Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions

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Radiotherapy for pancreatic cancer is limited by the tolerance of local organs at risk (OARs) and frequent overlap of the planning target volume (PTV) and OAR volumes. Using lexicographic ordering (LO), a hierarchical optimization technique, with generalized equivalent uniform dose (gEUD) cost functions, we studied the potential of intensity modulated radiation therapy (IMRT) to increase the dose to pancreatic tumors and to areas of vascular involvement that preclude surgical resection [surgical boost volume (SBV)]. We compared 15 forward planned three-dimensional conformal (3DCRT) and IMRT treatment plans for locally advanced unresectable pancreatic cancer. We created IMRT plans optimized using LO with gEUD-based cost functions that account for the contribution of each part of the resulting inhomogeneous dose distribution. LO-IMRT plans allowed substantial PTV dose escalation compared with 3DCRT; median increase from 52 Gy to 66 Gy ($a=-5, p<0.005$) and median increase from 50 Gy to 59 Gy ($a=-15, p<0.005$). LO-IMRT also allowed increases to 85 Gy in the SBV, regardless of a value, along with significant dose reductions in OARs. We conclude that LO-IMRT with gEUD cost functions could allow dose escalation in pancreas tumors with concomitant reduction in doses to organs at risk as compared with traditional 3DCRT. © *2007 American Association of Physicists in Medicine*. [DOI: 10.1118/1.2426403]

Key words: Pancreatic cancer, equivalent uniform dose, intensity modulated radiation therapy, lexicographic ordering

I. INTRODUCTION

Of the estimated 30,000 patients diagnosed annually in the United States with pancreatic cancer[1] only approximately 10% have potentially curable resectable disease. Another 30–40% have locally advanced disease without detectable metastasis, for which chemoradiotherapy is the standard of care. Local therapy can provide good palliation and, despite the high propensity of pancreatic cancer for distant metastases, radiotherapy may provide a survival advantage.[2] Unfortunately, radiotherapy dose is limited by the tolerance of the organs in the upper abdomen. Thus, current radiation regimens are limited to inadequate tumor doses of only ~54 Gy in 1.8–2.0 Gy per fraction. Results are poor with response rates of only 10–25%, and a median survival of 8–12 months.[3–7] Better regimens are sorely needed for these patients and radiation dose escalation carries the potential for improved local control and palliation.

There have been attempts, mostly unsuccessful, of intensification of regimens for unresectable pancreas cancer, both by combining radiation with more effective chemotherapy, and with radiation dose escalation. One approach has been to combine preoperative external beam irradiation with intraoperative radiation to reduce dose to the organs at risk. Median survival times have been 12 months, with a 20% 5 year survival.[5,8–10] Escalation of external beam irradiation has also been attempted using three-dimensional conformal radiation therapy (3DCRT) to 70–72 Gy in 41 patients.[11] However, severe, unacceptable, toxicity (including gastrointestinal toxicity leading to death in three patients) was encountered.

Tumor invasion into adjacent vessels, most often the celiac and superior mesenteric arteries, makes complete resection difficult or impossible because the *en bloc* resection would require sacrificing the arteries. Patients unable to undergo resection inevitably progress both locally and with distant metastases. Currently, the only long term survivors of pancreatic cancer are those with a complete surgical resection. Patients with partial vein involvement, previously considered unresectable, who undergo newer surgical resection with vein grafting, have survival rates comparable to patients with traditionally operable tumors.[12,13] In this study, we have defined the tumor vascular interface as a planning target volume (PTV) subvolume, the surgical boost volume (SBV), with the hypothesis that sterilization of this interface could convert patients to surgical candidates who could be expected to have improved clinical outcomes.

The proximity of organs at risk (OARs), the duodenum, small intestine, and stomach, limit conventional external beam radiation dose to ~54 Gy, as planning target volume (PTV) and OAR volumes often overlap. Intensity modulated radiation therapy (IMRT), by allowing flexible shaping of isodose surfaces and selective placement of steeper dose gradients, may allow escalation of effective dose to the whole

PTV as well as to subvolumes of the PTV (the tumor-vascular interface) that prevent tumor resection.

