy. The final dose calculation is performed in Eclipse by means of the AAA algorithm (Version 8.6.14) only.

Plan comparison

The main focuses of our comparison between the three techniques were plan quality and treatment delivery efficiency. Upon the completion and final approval of all treatment plans, dose files of the HT plans were imported into Eclipse and compared with the RA plans. Although the dose calculation grid sizes were different, dose statistics reports of the three sets of plans were generated using the same sampling resolution and the same treatment planning systems. For the ease of comparison, all HT, RA and Fixed field IMRT plans were normalized such that 95% of the target volume received 100% of the prescription dose. Target dose coverage was evaluated by Homogeneity index was defined by Wu et al. (25):

$$HI= (D_2-D_{98})*100/ D_P$$

Where D_2 and D_{98} represent the doses to 2% and 98% of the PTV; D_P represent the prescription dose. Equation indicates that lower homogeneity values indicate a more homogeneous target dose. Analysis was performed on Dose-Volume Histograms (DVHs) computing several standards (15,16) parameters. The confirmity index described by Feuvret et al. (26) and van't Riet et al. (27) is used to assess the target confirmity. It is defined as the product of the percentage of PTV encompassed by the 95% isodose volume, and the proportion of the 95% isodose volume accounted for by the PTV:

CI=(PTV encompassed by the 95% isodose/PTV)*(PTV encompassed by the 95% isodose/95% isodose volume)

The CI ranges from 0 to 1, where 1 is the ideal value.

