ORIGINAL ARTICLE

Dosimetric Comparison of Rapid arc, Intensity Modulated Radiotherapy and 3D Conformal Radiotherapy Plans in Periampullary and Pancreatic Head Carcinomas

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ABSTRACT

Background and purpose This study was done to compare dosimetric characteristics between Rapid Arc, Intensity Modulated Radiotherapy and 3D-Conformal Radiotherapy plans in periampullary and pancreatic head carcinomas. **Materials and methods** For a total of 15 patients requiring adjuvant or radical radiotherapy; rapid arc, intensity modulated radiotherapy and 3D-Conformal radiotherapy plans were evaluated. The clinical target volume included the postoperative tumour bed or the gross tumour with a 3 cm margin within the body of the pancreas and the draining lymph nodal areas. The dose prescribed was 50.4 Gy in 28 fractions over 5 weeks. Homogeneity and Conformity indices, Organs at risk and planning target volume doses; MUs delivered and treatment times were compared. **Results** The conformity indices was better in rapid arc, intensity modulated radiotherapy had better homogeneity indices; conformity indices and homogeneity indices were significantly inferior in 3D-Conformal radiotherapy. Right kidney mean dose could be reduced in rapid arc; left kidney mean doses were comparable in all three techniques. Mean doses of stomach, gut and liver were minimised in rapid arc. MUs delivered and treatment times were lessened in rapid arc compared to intensity modulated radiotherapy. **Conclusion** Rapid Arc plans could provide slight improvements in organs at risk sparing, lower MUs and decreased treatment times with a slightly better target coverage compared to intensity modulated radiotherapy and significantly better to 3D-Conformal radiotherapy.

INTRODUCTION

Periampullary carcinomas arise within 2 cm of the major papilla in the duodenum and encompass malignancies arising from the ampulla of Vater, intrapancreatic distal bile duct, duodenal tumours (usually the second part) involving the papilla and tumours of the head and uncinate process of the pancreas involving the ampulla [1]. They constitute 30% of malignant tumours that arise from the pancreatic head region [2]. They display unique characteristics due to their site specific origin and are a separate entity from the classical adenocarcinoma of the pancreatic head. Periampullary adenocarcinomas carry a better prognosis than adenocarcinoma of the pancreatic head [3].

Pancreatic cancer is currently the fourth leading cause of cancer death in the United States, and is anticipated to become the second by 2020 [4]. In 2015, an estimated 48,960 people are expected to be diagnosed with pancreatic cancer in the United States, and approximately 40,560 were expected to die from the disease [5].

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Abbreviations 3DCRT 3D-Conformal Radiotherapy; HI CI Homogeneity and Conformity indices; IMRT Intensity Modulated Radiotherapy; PTV planning target volume; OAR Organs at risk; RA Rapid Arc
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For all stages combined, the 1- and 5-year relative survival rates are 28% and 7%, respectively. Even for the small percentage of people diagnosed with local disease (9%), the 5-year survival is only 26%. More than half (53%) of the patients are diagnosed at a distant stage, for which 1- and 5-year survival is 15% and 2%, respectively [5]. Surgical resection remains the only potentially curative treatment strategy for patients with resectable pancreatic cancer [6]. The local failure rates are high (50-86%) despite resection because of retroperitoneal soft tissue infiltration in these cancers leading to surgeon's inability to achieve wide posterior margins secondary to anatomic constraints vide superior mesenteric vessels, portal vein and inferior vena cava [7, 8, 9, 10]. Thus, adjuvant radiation therapy along with chemotherapy would appear to be a logical choice for resectable pancreatic cancers [11].

The role of radiotherapy in pancreatic cancers in the adjuvant setting remains controversial. This is because; two decades ago, though the Gastrointestinal Tumour Study Group (GITSG) reported a survival benefit in patients treated with 5-fluorouracil (5-FU) and radiotherapy compared with radiotherapy alone [12]; the EORTC [13] trial reported otherwise. Subsequently the ECOG trial did demonstrate a survival benefit in patients treated with concurrent gemcitabine and radiation compared with gemcitabine alone [14].

For unresectable or borderline resectable pancreatic cancer, chemoradiotherapy remains a considerable option for treatment [15] as local progression rates range

from 38% to 55% [15, 16, 17]. Improved local control is crucial because of the potential for obstruction and pain associated with local progression. Furthermore, the need for improved local control may become more apparent as systemic modalities improve.