In principle, relaxing dose homogeneity constraints across the target can be used to increase the dose delivered to portions of the PTV.[14] For any given PTV, dose distributions could be nonuniformly rearranged in numerous ways, creating many differing heterogeneous dose distributions. In order to achieve clinically relevant dose escalation, it would be useful to characterize the biological significance (e.g., in terms of tumor-cell kill) of each of these dose distributions (i.e., evaluate the significance of small cold spots and larger hot spots within the target volume in terms of predicted clinical outcomes). The generalized equivalent uniform dose (gEUD) models the effect of heterogeneous dose distributions considering the assumed radiosensitivity of the target tissue.[15–17] Investigators have performed gEUD based IMRT planning studies, for prostate, head and neck, liver, and lung tumors.[18–20]

IMRT planning generally requires the use of optimization techniques, and various multi-criteria optimization strategies have begun to be applied to inverse planning problems, particularly when trade-offs between normal tissue and tumor must be made.[21,22] For inverse planning problems in which the planning goals show distinctive levels of importance, such as heterogeneous dose escalation for pancreatic tumors within the context of normal tissue limits, lexicographic ordering (LO)[23] provides an intuitive and efficient way of generating a plan solution. For LO-based optimization, the hierarchical planning goals are categorized into several levels of priority. The various priority level goals are optimized sequentially, one level of priority at a time, with the least important planning goals addressed last. By subdividing a large multi criteria problem into several somewhat smaller problems based on priority levels, the complex space of trade-offs can be significantly simplified, greatly decreasing the need for iterative optimization trials before a solution that satisfies the goals of the protocol is found.

Here, we combine the use of lexicographic ordering optimization for inverse planned IMRT with gEUD-based cost functions (for PTV dose escalation) and dose volume histogram (DVH) defined dose limits for OARs to test the following hypotheses: (1) LO optimized IMRT with gEUD as a cost function will allow dose escalation to pancreatic tumors while simultaneously lowering radiation doses to OARs, and (2) gEUD based IMRT will allow simultaneous boosting of the surgical boost volume (SBV), an obstacle to potential curative resection of pancreatic cancer.

II. MATERIALS AND METHODS

A. Treatment planning

With approval from the University of Michigan Institutional Review Board, we conducted retrospective treatment planning studies on the data from 15 patients who had undergone 3DCRT for unresectable pancreatic cancer. The original treatment planning computed tomography (CT) scans, with patients receiving dual-phase intravenous contrast as well as oral contrast in a fasting state, were used for this study. The gross tumor volume (GTV) was defined as the imaged tumor. There was no prophylactic irradiation planned for the draining lymph node basin, as these patients were generally treated at our institution using concurrent administration of systemic doses of gemcitabine.[24] The clinical target volume was defined as the GTV with a 0.5 cm expansion and an additional 0.5 cm expansion was added to define the planning treatment volume (PTV). Within each GTV, the area of vascular involvement precluding surgical resection of the tumor was identified and delineated as a surgical boost volume (SBV). The SBV was defined with input from experienced pancreaticoduodenal surgeons and corresponds to the area that would need to be a tissue plane between unresectable vessel and tumor to allow *en bloc* tumor resection. All significant OARs were contoured (liver, stomach, duodenum, small intestine, kidneys and spinal cord). Each case had overlap of one or more OARs with the PTV: stomach in 11, small intestine in 12, and duodenum in all 15 cases (Table I).

TABLE I. Overlap of organs at risk cases.

Case	Stomach overlaps PTV	Duodenum overlaps PTV	Small intestine overlaps PTV
1	x	x	x
2	x	x	x
3		x	x
4	x	x	
5	x	x	
6	x	x	x
7	x	x	x
8	x	x	x
9	x	x	x
10	x	x	x
11		x	x
12		x	x
13	x	x	x
14	x	x	
15		x	x
Total (%)	11 (73%)	15 (100%)	12 (80%)

1. 3DCRT plans

The 3D plans used for this study were the ones actually used for the treatment of these patients, and were designed by experienced clinical dosimetrists. The number and angle of fields was chosen to avoid OARs, with three fields most often used. Treatment planning objectives were defined by the institutional chemoradiation protocols, with the 54 Gy 95% isodose surface encompassing 99.5% or more of the PTV.