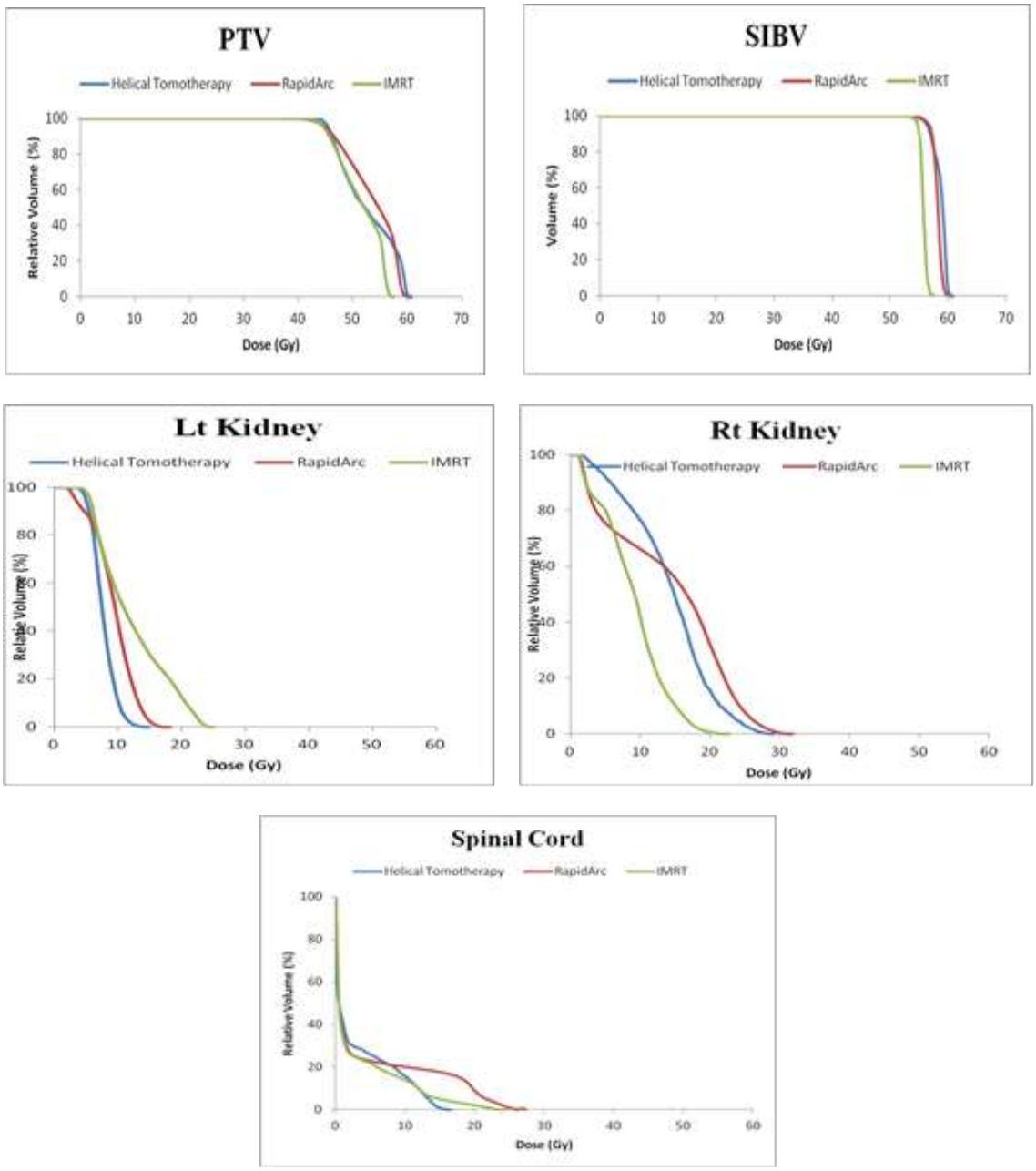

Fig. 3: (DVH)

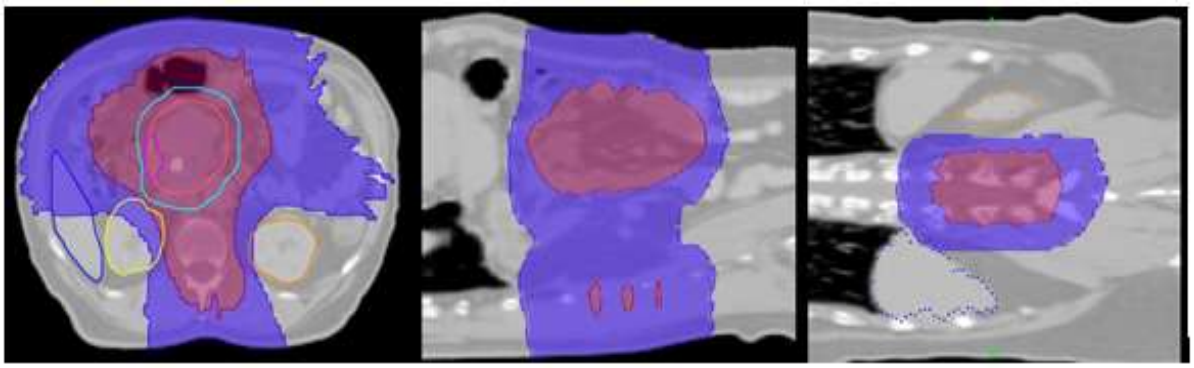

Fig. 2: (30 and 60 % isodose)

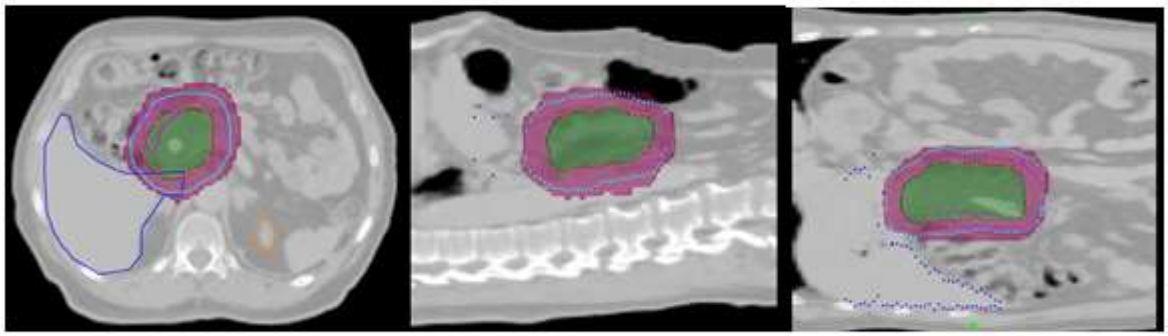

Fig. 1: (95 % isodose)

