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Volumetric-modulated arc radiotherapy for pancreatic malignancies: Dosimetric comparison with sliding-window intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy

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ABSTRACT

Volumetric-modulated arc radiotherapy (VMAT) is an iteration of intensity-modulated radiotherapy (IMRT), both of which deliver highly conformal dose distributions. Studies have shown the superiority of VMAT and IMRT in comparison with 3-dimensional conformal radiotherapy (3D-CRT) in planning target volume (PTV) coverage and organs-at-risk (OARs) sparing. This is the first study examining the benefits of VMAT in pancreatic cancer for doses more than 55.8 Gy. A planning study comparing 3D-CRT, IMRT, and VMAT was performed in 20 patients with pancreatic cancer. Treatments were planned for a 25-fraction delivery of 45 Gy to a large field followed by a reduced-volume 8-fraction external beam boost to 59.4 Gy in total. OARs and PTV doses, conformality index (CI) deviations from 1.0, monitor units (MUs) delivered, and isodose volumes were compared. IMRT and VMAT CI deviations from 1.0 for the large-field and the boost plans were equivalent (large field: 0.032 and 0.046, respectively; boost: 0.042 and 0.037, respectively; $p > 0.05$ for all comparisons). Both IMRT and VMAT CI deviations from 1.0 were statistically superior to 3D-CRT (large field: 0.217, boost: 0.177; $p < 0.05$ for all comparisons). VMAT showed reduction of the mean dose to the boost PTV (VMAT: 61.4 Gy, IMRT: 62.4 Gy, and 3D-CRT: 62.3 Gy; $p < 0.05$). The mean number of MUs per fraction was significantly lower for VMAT for both the large-field and the boost plans. VMAT delivery time was less than 3 minutes compared with 8 minutes for IMRT. Although no statistically significant dose reduction to the OARs was identified when comparing VMAT with IMRT, VMAT showed a reduction in the volumes of the 100% isodose line for the large-field plans. Dose escalation to 59.4 Gy in pancreatic cancer is dosimetrically feasible with shorter treatment times, fewer MUs delivered, and comparable CIs for VMAT when compared with IMRT.

Introduction

Pancreatic cancer continues to be a serious cause of morbidity and mortality worldwide.[1] The treatment of pancreatic cancer commonly consists of a trimodality approach of chemotherapy, radiation therapy, and surgical resection. Owing to the location of the tumor close to critical normal tissues, toxicity is a common occurrence. Traditionally, 3-dimensional conformal radiation therapy (3D-CRT) consisting of a 4-field radiation technique has been used for pancreatic malignancies. In randomized studies, the Radiation Therapy Oncologic Group grades 3 to 4 nausea or vomiting and diarrhea has been shown to affect 11% and 17% of patients treated with 3D-CRT, respectively.[2]

To further improve the dose conformality and decrease the toxicity seen with 3D-CRT, intensity-modulated radiation therapy (IMRT) has been increasingly used to treat pancreatic malignancies. Dosimetric analyses comparing IMRT with 3D-CRT have shown an improved ability of IMRT to achieve normal tissue dose goals.[3,4] Additionally, it has been shown that nausea, vomiting, and diarrhea are markedly reduced in IMRT as compared with 3D-CRT, with very few patients experiencing Radiation Therapy Oncologic Group grades 3 to 4 nausea or vomiting.[5] However, given the increased number of beams used for treatment as compared with

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3D-CRT, IMRT is associated with longer treatment times, negatively affecting patient comfort and intrafraction patient motion.

Volumetric-modulated arc therapy (VMAT) is a further iteration of IMRT, in which the radiation dose is delivered through 1 or more dynamically modulated arcs, allowing for a more rapid and highly conformal radiation treatment while delivering fewer monitor units (MUs).[6] Dosimetric comparisons of VMAT as compared with IMRT and 3D-CRT have recently been shown for many disease sites: the head and neck,[7,8] prostate,[9] brain,[10] anus,[11] and cervix.[12,13] To date, there have been only 2 dosimetric analyses of VMAT in patients with pancreatic cancer,[14,15] with prescribed doses ranging from 48.7 to 55.8 Gy.

