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Dose Escalation for Locally Advanced Pancreatic Cancer: How High Can We Go?

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Introduction

Locally advanced pancreatic cancer (LAPC) is particularly difficult to treat given that it exhibits a poor response to chemotherapy and is by definition unresectable. A large proportion of patients experience significant morbidity and mortality due to local progression. As systemic therapy improves with the advent of gemcitabine/ abraxane[1] and FOLFIRINOX[2], the burden of local disease will only increase. Standard radiation therapy doses have failed to improve survival, which is not unexpected given anatomical and technical limitations. Although the LAP-07 trial[3] failed to show an overall survival benefit to radiation at standard doses, it did show benefits in terms of local control and time off of chemotherapy. At higher radiation doses, however, our institutional data suggests improved overall survival (17.8 months vs 15 months)[4] and recurrence-free survival (10.2 months vs 6.2 months), in addition to decreased acute grade 3+ gastrointestinal toxicity (1% vs 14%)[5] even at higher doses (BED>70Gy) with advanced radiation delivery techniques including use of 4-dimensional computed tomography, breath-hold technique, and image-guided radiation therapy.

Given these initial retrospective data, we initiated a phase I/II adaptive dose escalation trial using image guided stereotactic body radiation therapy (SBRT) for LAPC at our institution (ClinicalTrials.gov Identifier: NCT03340974) to determine the clinical maximum tolerated dose using SBRT. In preparation for the activation of this protocol, we undertook a dosimetric feasibility study to determine a) whether all patients treated with IMRT could have also been planned with SBRT and b) the maximum feasible delivered biological effective dose (BED) using SBRT while maintaining standard organ at risk (OAR) constraints to gastrointestinal (GI) mucosa with daily imaging, motion

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management, and treatment planning techniques that would be available at most academic centers.

Methods

Patient Selection

The first ten sequential SBRT patients treated at our institution using SBRT at a dose of 40Gy in 5 fractions or 36Gy in 5 fractions (SD-SBRT) were selected for this study. Ten patients originally treated with dose-escalated hypofractionated IMRT (DE-IMRT; 67.5Gy in 15 fractions) were randomly selected from our previously published cohort in order to obtain a fair distribution of patients. All patients received 4 to 6 months of standard induction chemotherapy and on restaging exhibited unresectable disease based on a multidisciplinary review of computed tomography (CT) images using standard criteria[6]. Patients previously treated with DE-IMRT generally had tumors located >5mm from GI mucosa (OAR's) with no predefined size limit, while SD-SBRT patients had tumors <4cm in maximal dimension with no evidence of duodenal invasion on imaging or endoscopy.

Immobilization and Simulation

SD-SBRT patients had multiple fiducial markers implanted prior to simulation. DE-IMRT and DE-SBRT patients were immobilized using upper body vac-lock cradles. All patients were simulated NPO for three hours, using intravenous (IV) contrast and inspiration breath hold (IBH) with 5-6 scans for reproducibility. Typically two IBH CT scans were acquired without IV contrast followed by 3-4 IBH CT scans acquired after IV

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contrast injection performed in intervals of approximately 30 s between scans beginning 30 seconds after IV contrast administration. Simulation technique and example IBH CT scans are described in Figure 1.

Target Delineation and Creation of Simultaneous Integrated Boost (SIB)

All tumors from DE-IMRT and SD-SBRT patients were re-contoured and validated by two separate physicians (LE and CT) with identical targets using commercial treatment planning software (Phillips Pinnacle version 9.10). The IBH CT images were used to contour an integrated GTV (iGTV) and integrated OAR structures (iDuodenum, iStomach and iSmallBowel; Figure 2a). This is a similar concept to a respiratory internal target volume (ITV), created by accounting for physiologic movement of a target. The iOAR structures were uniformly expanded by 5mm expansion to create a GI mucosa planning risk volume (GI_PRV). Example contours are given in Figure 2.