III. RESULTS

In fig 1, 95 % isodose distributions of prescribed dose to PTV and SIBV on axial, coronal and saggital views are presented for all the techniques for a pancreas cancer cases to provide qualitative overview. In fig 2, shows two low-medium isodose (30% and 60%) to illustrate the differences present in healthy tissue irradiation among the techniques. Fig 3 shows, for PTV, SIBV and most involved OARs, respectively, the cumulative DVHs averaged over all the patients. Tables 2 summarise quantitative analysis of PTV, SIBV and OARs data.

Table - 2
An overview of all investigated DVH-parameters as mean values ± standard deviation (SD)

	Parameters	*Helical*	*RapidArc*	*IMRT*	*t-Test: Paired Two Sample for Means (p-value)*		
		Tomotherapy			*HT vs RapidArc*	*HT vs IMRT*	*RapidArc vs IMRT*
MU		*2129 ± 662*	*469 ± 27*	*1150 ± 223*	*0.0051*	*0.0152*	*0.0027*
Treatment Time (min)		*2.45 ± 0.76*	*1.17 ± 0.07*	*2.87 ± 0.56*	*0.0210*	*0.1669*	*0.0027*
Left Kidney	*V20 %*	*0.32 ± 0.44*	*11.95 ± 10.75*	*10.21 ± 9.77*	*0.0660*	*0.0868*	*0.8107*
	mean Dose (Gy)	*8.74 ± 1.18*	*13.70 ± 3.52*	*11.97 ± 2.46*	*0.0143*	*0.0401*	*0.4397*
Right Kidney	*V20 %*	*19.78 ± 17.7*	*51.63 ± 14.08*	*21.62 ± 19.11*	*0.0091*	*0.8503*	*0.0094*
	mean Dose (Gy)	*15.21 ± 4.14*	*19.67 ± 3.70*	*14.4 ± 3.79*	*0.0324*	*0.6984*	*0.0036*
Liver	*V30 %*	*13.18 ± 10.59*	*9.44 ± 7.95*	*11.01 ± 7.74*	*0.0594*	*0.2919*	*0.0533*
	V40 %	*6.54 ± 5.68*	*5.02 ± 4.49*	*5.14 ± 4.53*	*0.1703*	*0.1356*	*0.6445*
Spinal Cord Maximum Dose (Gy)		*21.10 ± 4.91*	*21.32 ± 8.57*	*32.86 ± 7.64*	*0.9790*	*0.0580*	*0.2826*
Duodenum	*max Dose (Gy)*	*60.43 ± 0.43*	*60.34 ± 1.06*	*54.84 ± 4.32*	*0.9220*	*0.0557*	*0.0740*
	V45 %	*69.02 ± 24.72*	*69.44 ± 26.35*	*64.05 ± 28.32*	*0.8058*	*0.1366*	*0.0173*
	V50 %	*51.65 ± 30.26*	*58.47 ± 29.87*	*45.7 ± 31.42*	*0.1570*	*0.1555*	*0.0083*
	V55 %	*37.10 ± 32.19*	*42.23 ± 32.22*	*24.22 ± 25.95*	*0.1061*	*0.0154*	*0.0106*
PTV	*max Dose (Gy)*	*60.84 ± 0.44*	*60.84 ± 0.96*	*57.53 ± 0.35*	*0.9952*	*0.0001*	*0.0005*
	mean Dose (Gy)	*53.97 ± 0.97*	*54.51 ± 0.79*	*51.48 ± 0.42*	*0.2358*	*0.0039*	*0.0005*
	D2 (Gy)	*59.86 ± 0.50*	*59.46 ± 0.84*	*56.43 ± 0.37*	*0.4223*	*0.0000*	*0.0012*
	D98 (Gy)	*44.68 ± 0.17*	*44.71 ± 1.63*	*43.46 ± 0.65*	*0.9684*	*0.0158*	*0.1349*
	Total Volume (cc)	*470.95 ± 179.46*	*474.5 ± 180.65*	*474.56 ± 180.71*	*0.0043*	*0.0047*	*0.3134*
	HI	*0.34 ± 0.01*	*0.33 ± 0.05*	*0.29 ± 0.02*	*0.7005*	*0.0010*	*0.1171*
	CI95%	*1.00 ± 0.00*	*0.63 ± 0.09*	*0.45 ± 0.06*	*0.0007*	*0.0000*	*0.0002*