There are currently no dosimetric analyses in peer-reviewed journals examining various radiation treatment techniques in patients with pancreatic cancer with prescribed doses more than 55.8 Gy. In this study, we dosimetrically compared 3D-CRT, IMRT, and VMAT with prescribed doses of 59.4 Gy in 20 patients with pancreatic cancer who did and did not undergo previous resection. Additionally, the ability of VMAT to meet normal tissue tolerances despite the dose escalation to 59.4 Gy was evaluated.

Methods and Materials

Patients

A retrospective planning study was performed in 20 patients with advanced pancreatic cancer who had undergone a pancreaticoduodenectomy or whose tumors were unresectable. Data collection was approved by the institutional review board.

Patient immobilization was achieved using the BodyFIX whole-body double-vacuum immobilization system (Medical Intelligence, Schwabmuenchen, Germany) without diaphragmatic control and with abdominal compression.[16] Each patient underwent a free-breathing respiratory-correlated 4D computed tomography (4D CT) on a dedicated 16-slice helical big-bore simulator (Philips Medical Systems, Cleveland, OH) in the supine position.

Treatment planning

The 4D CT scans were reconstructed in 10 equally spaced time bins of 3-mm slice thickness using respiratory phase binning. The 4D maximum-intensity projection image data set, the free-breathing CT, and the average-intensity projection CT were all exported to a treatment planning platform (Eclipse, Varian Medical Systems, Palo Alto, CA) for target and organs-at-risk (OARs) segmentation. For the large-field plans, an internal target volume based on the maximum-intensity projection, the free-breathing CT, and the 10 respiratory phases of the 4D CT was created. For postoperative patients, the large-field contours included the postoperative bed and the at-risk nodal regions (celiac, superior mesenteric artery, periaortic, porta hepatis, or peripancreatic). For nonoperative patients, the large-field contours included the pancreas and the at-risk nodal volumes mentioned previously. The planning target volume (PTV) was obtained by uniformly expanding the internal target volume with a 5-mm margin. Depending on the tumor location, OARs such as the spinal cord, kidneys, liver, and stomach were contoured on the average-intensity projection CT data set. The average-intensity projection CT was also used for dose calculation. Individual isodose constraints were placed to ensure that the maximal tolerated doses to the OARs per published Quantitative Analysis of Normal Tissue Effects in the Clinic guidelines were not exceeded.[17] The summated large-field and boost constraints used during planning included the following: the spinal cord $D_{max} < 40$ Gy; the left or the right kidney $D_{20\%} < 20$ Gy, $D_{10\%} < 26$ Gy; and the liver $D_{30\%} < 25$ Gy. All plans were computed such that the prescribed dose encompassed at least 95% of the PTV. In addition to the primary course of treatment of 45 Gy, a boost plan (encompassing the gross tumor for nonoperative patients or the postoperative bed for postoperative patients) was created on a new planning CT data set with a resultant cumulative dose of 59.4 Gy (1.8 Gy/fraction).

Planning techniques

The imaging data were electronically transferred to the Eclipse radiation therapy planning system. A total of 3 different planning techniques were compared in the study: 3D-CRT, IMRT, and VMAT. All plans were created using 10 MV photons and were planned for delivery on a Varian Clinac (Varian Medical Systems, Palo Alto, CA) equipped with a 120-leaf Millennium multileaf collimator system, with 40 central leaf pairs of 5 mm and 20 peripheral leaf pairs of 10 mm.

For each patient, 3D-CRT plans with 4 to 6 variably weighted fields were generated. We used 0 to 4 wedges. The IMRT plans were computed using a multiple fixed gantry sliding-window multileaf collimator IMRT technique for delivery. An anisotropic analytical algorithm was used for dose computation with a dose calculation grid of 2.5 mm^3. We used 6 to 9 beams to generate the plans. Beam angles were arranged in a manner according to the tumor and the OAR location for the purpose of achieving maximal target coverage and optimal dose distribution. VMAT plans were generated with 2 simultaneously optimized coplanar volumetric arcs with the same isocenter and with 358° rotation.