Radiotherapy in pancreatic carcinomas is a complex job considering the volumes that need to be treated. With conventional radiotherapy; acute toxicity and late complication rates were high due to close proximity of surrounding critical structures like spinal cord, stomach, duodenum, liver, gut and others. Radio biologically suboptimal radiation doses were rendered to overcome the limitations in delivery systems proving to be of inconsequential benefit. Modern radiotherapy using multifield conformal radiotherapy helps to minimise the dose to most of these organs leading to reduction in treatment related morbidity, thus permitting delivery of higher external beam radiation doses than were previously possible [18, 20, 21].

With the development of an advanced form of 3D Conformal Radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT) can improve radiation plan quality by using an inverse planning algorithm to generate complex spatial dose distributions to conform more closely to the target volume. In recent years, Rapid Arc (RA) plans have improved the time efficiency of dose delivery and produced highly conformal dose distribution by changing treatment apertures (defined by dynamic multiple leaf collimators) and a modulated dose rate [22].

Poon *et al*. [23] have reported a significant improvement in sparing organs at risk (OARs) and better conformity using RA compared with IMRT.

The purpose of this study was to compare the dosimetric parameters of RA, IMRT, and 3DCRT plans for pancreatic and periampullary carcinomas and the doses received by the OARs.

MATERIALS AND METHODS

Samples

A total of 15 patients with nonmetastatic resected or unresectable periampullary and pancreatic head cancers who received radiotherapy; with or without chemotherapy between May 2013 and September 2014 were included in the present study. All patients had a confirmed histopathology, were referred for either adjuvant or radical radiotherapy. Patients were staged according to the American Joint Committee on Cancer staging system (7th edition) [24]. All patients were immobilized in a supine position, with arms above the head using the whole body SecureVac immobilisation system. Contrast enhanced; both oral (negative contrast) and intravenous, 3 mm planning scans were acquired from carina to iliac crest using a multislice CT scanner (Philips Medical Systems). Respiratory control and abdominal compression were not employed. Following simulation, the CT images were exported to the eclipse (version 9.2) radiation treatment planning system (Varian Medical Systems). RTOG contouring guidelines [25], were used to delineate the clinical target volume (CTV) which included the tumour bed, pancreaticojejunostmy and or choledochojejunostomy in post-operative cases or gross tumour with 3cm margin within the body of pancreas in inoperable cases. Lymph nodal stations included were para-aortic, celiac axis, superior mesenteric, common hepatic, porta hepatis and peri-pancreatic. For cases with gross tumour; inferior pyloric and hepatoduodenal lymph nodal stations were incorporated following the recommendations by Caravatta [26]. The CTV to PTV expansion was typically 7 mm to account for daily setup error and organ motion. Normal structure contouring included the spinal cord, liver, bowel bag, stomach, duodenum, and kidneys. All the contours were drawn by the same Radiation Oncologist.

Planning

For each patient, 3DCRT plans used one anterior and two lateral fields. The IMRT plans were computed with multiple fixed gantries sliding window technique. An anisotropic analytical algorithm was used for dose computation with a dose calculation grid of 2.5 mm^3. 5/7fields were used to generate the IMRT plans. Two simultaneously optimized volumetric partial arcs were used for RA and all plans were done on Eclipse treatment planning system (version 11.0.42). The dose prescribed was 50.4 Gy in 28 fractions over 5 weeks in all the cases.

6 MV was used to generate all plans. For the PTV, the Conformity Index (CI) [(VDP) PTV/ (VDP) BODY] and Homogeneity index (HI) [D5%/D95%] was computed. Doses to OARs were analysed. The planning objective was to achieve >95% coverage to >95% of the Planning Target Volume (PTV) while meeting the normal-tissue dose constraints. Monitor units (MUs) delivered; beam-on-times (BOT) and treatment times were compared.

Statistical Analysis

Data entry was done in SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA) and all data are presented as the mean ± standard error of mean. Paired t test was performed to compare means and $P<0.05$(two –sided) was considered to indicate a statistically significant difference.

RESULTS

Patient Characteristics

The characteristics of patients are summarized in **Table 1**. There were 9 males and 6 females, and their median age was 54 years (range, 40–70 years). The mean PTV was (508.34±21.29) cm^3 (range, 345.11-653.85 cm^3). **Table 2** enumerates the PTV volumes of all the patients.

Target Coverage, Dose Homogeneity and Conformity

The coverage of PTVs of the three plans was evaluated by Dmax, Dmean, Dmin, HI and CI. The mean Dmax, Dmean and Dmin doses for RA, IMRT and 3DCRT are enumerated in **Tables 3, 4**. 3DCRT generated higher max and min doses in PTV; mean doses were higher in RA compared to IMRT

Table 1. Patient characteristics.