SIBV	*max Dose (Gy)*	*60.84 ± 0.44*	*60.71 ± 1.15*	*57.53 ± 0.36*	*0.7807*	*0.0001*	*0.0005*
	mean Dose (Gy)	*58.82 ± 0.15*	*58.26 ± 0.48*	*55.69 ± 0.37*	*0.0728*	*0.0000*	*0.0005*
	D2 (Gy)	*60.47 ± 1.41*	*59.67 ± 0.89*	*56.40 ± 0.53*	*0.3454*	*0.0009*	*0.0010*
	D98 (Gy)	*55.91 ± 0.51*	*56.30 ± 0.72*	*54.3 ± 0.20*	*0.4091*	*0.0009*	*0.1349*
	Total Volume (cc)	*211.45 ± 108.46*	*213.11 ± 109.64*	*213.22 ± 109.83*	*0.0464*	*0.0520*	*0.4207*
	HI	*0.08 ± 0.02*	*0.06 ± 0.02*	*0.04 ± 0.01*	*0.1832*	*0.0023*	*0.0800*
	CI95%	*1.00 ± 0.00*	*1.00 ± 0.00*	*0.98 ± 0.01*	*0.4591*	*0.0358*	*0.0002*

For PTV and SIBV, it can be seen from both average DVH graph and summary of numerical findings that all techniques provided good and equivalent results although statistically significant differences can be observed between the various couples from t-paired tests (p-value). The most relevant findings are linked to the superior coverage of HT and able to save the left kidney better than with the other techniques due to directional blocking. In terms of inter-patient dose variability, expressed by the standard deviation computed per each technique, all approaches are comparable. No statistical significance was observed between RA and HT independently from the MLC resolution meaning that for such small targets, although the resolution matters, the modulation capability of the optimization process is dominant.

Concerning organs at risk, all techniques achieved largely the planning objectives described in the methods and proved to have the same degree of inter-patient variability. The statistical significant differences revealed by paired t-paired tests should therefore be considered anymore subject to valuable costs in the optimisation process. With this disclaim enforced, it shall be noticed that with conventional fixed field IMRT, we are able to achieve better or comparable sparing for the Right kidney and duodenum compared with Rapid Arc by selecting beam angles that restricts the beam. Liver dose was comparable in all the three techniques. Relatively to the normal pancreas and the total healthy tissue (body volume in the CT dataset minus the target), RA plans improved HT findings independently from MLC resolution while, systematically, the plans based on High definition MLC resulted better results. The integral dose analysis showed that IMRT has the minimum impact while, among rotational techniques, the RA is potentially superior to HT (significantly for RA_HD120) and that finer MLC resolution can enhance the effect.

The number of monitor units and treatment time for all three techniques (RA, HT and IMRT) plans were noted in Table 2. Averaging over the 5 plans studied, the MUs with HT were 4.5 times more compared to RA and 1.85 times more compared to IMRT. When comparing the treatment time, RA had an average beam on time of 1.17 minutes (range, 1.09 -2.27 minutes), which was 2.09 times shorter than that for HT (range, 1.72 - 3.55 minutes) and 2.45 times shorter than that for IMRT (range, 2.19-3.53 minutes.