2. IMRT plans

For each case, an IMRT plan was also generated using six noncoplanar beams, with 0.5 cm beamlets applied to each beam to cover the PTV. Angles were similar to those reported previously.[25] Lexicographic ordering optimization of treatment plans[26–28] was performed using UMPlan/UMOpt,

an in-house 3D treatment planning and optimization system. In UMOpt, IMRT optimization is performed based on doses, D_v, calculated by

$$D_v = \sum_{j=1}^{n} T_{j,v}\Phi_j, \tag{1}$$

where Φ_j represents the fluence intensity for jth beamlet (among a total of n beamlets or n optimization variables) and $T_{j,v}$ is a predetermined coefficient matrix that quantifies dose contributions from the jth beamlet with unity intensity to dose calculation points in the region of interest, v. UMOpt utilizes a wide range of planning metrics.[29] Specifically in this study, planning criteria for the OAR and normal tissues are achieved by minimizing objective functions consisting of DVH or (Lyman[30]) normal tissue complication probability (NTCP) metrics while target dose escalations are performed using gEUD[15–17] as a planning metric

$$\text{gEUD} = \left(\frac{1}{m}\sum_{i=1}^{m} d_i^a\right)^{\frac{1}{a}} \tag{2}$$

for m-dose points in a volume of interest v; the corresponding doses $d_i \in D_v$ $(0 \leqslant i \leqslant m)$; and tissue-specific parameter a. A general structure of objective functions follows *nonlinear least-square problem* representation:[31]

For the OAR and normal tissues,

$$f = H[P(D_v) - \ell\,]^2. \tag{3}$$

For the target structures,

$$f = H[\ell - P(D_v)]^2, \tag{4}$$

where H is the Heaviside unit step function; $P(D_v)$ represents a planning metric determined from the regional dose, D_v (e.g., gEUD, NTCP, or mean dose); and finally ℓ is a constant value specified as a desired achievement level for a given planning criterion. DVH criteria are modeled as suggested by Bortfeld[32] and Wu.[33]

In this study, the LO-based planning solves three optimization problems sequentially in order of importance, i.e., three priority levels of optimization. Each problem is constructed by a linear combination of objective functions that are categorized as a same priority

$$F(\Phi) = \sum_k f_k(\Phi). \tag{5}$$

Before each subsequent level of optimization, the objective functions from the prior level are converted to individual inequality constraints with boundaries set by the optimized results[27]

$$f_k(\Phi) \leqslant f_k(\Phi^*) \tag{6}$$

(for all k in a given priority level), where

$$\Phi^* = \arg\min F(\Phi). \tag{7}$$

Consequently, the achievements for the important planning criteria are preserved while pursuing less important criteria in lower levels.

TABLE II. Dose constraints for organs at risk.

OAR[a]	Dose constrains using 1.8 Gy fractions
Duodenum	60 Gy maximum, with no more than 33% > 45 Gy.
Stomach	54 Gy maximum, with no more than 2% > 50 Gy, and no more than 25% > 45 Gy.
Small intestine	54 Gy maximum, with no more than 2% > 50 Gy, and no more than 25% > 45 Gy.
Liver	minimize NTCP[b] using parameters for 1.8 Gy *fx*
Kidneys	20 Gy maximum, no more than 10% > 18 Gy, minimize overall
Spinal cord	45 Gy maximum, minimize overall

[a]OAR=organs at risk.
[b]NTCP=normal tissue complication probability.

For each optimization level, the use of nonlinear metrics in both objective functions and constraints requires to solve nonlinearly constrained optimization problems. For these problems, UMOpt uses a Sequential Quadratic Programming (SQP) algorithm[31,34] which is a well-established constrained optimization method exhibiting a high performance for large-scaled problems with significant nonlinearity. In SQP, search directions are generated by solving convex quadratic subproblems. A *line search* method is used to ensure the SQP method converges from remote starting positions by enforcing a sufficient decrease of an augmented Lagrangian function. Exact Jacobians are computed using an Automatic Differentiation algorithm[27] and Hessians are estimated by a Broyden-Fletcher-Goldfarb-Shanno-reduced algorithm.[31] For all results shown in this study, optimizations always converged to optimality, resulting in both optimal and feasible solutions.

IMRT planning for all tumors is represented by gEUD with negative a values, with variation depending on the grade or aggressiveness of the individual tumor.[15–19] If $a=-\infty$, the gEUD is equal to the minimal tumor dose, representing a very aggressive tumor in which tumor control will be adversely affected by even the smallest cold spot. When the biologic behavior of tumors is more benign, the a values can be adjusted to be correspondingly less negative. In this study, a values of −15 and −5 were used. Optimization constraints were placed to ensure that the maximal tolerated doses to the spinal cord, kidneys, stomach, duodenum, liver, and small intestine were not exceeded in all cases (Table II). In this study, the OAR dose goals were identified as the most important, therefore addressed at the first level in LO. After these dose limits were ensured, escalation of the PTV dose was pursued at the second level. The goals were to maximize the minimum target dose, maximize the target gEUD, and keep maximum target dose <90 Gy. Escalation of dose over 90 Gy in small subvolumes was felt to be, most likely, clinically not important. Finally, a general goal of dose reduction in all normal tissues was pursued at the third level.