Cumulative dose

Deformable registration is an optimization process that can correlate anatomical features observed in 2 different images of the same patient and region. An interactive process is employed to modify the transformation parameters until an optimal match is found between input images.[13] The CT data sets with contours and isodose lines were electronically transferred to the VelocityAI image registration package (Velocity Medical Solution, Atlanta, GA) to determine the cumulative dose delivered during the 2 courses of radiotherapy (original plan and boost plan).

Comparison of techniques

Dose-volume histograms (DVH) for OARs and the PTV were obtained for all patients. The following dosimetric parameters were evaluated and compared amongst treatment planning techniques: D_{mean} (mean dose) and $D_{95\%}$ (the dose received by 95% of the PTV) for the PTV, D_{mean} and V_{30} (the volume receiving 30 Gy or more) for the liver, D_{mean}, V_{15}, and V_{20} (volume receiving more than 15 and 20 Gy, respectively) for the kidneys, and D_{max} (maximum dose) for the spinal cord.

The conformality index (CI) of the plans was defined as the ratio between the volume of the 100% isodose line and the PTV volume. The CIs were calculated for the 2 different treatment courses separately (the large-field and the boost plans). The CI deviation from 1.0 was used for statistical analysis. The volumes of the 25%, 50%, and 90% isodose lines were also obtained. Additionally, the number of MUs per fraction and the estimated treatment time for all the treatment planning techniques were compared. All 2-way comparisons were performed using a paired, 2-sided Student t-test with a significance level of $p < 0.05$.

Results

The tumor and treatment characteristics for all 20 patients are presented in Table 1. Table 2 shows the comparisons for PTV D_{mean}, PTV $D_{95\%}$, CI deviations from 1.0, and MUs delivered per fraction for the 3 treatment techniques.

Table 1
Tumor and treatment characteristics for 20 patients

Age at diagnosis (y)	
Median	64
Range	24 to 84
Histology	
Adenocarcinoma	15
Mucinous adenocarcinoma	3
Infiltrating ductal carcinoma	1
Signet ring cell carcinoma	1
Tumor stage	
IB	2
IIA	3
IIB	10
III	5
Subsite	
Head	13
Tail	1
Body	3
Overlapping	3
Pancreaticoduodenectomy	
Yes	12
No	8
Margins	
Negative	6
Positive	6
CTV volume mean (cm^3)	563
PTV volume mean (cm^3)	787
CTV boost volume mean (cm^3)	193
PTV boost volume mean (cm^3)	309

CTV = clinical target volume.

Table 2
PTV D_{mean}, PTV $D_{95\%}$, conformity index deviation from 1.0, and monitor unit parameters and t-test comparisons for the 3 different treatment planning techniques

	3D-CRT	IMRT	VMAT	t-test		
				3D-CRT *vs* IMRT	3D-CRT *vs* VMAT	IMRT *vs* VMAT
PTV D_{mean}						
Mean (Gy)	62.3	62.4	61.4	0.875	0.005	0.009
Range	60.3 to 67.1	59.7 to 65.0	59.0 to 64.0			
PTV $D_{95\%}$						
Mean (Gy)	58.5	57.7	56.9	0.126	0.011	0.041
Range	37.4 to 65.2	35.0 to 63.0	35.3 to 62.0			
Conformity index deviation large field						
Mean	0.217	0.032	0.046	< 0.001	< 0.001	0.343
Range	0.098 to 0.513	0 to 0.240	0.012 to 0.202			
Conformity index deviation boost						
Mean	0.177	0.042	0.037	< 0.001	< 0.001	0.937
Range	0.090 to 0.270	0 to 0.321	0.009 to 0.197			
MU per fraction large field						
Mean	275	1120	408	< 0.001	< 0.001	< 0.001
Range	195 to 342	687 to 1700	347 to 471			
MU per fraction boost						
Mean	293	795	454	< 0.001	< 0.001	< 0.001
Range	239 to 349	231 to 1300	292 to 577			

A significant reduction of the mean PTV dose was observed with VMAT when compared with both 3D-CRT and IMRT (all $p < 0.05$). Equivalence of plan conformality between the VMAT and the IMRT techniques was seen for both the large-field and the boost plans. Conformality of both the VMAT and the IMRT techniques for the large-field and the boost plans was superior to that of 3D-CRT technique ($p < 0.05$ for all comparisons). The mean number of MUs per fraction that was needed to deliver the prescription dose was significantly lower for VMAT when compared with IMRT ($p < 0.001$). The "beam-on" time (after the completion of patient setup) for each fraction was less than 3 minutes for VMAT compared with 8 minutes for IMRT.