IV. DISCUSSIONS

Our study showed that the optimal choice of radiation therapy modality for safe dose escalation depends on the pancreatic tumor position in relation to OAR anatomy. Rapidarc, Helical tomotherapy, IMRT and 3DCRT plans showed advantageous results, but for different tumor positions. 3DCRT plans presented considerably inferior target coverage compared with the other three modalities. Due to PTV, SIBV and OAR overlap, full target coverage was not met by any technique or tumor position for plans that fully respected OAR constraints with the best coverage achievable. However, interesting conclusions can be drawn from the plans generated with full target coverage which can be extrapolated to new cases.

This study reports a comparison of the helical tomotherapy (HT) technique compared to RapidArc, fixed beam IMRT. Similar investigations on different indications are appearing. Palma et al. investigated RapidArc progenitor on prostate showing that variable dose rate volumetric arc modulation is beneficial compared to IMRT or constant dose rate [29]. Fogliata et al. investigated RapidArc on small benign brain tumors compared to IMRT and helical tomotherapy [16]. It is expected that in a relatively short time-frame a systematic insight of the clinical role of the novel volumetric modulated arc therapy approaches will appear. The planning case selected for this investigation was the cancer of pancreatic since it is a demanding indication.

As all comparative studies, also the present one is potentially affected by limitations that shall be clarified. The most important are linked to the difficulty to eliminate any type of bias in the elaboration of dose plans induced different calculation algorithm. The dose calculation algorithm and all tools to generate dose distributions, DVH and analysis are the same for all plans.

Compared to IMRT, which has been proven to be superior to conventional treatments [17,20,27,30,34,41], RapidArc and helical tomotherapy allows one to keep the same PTV and SIBV coverage with an improved homogeneity and better conformality and, at the same time, presented a major reduction of irradiation of kidney, liver and spinal cord over the entire medium to high dose levels with highly statistically significant differences.

RapidArc allowed a strong reduction of MU/Gy compared to IMRT (roughly a factor 2) and helical tomotherapy. It is known and accepted that, in treatments with linear accelerators, the scattered radiation impinging on the patient's body outside the treated volume is at first-order directly proportional to the monitor units applied (lucca cozzy paper ref).

One of the objectives of RapidArc is the capability to deliver treatments in short times. For the cases under investigation, beam-on time was estimated to be less than 1.5 min. Studies from other IMAT approaches [12,13] reported mean delivery time of 6.3

min for medium size tumors increasing to about 14 min for large volumes. Helical Tomotherapy [4] reported average beam-on time of 11 min.

V. CONCLUSION

Our study showed that the optimal choice of radiation therapy modality for safe dose escalation depends on the pancreatic tumor positions relative to OAR anatomy. IMRT allows more conformal dose distribution in the high-dose regions, whereas PT reduces low doses to GI-OAR. This GI-OAR sparing gain with PT is an interesting aspect for further clinical investigation in combination with future attempts of systemic treatment intensification.