B. End points and statistical analysis

To evaluate the magnitude of dose escalation which might be possible, the gEUD values for the PTV and SBV were recalculated with a values of −15 and −5 for each plan re-

TABLE III. Target volumes (cm^3) and EUD (Gy) achieved with dose escalation.

Case	Volume PTV	$a=-5$ EUD PTV	$a=-15$ EUD PTV	Volume SBV	$a=-5$ EUD SBV	$a=-15$ EUD SBV
1	112	72	63	8	89	88
2	240	60	54	40	66	58
3	193	58	52	13	87	86
4	282	67	60	25	89	89
5	151	67	58	20	87	87
6	162	68	60	18	89	88
7	313	69	59	38	85	84
8	145	74	64	12	88	87
9	415	60	54	9	88	88
10	195	60	54	11	84	84
11	287	67	60	22	90	90
12	176	66	59	10	88	88
13	135	66	59	15	82	77
14	344	64	57	35	81	79
15	406	75	68	23	87	87
R^2		0.1	0.1		0.37	0.34

gardless of planning technique. In order to compare the effect of dose escalation on the normal organs at risk, for both the IMRT and 3DCRT plans the equivalent uniform dose of each was calculated using a values of 6 and 10, consistent with the range of published values.[19,35,36] A paired t test was used to test differences between means for significance. In order to determine if IMRT dose escalation was inversely correlated with target volumes, a Pearson correlation regression analysis was done, as shown in Table III.

III. RESULTS

An example IMRT plan obtained with LO optimization is provided in Fig. 1. In this patient, the stomach, duodenum, and small intestine all overlap with the PTV. A noncoplanar arrangement of 6 IMRT fields (0.5 cm beamlets) was used to produce steep dose gradients in the overlap region. DVHs of the 3DCRT and IMRT plans illustrate that the IMRT plan results in higher PTV doses and lower OAR doses.

The potential improvement in delivered dose using IMRT with lexicographic ordering did require some additional time following structure definition over 3DCRT. The 3DCRT plans took approximately one half hour to plan and compute dose for templated beam arrangement, although selection of appropriate noncoplanar beam arrangements[37,38] could often take up to two or three times as much time. Generation of an IMRT plan with lexicographic ordering took approximately twice as long, primarily due to the initial dose to points calculation (offline). However, the increase in planning time with LO-IMRT was much less than what we previously experienced with our more conventional IMRT optimization approaches.

The resultant dose increases in the PTVs with the current approach are not confined to small subvolumes. Figure 2(A) describes the average proportion of the PTV above 54, 70.2, 75, and 80 Gy, respectively. Nearly all cases had greater than 90% of the PTV above 54 Gy, (average 91±7.5%), with 47±16% above 75 Gy, and 35±15% above 80 Gy. The mean gEUD achieved with LO IMRT and 3DCRT for the 15 cases is shown in Fig. 2(B) for two a values, −5 (66±5 Gy