For each DE-IMRT and SD-SBRT, we attempted to created a dose-escalated SBRT (DE-SBRT) plan with an SIB to 40 Gy (8Gy/fx) and 70Gy (14Gy/fx) in 5 fractions. The PTV_40 was created by adding 3mm to the iGTV and subtracting the GI_PRV. A PTV_70 was created from the iGTV with 3mm contraction in 3 dimensions. DE-IMRT patients were re-planned for a 40Gy in 5 fractions SBRT plan and a 40Gy in 5 fraction plan with an increased simultaneous integrated boost (SIB) dose until the highest possible dose was reached (up to 70 Gy), while maintaining set OAR constraints (Table 1). The ten SD-SBRT patients were re-planned with a DE-IMRT plan and a DE-SBRT plan with an increased SIB. A tumor-vessel interface (TVI) has been included in recent

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trials to escalate dose to the SMA/ tumor interface. This was not used in our study to simplify plan comparisons, but areas of increased dose were pushed posteriorly to vessel interface rather than anteriorly whenever possible.

Treatment Planning and Evaluatio

Planning was performed in one of the IV contrast IBH CT scans without density override for the IV contrast. 40Gy was prescribed to the PTV_40 with a SIB technique prescribing 70Gy to the PTV_70. There was no minimum coverage requirement for the iGTV, but >95% coverage was requested for the PTVs. OAR's were prioritized during IMRT planning over target coverage. Successful plans typically had between 7 and 12 coplanar beam angles. VMAT was acceptable if available for treatment delivery with breathhold. Example treatment plans are presented in Figure 3. Based on toxicities observed in previous SBRT trials and the associated constraints (Table 1), dose constraints defined for planning purposes (Table 2) were: Duodenum V20<20cc, V35<1cc, Dmax<40Gy; Small Bowel V20<20cc, V35<1cc, Dmax<40Gy; Stomach V20<20cc, V35<1cc, Dmax<40Gy.

Conformality index was calculated using prescription isodose volume (PIV; 40Gy)/ prescription target volume (PTV) and homogeneity index was calculated using both D95/D5 and Dmax/Dmin formulas. Gradient index was calculated using 50% PIV / 100% PIV.

Statistical Analysis

Descriptive statistics were generated for all targets and all OAR. The 90th percentile was used as a minimum threshold for reasonably achievable OAR

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contstraints. A minimum coverage percent of 60 percent was defined as acceptable for a dose escalation level.

Treatment Delivery

All DE-IMRT were treated in a Clinac 2100 EX (Varian Medical Systems, Palo Alto, CA) equipped with a CT on rails (CTOR) (Smart Gantry, GE Healthcare, Chicago, IL). SD-SBRT patients were treated in a Truebeam (Varian Medical System) or the Clinac 2100 EX. For CTOR treatments, patients were initially set up under IBH using radiopaque skin marks placed on the planning final isocenter followed by CTOR under IBH. In-house software (Court and Dong 2003, Med Phys 30:2750) was used to register the CTOR to the planning CT using a contour of the vertebral body located just posterior to the iGTV. The final targets were then manually aligned using the implanted fiducial markers. The auto registration software then provides the couch shifts relative to the radiopaque skin marks to align the patient to the treatment final isocenter. Finally, a MV image pair is acquired to verify the bony alignment and treatment is delivered. For the Truebeam treatments, patients were initially set up to the planning final isocenter then aligned to fiducials using a kilovoltage image pair with cone beam CT (CBCT) for verification. Schema for standard treatment delivery using CTOR is given in Figure 5.

Results

Clinically acceptable DE-SBRT plans based on iGTV and PTV coverage and OAR constraints were generated for 100% of patients originally treated with DE-IMRT. Acceptable DE-IMRT plans were also generated for 100% of patients originally planned

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with SD-SBRT. For the maximum dose escalated SBRT plans (Figure 4), mean PTV volume was 58.8cc (range 8.7-171.91; ±41.3cc). Mean iGTV volume was 40.4cc (range 3.3-119.06; ±31.9). Mean conformality index was 0.98 (±0.24). Mean homogeneity index using Dmax/Dmin was 2.26 (±0.21) and using D95/D5 was 1.77 (±0.05). Mean PTV coverage by the 40Gy line was 97.6% (±0.02%). Mean iGTV coverage by 50Gy was 91% (±0.07%), by 60Gy was 61.3% (±0.08%) and by 70Gy was 24.4% (±0.05%). Maximum PTV coverage by 70Gy was 33%. Maximum PTV coverage by 60Gy was 77.5%. Distributions for conformality and homogeneity and gradient indices and target coverage are given in Figure 3. Distributions for V20, V30 and V35 for all OAR's are given in Figure 3. The following OAR constraints were achieved for ≥90% of generated plans: Duodenum V20<30cc, V30<3cc, V35<1cc; Small Bowel V20<15cc, V30<1cc, V35<0.1cc; Stomach V20<20cc, V30<2cc, V35<1cc. V40<0.5cc was achieved for all OAR. These post-study dose constraints are listed in table 2.