REFERENCES

[1] Agren-Cronqvist AK. Quantification of the response of heterogeneous tumours and organized normal tissues to fractionated radiotherapy. PhD thesis, Stockholm University, Department of Medical Radiation Physics Stockholm; 1995.
[2] Ahmed R, Kim R, Duan J, Meleth S, De Los Santos J, Fiveash J. IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cancer while reducing dose to bone marrow and other organs at risk. Int J Radiat Oncol Biol Phys 2004;60:505–12.
[3] Barraclough L, Swindell R, Livsey J, Hunter R, Davidson S. External beam boost for cancer of the cervix uteri when intracavitarz therapy cannot be performed. Int J Radiat Oncol Biol Phys 2008;71:772–8.
[4] Bijdekerke P, Verellen D, Tournel K, Vinh-Hung V, Somers F, Biesman P, et al. TomoTherapy: implications on daily workload and scheduling patients. Radiother Oncol 2008;86:224–30.
[5] Bragg C, Windate K, Conway J. Clinical implications of the anisotropic analytical algorithm for IMRT treatment planning and verification. Radiother Oncol 2008;86:276–84.
[6] Cameron C. Sweeping-window arc therapy: an implementation of rotational IMRT with automatic beam-weight calculation. Phys Med Biol 2005;50:4317–36.
[7] Chui C, LoSasso T, Spirou S. Dose calculation for photon beams with intensity modulation generated by dynamic jaw or multileaf collimations. Med Phys 1994;21:1237–44.
[8] Chui C, Chan M, Yorke E, Spirou S, Ling C. Delivery of intensitymodulated radiation therapy with a conventional multileaf collimator: comparison of dynamic and segmental methods. Med Phys 2001;28:2441–9.
[9] Convery D, Rosenbloom M. The generation of intensity-modulated fields for conformal radiotherapy by dynamic collimation. Phys Med Biol 1992;37:1359–74.
[10] Cotrutz C, Kappas C, Webb S. Intensity modulated arc therapy (IMAT) with centrally blocked rotational fields. Phys Med Biol 2000;45:2185–206.
[11] Creutyberg C, Van Putten W, Koper P, et al. For the PORTC (Post Operative Radiation Therapy in Endometrial Carcinoma) Study Group. Surgery and postoperative radiotherapy versus surgery alone for patients with stage 1 endometrial carcinoma. Multicentre randomized trial. Lancet 2000;355:1404–11.
[12] Duthoy W, De Gersem W, Vergote K, Botenberf T, Derie C, Smeets P, et al. Clinical implementation of intensity modulated arc therapy (IMAT) for rectal cancer. Int J Radiat Oncol Biol Phys 2004;60:794–806.
[13] Duthoy W, De Gersem W, Vergote K, Coghe M, Botenberf T, De Deene Y, et al. Whole abdominal radiotherpay (WAPRT) using intensity modulated arc therapy (IMAT): first clinical experience. Int J Radiat Oncol Biol Phys 2003;57:1019–32.
[14] Earl M, Shepard D, Naqvi S, Li X, Zu CX. Inverse planning for intensity modulated arc therapy using direct aperture optimization. Phys Med Biol 2003;21:1075–89.
[15] Fogliata A, Vanetti E, Albers D, et al. On the dosimetric behaviour of photon dose calculation algorithms in the presence of simple geometric heterogeneities: comparison with Monte Carlo calculations. Phys Med Biol 2007;52:1363–85.
[16] Fogliata A, Clivio A, Nicolini G, Vanetti E, Cozzi L. Intensity modulation with photons for benign intracranial tumours. A planning comparison of volumetric single arc, helical arc and fixed gantry techniques. Radiother Oncol 2008; doi:10.1016/j.radonc.2008.07.021.
[17] Georg P, Georg D, Hillbrand M, Kirisits C, Poetter R. Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. Radiother Oncol 2006;80:19–26.
[18] Green J, Kirwan J, Tierney J, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer on the uterine cervix. A systematic review and meta analysis. Lancet 2001;358:781–6.
[19] Grisby P. Update on radiation therapy for endometrial cancer. Oncology 2002;16:777–86.
[20] Guckenberger M, Baier K, Richter A, Vordermark D, Flentje M. Dose Intensity Modulated Radiation Therapy (IMRT) prevent additional toxicity of treating the pelvic lymph nodes compared to treatment of the prostate only? Radiat Oncol 2008;3:3.
[21] Hall EJ. Intensity modulated radiation therapy, protons and the risk of second cancers. Int J Radiat Oncol Biol Phys 2006;65:1–7.
[22] Ka¨llmann P, Agren A, Brahme A. Tumour and normal tissue esponses to fractionated non-uniform dose delivery. Int J Radiat Biol 1992;62:249–62.
[23] Kno¨o¨s T, Wieslander E, Cozzi L, et al. Comparison of dose calculation algorithms for treatment planning in external photon beam therapy for clinical situations. Phys Med Biol 2006;51:5785–807.
[24] Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin based chemotherapy plus radiotherapy for cervical cancer. A meta analysis. Clin Oncol 2002;14:203–12.
[25] MacKenzie MA, Robinson DM. Intensity modulated arc deliveries approximated by a large number of fixed gantry position sliding window dynamic multileaf collimator fields. Med Phys 2002;29:2359–65.
[26] Moiseenko V, Duzenli C, Durand R. In vitro study of cell survival following dynamic MLC intensity-modulated radiatioh therapy dose delivery. Med Phys 2007;34:1514–20.
[27] Mundt A, Lujan A, Rotmensch J, Waggner S, Yamada D, Fleming G, et al. Intensity modulated whole pelvic radiotherapy in women with gynaecologic malignancies. Int J Radiat Oncol Biol Phys 2002;52:1330–7.
[28] Otto K. Volumetric modulated arc therapy: IMRT in a single arc. Med Phys 2008;35:310–7.
[29] Palma D, Vollans E, James K, Nakano S, Moiseenko V, Shaffer R, et al. Volumetric modulated arc therapy for delivery of prostate radiotherapy. Comparison with intensity modulated radiotherapy and three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2008. e-pub.
[30] Portelance L, Chao C, Grisby P, Benner H, Low D. Intensity modulated radiation therapy (IMRT) reduces small bowel, rectum and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys 2001;51:261–6.
[31] Ramsey C, Seibert R, Mahan S, Desai D, Chase D. Out of field dosimetry measurements for a helical tomotherapy system. J Appl Clin Med Phys 2006:7.
[32] Rancati T, Fiorino C, Gagliardi G, et al. Fitting late rectal bleeding data using different NTCP models: results from an Italian multi-centric study (AIROPROS0101). Radiother Oncol 2004;73:21–32.
[33] Roeske J, Mundt A, Halpen H, et al. Late rectal sequelae following definitive radiation therapy for carcinoma of the uterine cervix. A dosimetric analysis. Int J Radiat Oncol Biol Phys 1997;37:351–8.