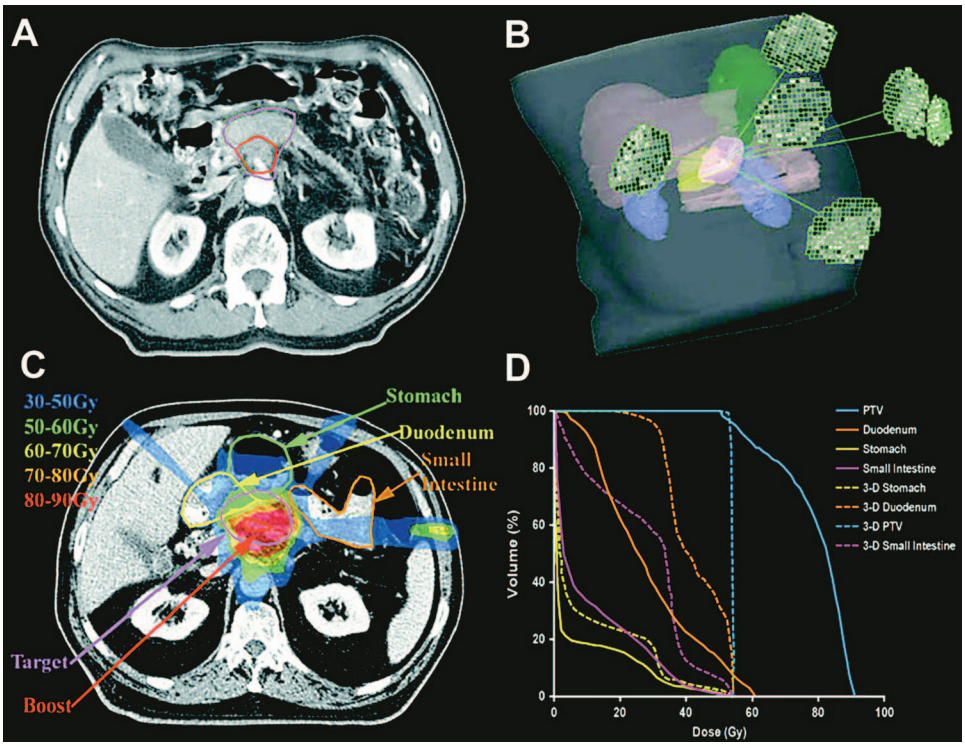

FIG. 1. Representative plan and DVH. (A) Abdominal CT demonstrating the surgical boost volume, SBV (red contour), defined as a specific boost region within the PTV (pink contour). (B) An example plan showing six-field noncoplanar IMRT beamlet intensity maps. Structures: PTV is pink, SBV is red, duodenum is yellow, small intestine is tan, stomach is green, kidneys are blue, and liver is brown. (C) Axial CT slice demonstrating OAR and PTV, along with a temperature scale transparent isodose colorwash. (D) Dose-volume histogram for case in 1C planned both with IMRT (solid lines) and 3DCRT (dashed lines).

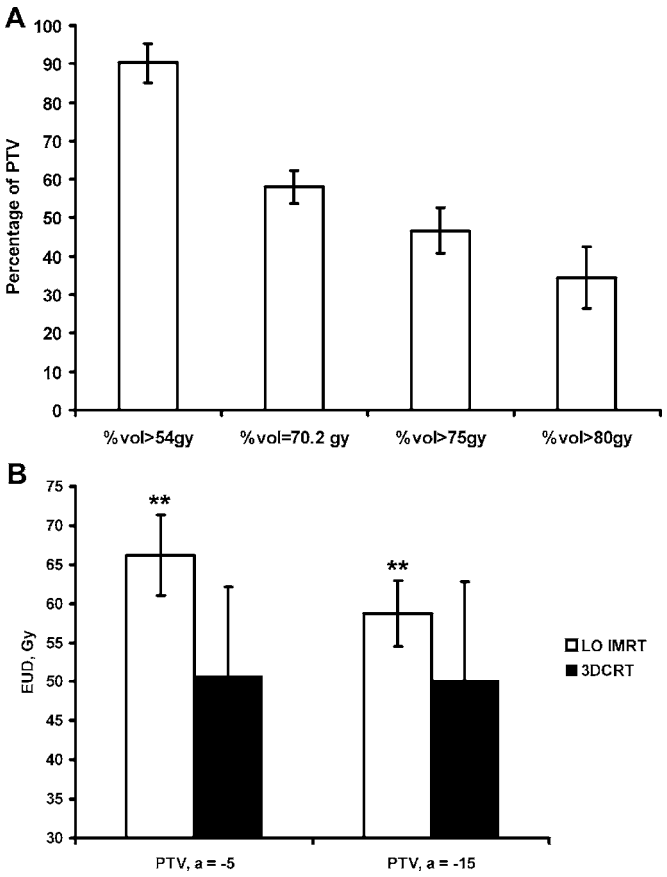

FIG. 2. EUD optimized IMRT PTV dose escalation. (A) Mean percentage of PTV above 54, 70.2, 75, and 80 Gy ± the standard deviation. (B) Mean EUD ± standard deviation for the PTV for 15 pancreas cancer cases using LO optimized IMRT using EUD cost functions (white) or 3DCRT (black). For an $a=-5$ (radiosensitive) tumor, and for an $a=-15$ (radioresistant) tumor. An ** indicates $P<0.005$.