Parameters	Patients, N (%)
Gender	
Male	9(60)
Female	6(40)
T classification	
T1	0(0)
T2	2(13.33)
T3	8(53.33)
T4	5(33.33)
Nodal Status	
Node negative	2(13.33)
Node positive	5(33.33)
Unknown	8
Surgery	
Total pancreatectomy	1(6.66)
Whipple's resection	8(53.33)
Borderline resectable	1(6.67)
Inoperable	5(33.33)

Table 2. Planning Target Volumes (PTVs) of all the patients.

Patients	PTV Volumes(cc)
2	515.92
3	497.22
4	467.59
5	653.85
6	468.67
7	529.74
8	472.31
9	480.12
10	345.11
11	570.35
12	595.8
13	541.3
14	612.41
15	374.14

or 3DCRT. RA and IMRT plans had excellent coverage of the PTV with at least 95% of the PTV receiving ≥ 95% of the prescribed dose. The conformity was better in RA (0.98); homogeneity was better in IMRT (1.04); 3DCRT plans had significantly inferior CI (0.75) and HI (1.09).

OARs

Kidneys

The mean dose of the right kidney was low in RA and IMRT compared to 3DCRT though not statistically significant. The mean doses of left kidney were comparable in all the three plans. For the low-dose region, V10 Gy of right kidney was lowered in RA and IMRT compared to 3DCRT though not statistically significant. V10 Gy of left kidney were almost equivalent in all the three plans. V20 Gy of right kidney was significantly decreased in RA compared to IMRT (p=0.040) and 3DCRT (p=0.006), whereas for left kidney it was significantly lessened in RA compared to 3DCRT (p= 0.02) only. V30 Gy doses of right kidney were comparable between RA and IMRT but were significantly lessened in comparison to 3DCRT (p=<.001). For the left kidney V30 Gy though; RA attained doses much less than IMRT (p=0.035) and 3DCRT (p=0.001); the dose difference between IMRT and 3DCRT was significant too (p=0.002).

Liver

3DCRT obtained the highest high-dose distribution in the liver compared to IMRT and RA. The difference in means between RA and IMRT, IMRT and 3DCRT, 3DCRT and RA were statistically significant (p<0.001). For V10 Gymean, the difference in dose between RA and 3DCRT were statistically significant (p=0.007). There was significant reduction of V20 Gymean and V30 Gymean of liver in RA plans (p=.003, p-.019) compared to IMRT (p=0.003, p=0.001) or 3DCRT (p<0.001, p<0.001). The difference in doses between IMRT and 3DCRT were also statistically significant (p=0.019, p<0.001).

Stomach, Duodenum, Gut and Spinal cord

The max dose in stomach was higher in 3DCRT than RA and was the least in IMRT; the difference in doses between them being statistically significant (RA *vs*. IMRT; p<0.001, IMRT *vs*. 3DCRT; p<0.001, 3DCRT *vs*. RA; p=0.004). The mean dose was higher in 3DCRT (20.60±1.67) compared to RA (16.77±1.30)/IMRT (17.18±1.19); where the doses were comparable. Data for duodenum was obtained for 12 patients only as the rest had duodenal involvement. Both max and mean doses to duodenum were comparable among the three plans. The mean dose received by gut was higher in 3DCRT compared to IMRT/ 3DCRT (p<0.001). Considering the meanV45 Gy doses, 3DCRT attained higher dose distribution than IMRT/RA (p<0.001).Spinal cord max doses were actually lower in 3DCRT compared to IMRT / RA (P<0.001).

Monitor Units, and Delivery Time

The MUs delivered in RA (474) could be significantly reduced from IMRT (727, p<0.001). MUs delivered in 3DCRT though were considerably lower (276). Though mean beam –on times were higher for RA (1.60 mins) than IMRT (1.13 mins), mean treatment times were actually longer in IMRT (4 mins) than RA (2mins).

DISCUSSION

Table 3. OARs dose constraints.

OARs	Prescribed dose limit
Spinal Cord	
Dmax	<40 Gy
Liver	
V30	<30%
Kidney	
V13	<50%
V18	<33%
Small Intestine	
Dmax	<50 Gy
V50	<10%
V45	<15%
Duodenum	
Dmax	<50 Gy
V50	<10%
Vn, percentage of volume receiving at least x Gy	

Table 4. Organs at risk (OARs) DVH mean parameters and t-test comparisons for the 3 different treatment planning techniques.