Table 3 lists the DVH parameters for the contoured OARs. For most DVH parameters, the IMRT and the VMAT plans showed a statistically significant dose reduction to the OARs when compared with the 3D-CRT plan; however, no statistical significance was identified when comparing IMRT with VMAT. Additionally, the volumes of the 25%, 50%, 90%, and 100% isodose lines were compared (Table 4). There was a significant difference between the volumes of the 100% isodose line for the large-field plans ($p < 0.05$), with the VMAT plans showing overall decreased volumes. There was a trend between the values of the volumes of the 25%, 50%, and 90% isodose lines in favor of the VMAT plans.

Discussion

This study examines the utility and dosimetric benefit of VMAT when compared with IMRT and 3D-CRT for radiation treatment of

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

	OAR			t-test		
	3D-CRT	IMRT	VMAT	3D-CRT *vs* IMRT	3D-CRT *vs* VMAT	IMRT *vs* VMAT
Left kidney						
D_{mean} (Gy)	18.6	15.9	15.5	0.006	0.030	0.606
Range	7.30 to 42.2	5.55 to 31.2	6.62 to 20.2			
V_{15} (%)	44.9	43.0	45.3	0.585	0.909	0.526
Range	14.0 to 88.6	12.0 to 82.2	16.0 to 80.0			
V_{20} (%)	37.8	27.2	24.1	0.005	< 0.001	0.129
Range	8.01 to 83.2	8.12 to 74.0	11.1 to 40.0			
Right kidney						
D_{mean} (Gy)	22.3	14.7	15.0	< 0.001	< 0.001	0.669
Range	4.62 to 37.2	7.01 to 29.3	6.63 to 21.3			
V_{15} (%)	56.4	40.7	42.7	0.006	0.005	0.577
Range	4.61 to 88.0	17.0 to 94.5	14.6 to 70.0			
V_{20} (%)	49.3	24.9	23.7	< 0.001	< 0.001	0.129
Range	3.01 to 82.0	5.22 to 70.2	4.04 to 46.0			
Liver						
D_{mean} (Gy)	16.3	13.7	13.7	< 0.001	< 0.001	0.936
Range	6.54 to 27.7	5.01 to 25.2	4.52 to 23.0			
V_{30} (%)	25.2	12.2	11.3	< 0.001	< 0.001	0.391
Range	10.1 to 49.0	1.22 to 35.0	1.01 to 29.2			
Spinal cord						
D_{max} (Gy)	37.2	36.9	35.1	0.914	0.291	0.572
Range	22.4 to 50.5	19.2 to 46.2	19.0 to 41.2			

Table 4
Mean isodose volumes in cm^3 and t-test comparisons for the 3 different treatment planning techniques

	3D-CRT	IMRT	VMAT	t-test		
				3D-CRT *vs* IMRT	3D-CRT *vs* VMAT	IMRT *vs* VMAT
Large field						
25% Isodose volume	5770	5560	5670	0.004	0.080	0.112
50% Isodose volume	3510	2740	2540	< 0.001	< 0.001	0.533
90% Isodose volume	1210	978	932	< 0.001	< 0.001	0.061
100% Isodose volume	959	798	757	< 0.001	< 0.001	0.008
Boost						
25% Isodose volume	3210	3030	2810	0.018	< 0.001	< 0.001
50% Isodose volume	1650	1110	1070	< 0.001	< 0.001	0.670
90% Isodose volume	444	358	348	< 0.001	< 0.001	0.096
100% Isodose volume	366	292	297	< 0.001	< 0.001	0.703