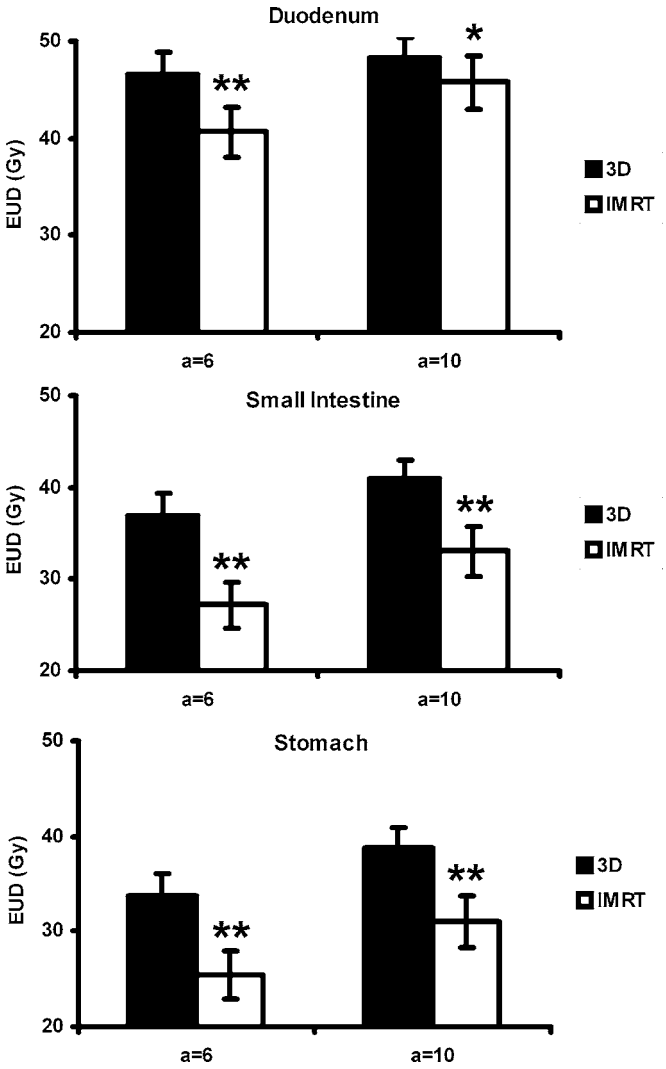

FIG. 3. Equivalent uniform dose optimized IMRT decreases dose to organs at risk. Average doses (15 cases) ± standard error to organs at risk during radiation delivery to pancreas cancer (duodenum, small intestine, and stomach) for 3DCRT (black bars) and LO-IMRT (white bars) computed for two values for normal tissue, 6 and 10. An * indicates $p<0.05$, and ** indicates $p<0.005$ for 3DCRT vs IMRT.

versus 52±11, $P<0.005$) or −15 (59±4 Gy versus 50±13, $P<0.005$). The increased PTV gEUD did not correlate with size of the PTV, as shown in Table III.

The dose escalation to the PTV provided by the IMRT plans did not result in increased doses to normal tissues in close proximity to the PTV (Fig. 3). For these normal tissue EUD calculations a parameter values of 6 and 10 were used; values are considered representative of the tissue tolerance of gastrointestinal organs.[39–41] LO optimized IMRT resulted in a significant decrease in gEUD for both a values for all three organs (duodenum, small intestine, stomach). For the duodenum, the 3DCRT doses were 47±1 ($a=6$), and 48±1 ($a=10$), compared with IMRT doses of 41±1 ($a=6$, $P<0.005$), and 46±1 ($a=10$, $P<0.05$). For the small intestine, the 3DCRT doses were 37±2 ($a=6$), and 41±1 ($a=10$), compared with IMRT doses of 21±2 ($a=6, P<0.005$), and 33±2 ($a=10, P<0.005$). For the stomach, the 3DCRT doses were 34±2 ($a=6$), and 39±2 ($a=10$), compared with IMRT doses of 25±3 ($a=6, P<0.005$), and 31±3 ($a=10, P<0.005$).

The simultaneous boosting of the SBV resulted in an average gEUD in the vascular interface of 85 Gy, regardless of a value (85±5 Gy for $a=-5$ and 85±8 Gy for $a=-15$, Fig. 4).