Organs	Dose/Volume(± SE)			t test		
PTV	**RA**	**IMRT**	**3DCRT**	**RA *vs.* IMRT**	**IMRT *vs.* 3DCRT**	**3DCRT *vs.* RA**
Dmax (Gy)	53.68±0.15	51.86±0.15	54.02±0.14	<0.001	<0.001	0.051
Dmean (Gy)	50.58±0.04	49.73±0.08	50.30±0.06	<0.001	<0.001	0.001
Dmin (Gy)	41.99±0.15	40.63±0.48	43.68±0.41	0.005	<0.001	<0.001
CI	0.98±0.00	0.95±0.00	0.75±0.01	0.002	<0.001	<0.001
HI	1.05±0.00	1.04±0.00	1.09±0.00	0.011	<0.001	<0.001
Right Kidney						
Dmean (Gy)	11.92±0.61	12.48±0.90	17.27±2.43	0.331	0.102	0.055
V10 (%)	50.29±4.72	50.27±5.15	58.93±5.30	0.996	0.099	0.112
V20 (%)	13.48±1.57	20.25±3.11	21.75±2.29	0.040	0.599	0.006
V30 (%)	3.91±0.83	5.29±1.04	12.91±1.40	0.116	<0.001	<0.001
Left Kidney						
Dmean (Gy)	11.61±0.76	11.41±0.94	11.78±1.13	0.735	0.625	0.850
V10 (%)	49.54±5.85	46.45±6.11	45.46±5.39	0.606	0.865	0.561
V20 (%)	11.79±2.40	14.73±2.59	17.71±2.62	0.196	0.181	0.021
V30 (%)	2.70±0.65	4.02±0.98	10.87±2.23	0.035	0.002	0.001
Liver						
Dmean (Gy)	15.27±0.64	16.22±0.69	19.22±0.66	<0.001	<0.001	<0.001
V10 (%)	47.06±2.16	49.99±1.69	51.81±1.92	0.091	0.053	0.007
V20 (%)	32.57±1.86	38.41±1.98	41.40±1.65	0.003	0.019	<0.001
V30 (%)	18.62±1.63	22.07±1.72	37.66±2.63	0.001	<0.001	<0.001
Stomach						
Dmax (Gy)	52.09±0.30	50.76±0.27	53.62±0.23	<0.001	<0.001	0.004
Dmean (Gy)	16.77±1.30	17.18±1.19	20.60±1.67	0.604	0.001	0.004
Duodenum						
Dmax (Gy)	51.75±0.39	50.29±0.33	51.10±0.86	0.242	0.281	0.314
Dmean (Gy)	40.65±2.55	40.21±2.69	43.47±2.89	0.357	0.076	0.062
GUT						
Dmean (Gy)	17.81±1.57	17.28±1.44	22.33±1.82	0.051	<0.001	<0.001
V45 (Gy)	5.36±1.34	5.45±1.29	9.39±1.77	0.583	<0.001	<0.001
Spinal Cord						
Dmax (Gy)	27.62±1.32	28.12±1.53	16.46±0.88	0.638	<0.001	<0.001
MUs	474±9.67	727±34.89	276±2.90	<0.001	<0.001	<0.001
Time	1.60±0.06	1.13±0.04	0.70±0.10	<0.001	<0.001	<0.001

The primary benefit of IMRT over 3DCRT treatment planning as we know today is its ability to generate highly conformal treatment plans, which can theoretically deliver a high tumour dose while sparing the surrounding critical organs. IMRT has proved to be worthwhile in prostate cancer as it has facilitated dose escalation thereby increasing biochemical relapse free survival rates [27]. Toxicity profiles have improved vastly in head and neck cancers with IMRT [28, 29].

IMRT may prove to be valuable in pancreatic cancers as it may limit treatment-related toxicity and provide ample scope for dose escalation given the historically poor survival outcomes in this disease. One of the major goals of treatment would be optimizing quality of life in addition to maximizing tumour control.

Several studies have looked at IMRT plans in pancreatic cancers and found them superior to 3DCRT in reducing the mean doses to the organs at risk [30, 31]. Milano *et al*. [32] published a dosimetric comparison of 3DCRT and IMRT in 25 patients of pancreatic and bile duct malignancies with CTV encompassing the draining lymphatics; IMRT reduced the mean doses in all critical structures with a statistically significant reduction in mean doses only for the right kidney and small bowel; the differences were greater when considering volumes receiving more than the threshold doses (30 Gy for liver and small bowel, 22 Gy for right kidney).

Dosimetric parameters of VMAT plans in pancreatic cancers have been enumerated in some studies. Eppinga *et al*. [33] in his study compared IMRT with RA in 11 patients of advanced pancreatic cancer with doses prescribed to 50.4 Gy. They reported a superior mean CI and improved organ sparing with the VMAT plan. Ali *et al*. [34] in his study compared the VMAT plans with 7-field IMRT plans in 10 patients with advanced pancreatic cancer with total prescribed doses ranging from 48.7 to 55.8 Gy. The study failed to detect any statistically significant difference between CIs of the VMAT plans versus the IMRT plans.