Discussion

Dosimetrically, all patients treated with IMRT could also have been treated with SBRT, with similar (or improved) BED delivery. Given this, it is worth investigating SBRT techniques for patient convenience and continuity of systemic therapy. Based on the 90th percentile used in the above data, dose escalation with an SIB technique to 60Gy in 5 fractions is achievable while maintaining acceptable target coverage and standard OAR constraints. We note that our study was enriched in patients with more favorable anatomy (uncinate and body tumors), but we believe that our approach and dose constraints would also apply to any patient that is eligible for pancreatic SBRT.

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Our SIB approach covered the GTV between 60% and 80% by the highest doses while still maintaining >98% PTV coverage by the 40Gy line. Pancreatic tumors are particularly hypoxic at their core[7], and delivering high doses to this hypoxic core may have a radiobiologic advantage despite not achieving full target coverage. This concept is similar to acceptance of dose heterogeneity within the GTV in other forms of SBRT[8]. Past SBRT trials, even with three and one fraction regimens have shown that duodenum, small bowel and stomach constraints of V20<30cc, V35<1cc, and max dose<40Gy are safe and well tolerated (Table 1). Using the above planning technique, these same dose constraints are achievable in 90% of cases, which supports the idea that dose escalation for LAPC is feasible and should be investigated in clinical trials. Our data provide a roadmap for other clinicians looking to achieve dose escalation up to 60Gy in 5 fractions for pancreatic cancer in the appropriate setting.

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Table 1. Previously Reported Dose Constraints and Associated Toxicities

Table 2. Pre-study and post-study Dose Constraints for Dose Escalated SBRT

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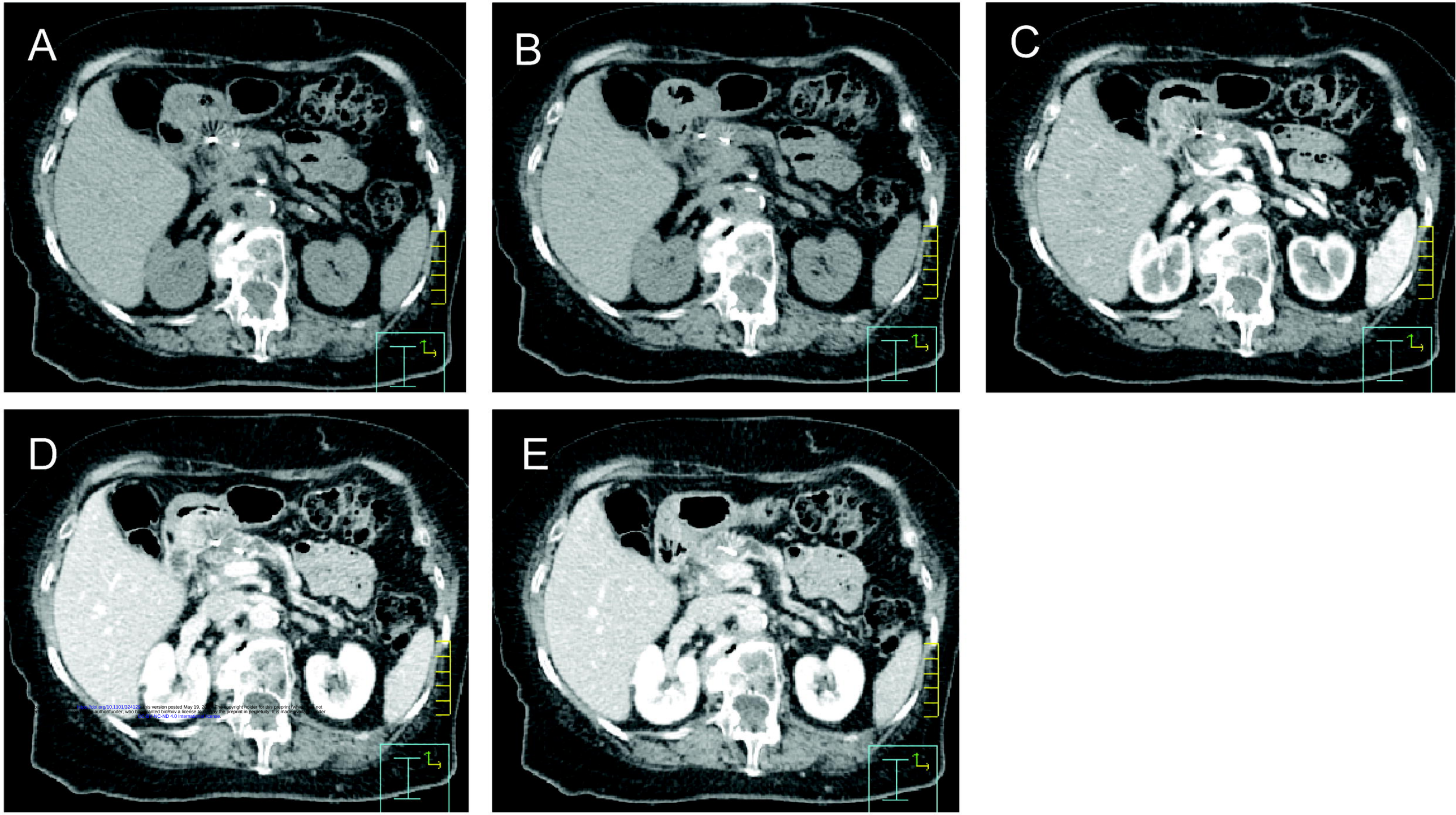