[34] Roeske J, Lujan A, Rotmensch J, Waggner S, Yamada D, Mundt A. Intensity modulated whole pelvic radiation therapy in patients with gynaecologic malignancies. Int J Radiat Oncol Biol Phys 2000;48:1613–21.
[35] Spirou S, Chui C. Generation of arbitrary intensity profiles by dynamic jaws or multileaf collimators. Med Phys 1994;21:1031–41.
[36] Spirou S, Chui C. A gradient inverse planning algorithm with dose–volume constrains. Med Phys 1998;25:321–33.
[37] Ulmer W, Pyyry J, Kaissl W. A 3D photon superposition/convolution algorithm and its foundation on results of Monte Carlo calculations. Phys Med Biol 2005;50:1767–90.
[38] Vrdoljak E, Prskalo T, Omrcen T, Situm K, Boraska T, Frleta I, et al. Concomitant chemobrachyradiotherapy owith ifosfamide and cisplatin followed by consolidation chemotherapy in locally advanced squamous cell carcinoma of the uterine cerix. Results of a phase II study. Int J Radiat Oncol Biol Phys 2005;61:824–9.
[39] Yu CX. Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy. Phys Med Biol 1995;40:1435–49.
[40] Yu CX, Li XA, Ma L, et al. Clinical implementation of intensitymodulated arc therapy. Int J Radiat Oncol Biol Phys 2002;53:453–63.
[41] Wong E, D'Souza D, Chen J, Lock M, Rodrigues G, Coad T, et al. Intensity modulated arc therapy for treatment of high risk endometrial malignancies. Int J Radiat Oncol Biol Phys 2005;61:830–41.