A similar dosimetric analysis was performed by Veillot *et al*. [35] in 21 patients of pancreatic/bile duct malignancies who were prescribed 50.4 Gy at 1.8 Gy per fraction over 5 weeks. RA was shown to be superior to 3DCRT in terms of OARs sparing except for contralateral kidney. Mean dose to bowel and homolateral kidney was reduced in RA but 3D-CRT significantly reduced contralateral kidney mean dose.

Besides the dosimetric advantages of VMAT in

comparison with IMRT or 3D-CRT, there is also marked reduction in overall treatment time with VMAT. Several studies have reported significant craniocaudal movement of the pancreas secondary to active respiration; Bussels *et al*. [36] in his study of respiration-induced centre of mass movement of the upper abdominal organs; assessed 12 patients using dynamic magnetic resonance imaging. He noted largest movements for liver and pancreas; which was an average of 24.4 and 23.7 mm in the craniocaudal direction. Abdominal compression, respiratory-gating, and breath-hold techniques have been widely used to take into account for this organ motion. Diminished treatment times with VMAT may serve a greater purpose for patients facing discomfort with abdominal compression or increased treatment time secondary to respiratory-gating or breath-hold techniques.

Traditionally radiation doses of 45 to 50.4 Gy have been used in studies considering dose limiting toxicity of surrounding normal structures [37]. However with more conformal VMAT/Rapid arc plans and reduction in PTV margins using 4DCT simulation and daily image guided radiotherapy delivery; dose escalation may seem feasible. Sangalli *et al*. [38] conducted a comparative study between 3DCRT and Helical Tomotherapy (HT) using 4DCT in 15 patients of unresectable pancreatic cancer with a prescription dose of 60 Gy. The 4D-PTVs were smaller than standard-PTVs with a volume reduction equal to 37%. 3DCRT plans on 4D-PTV showed a significant sparing of most OARs, the use of IMRT allowed a further significant dose reduction. Nabavizadeh *et al*. [39] did a planning study comparing 3DCRT, IMRT, and VMAT in 20 patients of pancreatic cancer. Dose prescribed was 45 Gy in 25 fractions to a large field followed by a reduced volume 8-fraction boost to 59.4 Gy. VMAT delivery time was less than 3 minutes compared with 8 minutes for IMRT. They concluded that dose escalation to 59.4 Gy in pancreatic cancer was dosimetrically feasible with shorter treatment times and with fewer MUs delivered. Another study by Bahl *et al.* [40] comparing 3D *vs*. IMRT concluded that doses to bowel bag, liver and kidneys were significantly reduced using IMRT leaving ample scope for dose escalation. A more recent study has also looked into the advantage of proton therapy in the treatment of these tumours [41].

This study was done with a view to compare dosimetric parameters of 3DCRT, IMRT and RA plans. We obtained a better conformity and homogeneity with RA compared to IMRT and 3DCRT. There was not much difference in doses of the contralateral kidney in any of the three plans. Mean dose to the homolateral kidney could be reduced in RA though not significantly; V20 Gy and V30 Gy though were lessened considerably. Mean dose to liver was significantly reduced in RA compared to IMRT /3DCRT. V20 Gy and V30 Gy means could also be decreased with RA. Max and mean doses to stomach, mean dose and V45 Gy of gut were lowered with RA. Spinal cord doses though were less with 3DCRT. MUs were significantly lower in RA compared to IMRT with lesser delivery times in RA.

Drawbacks of the study include fewer numbers of patients and heterogeneous population which included both adjuvant and radical cases. The volumes for radical cases tended to be larger and also the peri-ampullary cases had duodenum involvement; which could not be included for estimating doses to duodenum. 4DCT was not used for simulation and no techniques were employed (abdominal compression, respiratory gating) to take into account respiratory excursion of pancreas.

CONCLUSIONS

Conventional radiotherapy protocols have treated pancreatic and periampullary cancers with doses ranging from 40 to 50.4 Gy. Few recent trials have addressed the issue of dose escalation. Our results show that with a commonly used dose schedule of 50.4 Gy in 28 fractions the dose to the OARs is reduced in RA compared to IMRT or 3DCRT; with significant differences in doses received in liver, gut and homolateral kidney. The profile of doses received by OARs leaves ample scope for dose escalation in postoperative or radical cases using IMRT or RA.

Conflict-of-interest

The authors have no conflict of interest to declare.

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