IV. DISCUSSION

In the current study, we investigated the possibility of escalating the effective radiation dose to the tumor in locally advanced unresectable pancreatic cancers by creating nonuniform target volume dose distributions using lexicographic ordering optimized IMRT with gEUD as a cost function. Although all cases had significant overlap of OAR with PTV, significant dose escalation was achievable compared to the current 3DCRT standard. As shown in Fig. 2(A), moderate increases in effective dose to the whole PTV were possible in most cases and substantial increases in dose to large fractions of the PTV were possible in all cases. These increases in dose were independent of tumor size.

By relaxing constraints on tumor dose homogeneity, additional dose may be delivered to PTV subvolumes that do not overlap the local organs at risk. Although the significance of selectively boosting tumor subvolumes to higher doses is

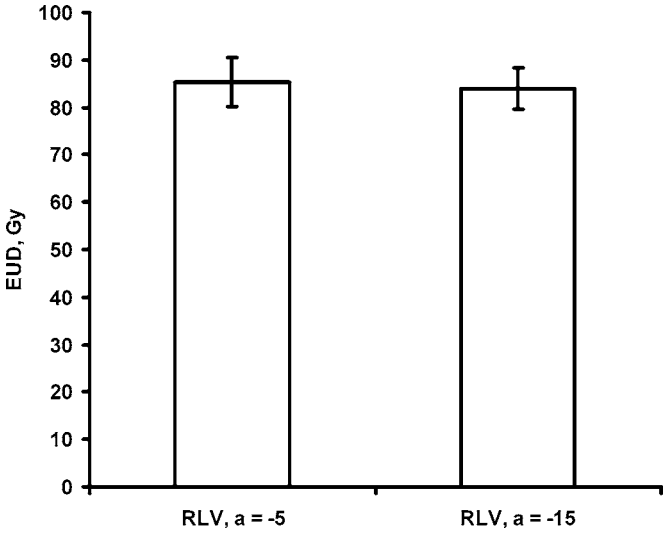

FIG. 4. Dose escalation to resection limiting volume (RLV). Resulting mean RLV EUD values (15 cases), ± standard error of the mean, for $a=-5$ (radiosensitive) and $a=-15$ (radioresistant) tumors.

controversial, recent work suggests that this may increase tumor control probability.[42,43] We elected to use gEUD in the cost function within the optimizing process because this model takes into account the potential contribution to tumor control of all parts of the dose-volume distribution, based on the presumed tumor radiosensitivity. Therefore, we feel this represents a rational method to drive the process of dose escalation and may provide biologically optimal dose distributions. As would be expected, we also found that unlimited heterogeneity in the PTV does not increase the gEUD significantly (data not shown). Depositing high doses in minute volumes would not be expected to contribute to tumor control probability. However, rearranging the dose to selectively boost regions of higher tumor burden or a tumor subvolume for (in this case, see more below) the potential of making the patient a surgical candidate remain worthy goals.

To assess the biologic significance of the heterogeneous dose distribution achieved, an estimate of the tumor radiosensitivity is required. We chose to evaluate this with two values of a, −5 and −15. Unfortunately, the "a" values of both normal tissue and tumor are approximations. To overcome this limitation we have used values that cover the range of what is currently thought to represent the a value for the tissues studied. In this gEUD model, negative numbers of larger magnitude indicate increasing radioresistance. Given that pancreas tumors clinically have a poor response rate, and based on published preclinical data generated with pancreatic cancer cell lines and xerographs, it is likely that an a value of −15 more accurately represents pancreas tumors. Although our results indicate that the magnitude of gain was greater in radiosensitive tumors, substantial dose escalation was possible even under the assumption of extreme radioresistance. For $a=-15$ the mean PTV gEUD increased from 50 to 59, an increase representing at least three fractions more than currently achievable.

LO optimized IMRT in this study also resulted in a decrease in dose delivered to normal tissues. In computing gEUD in normal tissues, we have used a values within the established range (6–14) for the normal tissues concerned.[18,19] Our findings are in agreement with a previous report showing reduction in normal tissue doses in the treatment of pancreatic tumors with IMRT.[44] Although it is likely that such reduction would translate into a reduction in toxicity, the impact of cytotoxic chemotherapy (or biological agents), commonly used concurrently with radiotherapy in this disease, is hard to predict. It is possible that the use of such agents would negate some of the expected gains. A clinical trial will be needed to evaluate the clinical impact of our approach on toxicities and on local control. It is worth noting that in this work we minimized doses to OARs using cost functions with DVH dose constraints. Although this resulted in substantial reductions in dose to OARs, it is possible that further gains may be realized by use of gEUD-based constraints for normal tissues.