20 patients with resected and unresectable pancreatic cancer. Several publications have shown the superiority of IMRT when compared with 3D-CRT in reducing radiation mean doses to the OARs in patients with pancreatic cancer.[3,18] Dosimetric parameters of VMAT specifically in patients with pancreatic malignancies have been examined in 2 recent studies. The study by Eppinga *et al.*[15] compared the VMAT plan with the 5-field IMRT plan in 10 patients with advanced pancreatic cancer with total prescribed doses of 50.4 Gy. With the VMAT plan, they reported a superior mean CI and improved organ sparing. Similarly, Ali *et al.*[14] compared the VMAT plan with a 7-field IMRT plan in 10 patients with advanced pancreatic cancer with total prescribed doses ranging from 48.7 to 55.8 Gy. Unlike the previous study, this study failed to identify a statistically significant difference between CIs when comparing the plan VMAT with the IMRT plan.

As radiation prescription dosages are limited by the tolerance of surrounding normal tissues, maximally tolerated doses have historically been in the range of 45 to 50.4 Gy.[19] However, more conformal radiation delivery techniques, such as IMRT or VMAT, and the minimization of PTV margins using 4D CT simulation[20] and daily image-guided radiotherapy[21] have allowed for a greater therapeutic ratio, which is defined as the ratio of the amount of radiation causing tumor kill to the amount of radiation causing death or toxicity. Given the highly malignant nature of pancreatic cancer and the poor outcomes, treatment intensification by means of dose escalation has been shown to be feasible and relatively well tolerated.[22,23] Although most patients ultimately succumb to metastatic disease burden, the extremely poor local control seen following resection and adjuvant therapy has significant implications for patient mortality and morbidity. In a study by Iacobuzio-Donahue *et al.*[24] examining autopsy specimens of patients with Stage I/II pancreatic cancer following pancreaticoduodenectomy, 16 of 22 patients were found to have gross local disease at death, with most patients receiving adjuvant chemoradiotherapy. Additionally, as 80% to 85% of patients with locally advanced disease present with pain,[25] dose escalation may provide better long-term palliation and improved quality of life. Unlike the studies by Eppinga *et al.* and Ali *et al.*, which looked at prescribed doses (large field and boost) ranging from 48.7 to 55.8 Gy, patients in the current study were treated to a dose of 59.4 Gy to the PTV. Even with this dose escalation, the current study has shown good adherence to normal tissue constraints of the kidneys, liver, and spinal cord.

In addition to the dosimetric advantages of VMAT when compared with IMRT or 3D-CRT, one must consider the marked reduction in overall treatment time with VMAT. Multiple studies have shown substantial and uncertain craniocaudal positional changes of the pancreas secondary to active respiration. Using dynamic magnetic resonance imaging in 12 patients, Bussels *et al.* noted an average 23.7 mm craniocaudal pancreatic center-of-mass respiration-induced movement.[26] Abdominal compression, respiratory-gating, and breath-hold techniques have been implemented widely to account for this organ motion. Overall decreased treatment times with VMAT may be of substantial benefit when taking into account patient discomfort with abdominal compression or increased treatment time secondary to the respiratory-gating or the breath-hold techniques negatively affecting intrafraction patient motion.

A major limitation of this study was the inhomogeneous patient population, which included both patients with resected tumors and patients with unresectable tumors (Table 1). Our treatment volumes tended to be larger for the postoperative patients to ensure that any potential seeding of disease from surgical manipulation was covered. Therefore, a meaningful analysis of the small bowel, duodenum, or stomach DVHs for each treatment technique was not possible given the fact that portions of these organs were frequently included in the PTV.

Conclusion

The current study demonstrates that dose escalation to 59.4 Gy in pancreatic cancer is dosimetrically feasible, with VMAT providing a comparable CI when compared with IMRT, reduced mean dose to the PTV, and overall reduction in treatment time and MUs. Furthermore, normal tissue constraints of the liver, spinal cord, and kidney are attainable despite dose escalation to 59.4 Gy.

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