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Figure 1. Serial BH images post contrast. Using a standard contrast enhanced protocol. Representative image from same axial slice in same patient at: A) 30s post-contrast infusion, B) 60s post-contrast infusion, C) 90s post-contrast infusion, D) 120s post-contrast infusion, and E) 150s post-contrast infusion

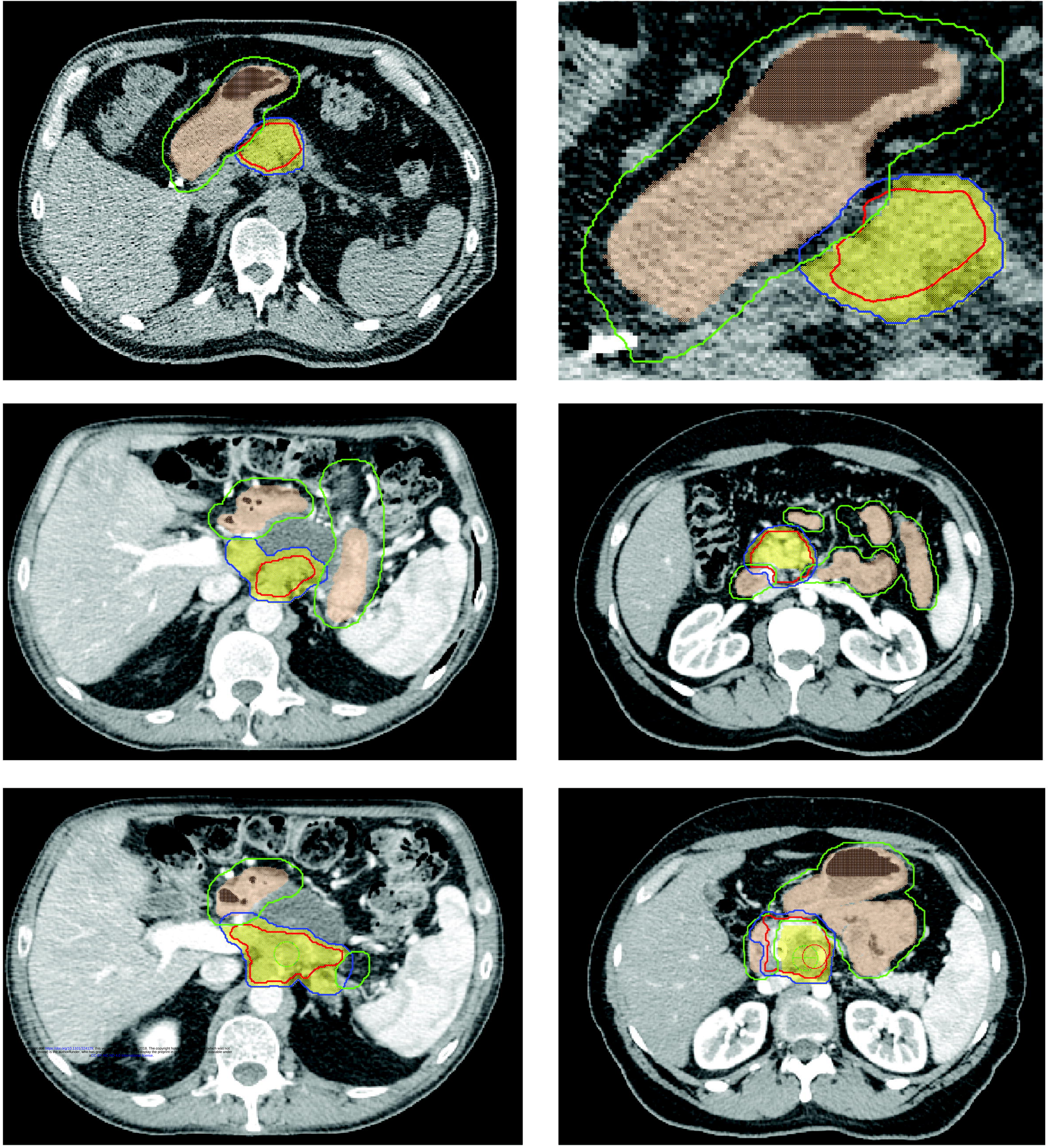

Figure 2. Target and OAR contouring technique using BH scans

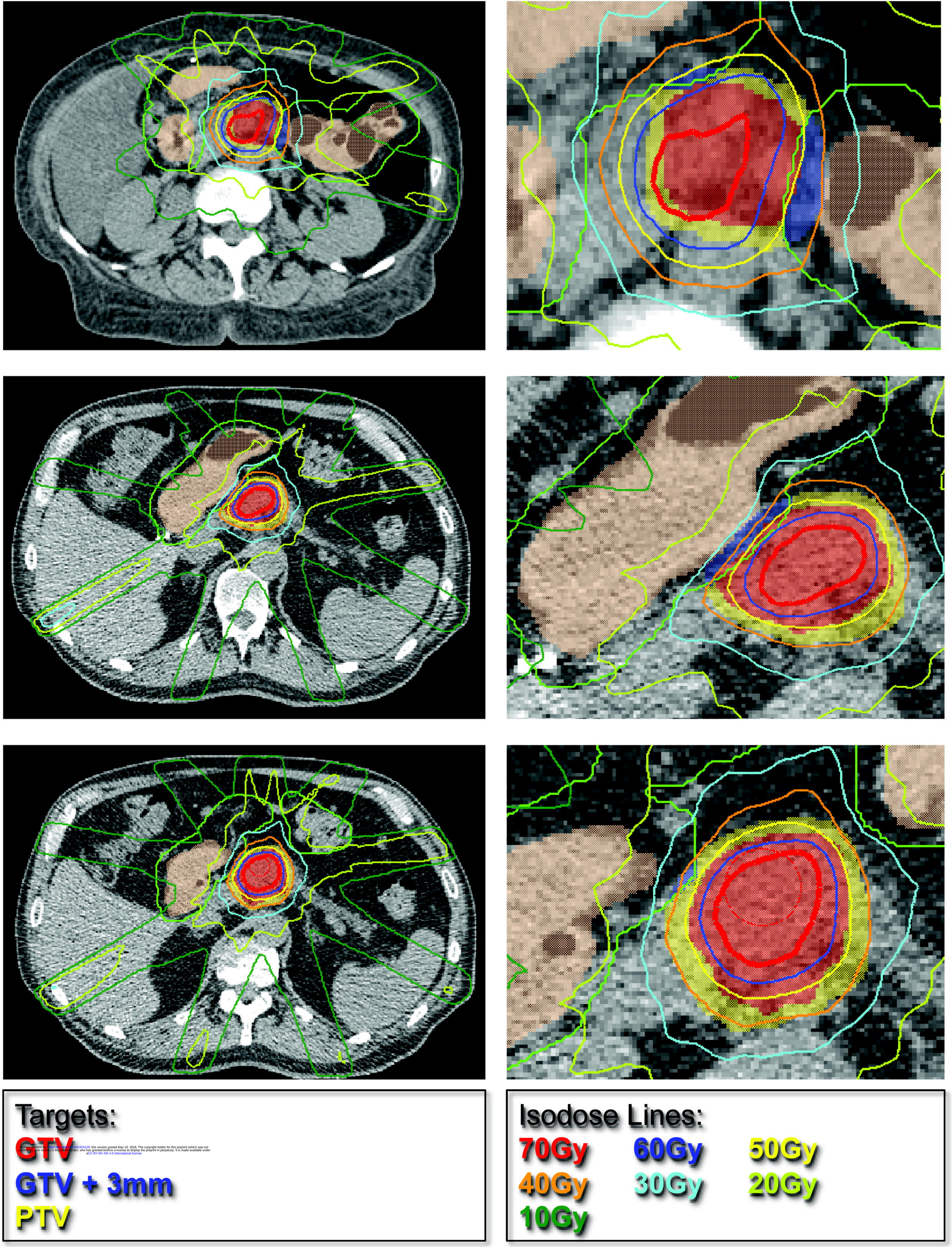

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Figure 3. Sample plans for deSBRT patients. Each row is a different set of patients. Left column is full axial slice and accompanying right column is zoomed in on areas of interest.