Due to the poor outcome in the treatment of pancreatic cancer with radiation therapy,[3–7] further information on the dose response of pancreatic cancer would be helpful. Unfortunately, the data directly addressing this issue are sparse. The use of 54 Gy in conventionally fractionated radiation produces responses from 10–25% with concurrent 5-FU or gemcitabine based chemotherapy. There have been a few recent studies intensifying therapy with different radiation dose regimens. Tsujie *et al.*[45] demonstrated a 35% partial response rate with 1.5 Gy twice daily fractions to 45 Gy with concurrent 5-FU and cisplatin chemotherapy. Hypofractionated radiation with five 3 Gy fractions per week combined with concurrent 5-FU resulted in a partial response in three of eight patients.[46] Stereotactic radiation therapy by Hoyer *et al.*[47] with three 15 Gy fractions resulted in a 9% response rate. Rich *et al.*[48] showed the addition of paclitaxel to 50.4 Gy in 1.8 Gy fractions resulted in a 32% response rate in a multi-institutional phase II trial. However, it appears that these different regimens have not produced clearly superior results to concurrent gemcitabine and radiation. To our knowledge, there have been no formal studies of radiation dose response in pancreatic cancer patients. We hope that the application of optimization strategies such as those presented here will enable studies that will enhance our understanding of the dose response of pancreatic cancer.

In this study we have ignored the dosimetric consequences of organ motion, and we have used a fixed 1 cm expansion from GTV to PTV, which may not account fully for pancreatic tumor motion.[49–51] We have taken this approach since this has been the guideline in all University of Michigan pancreas clinical trials over the past decade, and has been the de facto clinical standard at our institution. Any future clinical application of this algorithm would have to address both target and normal tissue motion and shape change. Accounting for organ motion and shape change with respiration and digestion remains a technical challenge in the clinical delivery of IMRT to the abdomen.[49] Intra-fraction reproducibility can be improved with active breathing control.[52] Additionally, online imaging[53] and implanted

markers[51,54] can improve set up error to improve interfraction target localization. We are currently conducting a study measuring pancreas motion and deformation, to specifically determine how to account for target localization for IMRT delivery. Only with safe tumor immobilization and localization could this technique be implemented.

Clinical implementation of the methodologies described herein could potentially result in increases in resectability of borderline-resectable or unresectable tumors. Surgical resection continues to have the strongest impact on outcome of patients with pancreatic cancer. Recent advances in surgical techniques allow resection of tumors with minimal superior mesenteric vein, inferior vena cava, or hepatic artery involvement.[4,12,13,55] It appears that these more aggressive vein-resection procedures may extend survival in patients who would not be considered surgical candidates by conventional standards.[55] Similarly, patients with unresectable disease who are rendered resectable by standard chemoradiotherapy and undergo surgery appear to have a survival similar to patients who are surgical candidates at presentation.[56,57] Together, these data suggest that aggressive local therapy could result in improved local control and survival.

In this study we have shown that LO optimized IMRT with gEUD cost functions can deliver dramatically increased doses to the surgical boost volume, with doses approaching 90 Gy regardless of a value of −5 or −15. It is conceivable that such dose escalation in the context of a neoadjuvant regimen could potentially allow more patients to undergo curative resection by sterilizing the tumor-vascular interface. Dose escalation to the areas of vascular involvement could also be associated with additional toxicity. For instance, reirradiation of squamous cell carcinoma of the head and neck has shown that total doses exceeding 100 Gy can lead to vessel necrosis ranging in 2% to 15% of cases.[58] Thus, the clinical utility of such strategy needs to be evaluated in carefully conducted clinical trials.

In summary, this work demonstrates that lexicographic ordering optimization of IMRT with gEUD-based cost functions for locally advanced pancreatic cancer can allow dose escalation with decreased dose to organs at risk. Furthermore, simultaneous additional boosting of the tumor subvolumes precluding resection, the SBV, is possible. A radiation dose escalation study in patients with unresectable pancreatic cancer, using the methodology described herein, is currently under way at our institution. That study will help evaluate the potential benefits and toxicity associated with this approach.

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