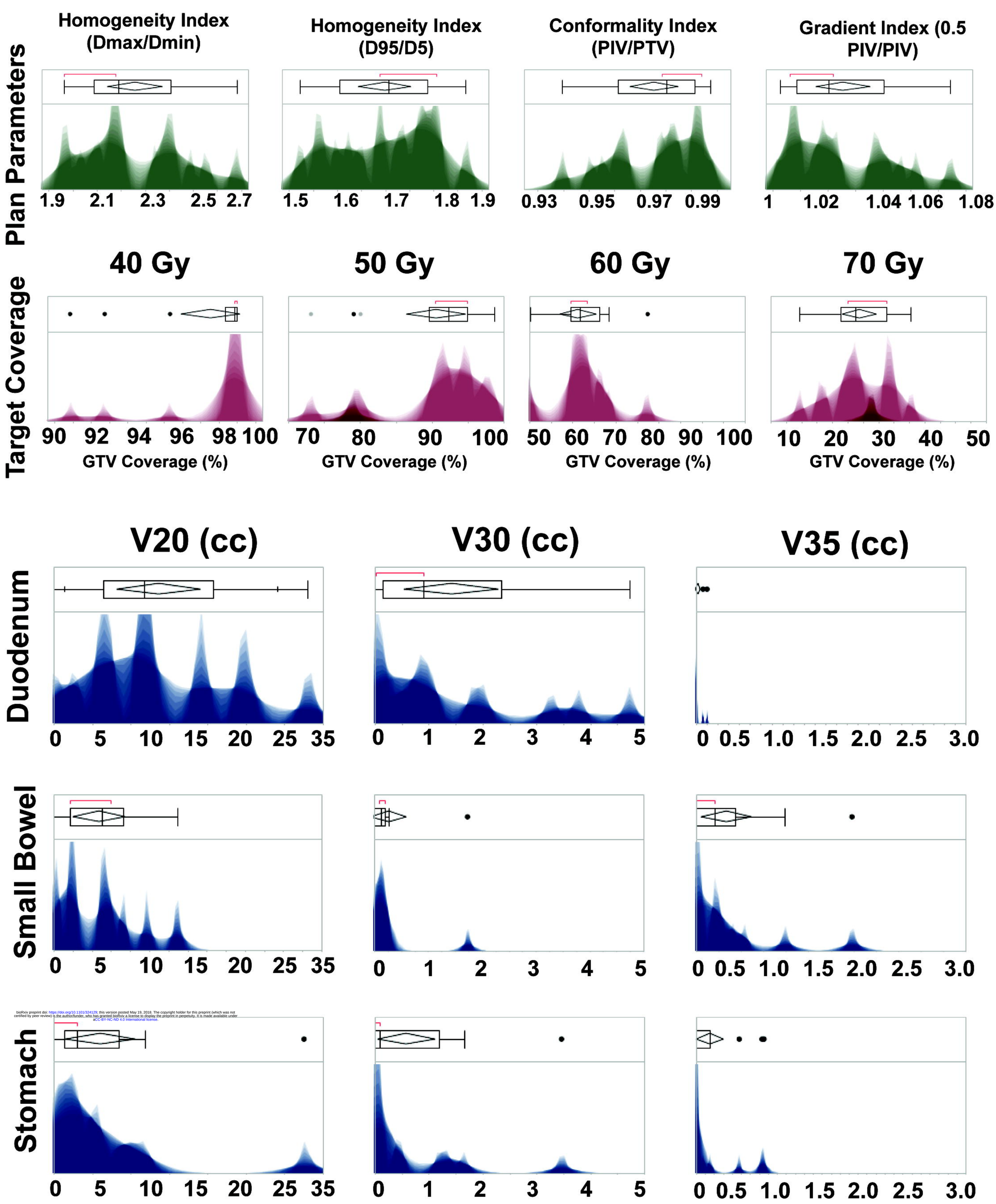

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Figure 4. Distribution of OAR constraints and GTV/PTV coverage tradeoff

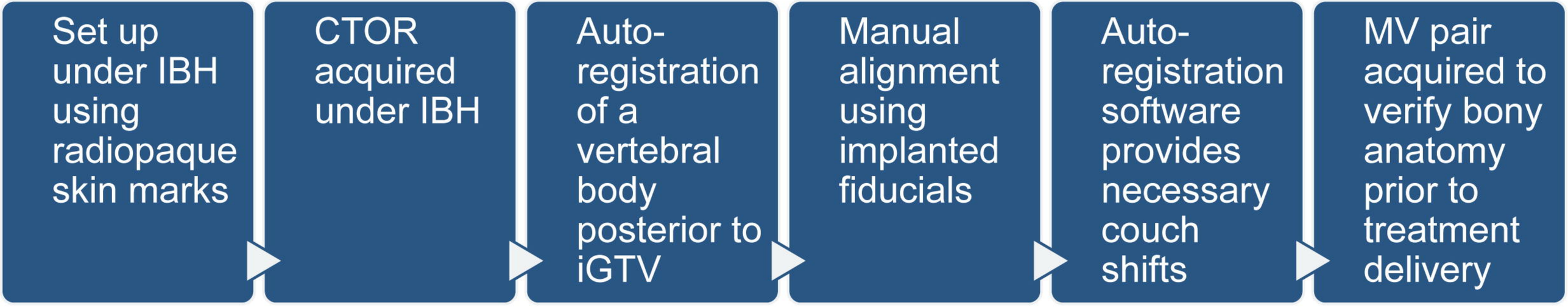

Figure 5. Typical Daily IGRT Process for DE-SRBT

Table 1. Previously reported Dose Constraints and Associated Toxicities

Target	*Overall Dose*	*Constraint*	*Toxicity Seen*	*Study*
Duodenum	45Gy in 6 fx	D1<36Gy	None >G3	Comito et al 2017[1]
Duodenum	25Gy in 1 fx	<5% of volume <22.5Gy; <50% of volume<12.5Gy	1% G3 (duodenal stricture), 1% G4 (perforation)	Chang et al 2009[2]
Stomach	25Gy in 1 fx	<4% of volume<22.5Gy	4% G3 (gastric ulcers)	Chang et al 2009[2]
All GI Mucosa		V38<5cc; V32.5<15cc; V20<30cc; Max dose 42Gy	No Acute G3+; No late G3+	Barney et al 2012[3]
Duodenum/Stomach/Small Bowel	35-50Gy in 5 fx	Max 35Gy; Mean<20Gy, V30<5cc, V35<1cc	No acute G3+; 5% Late G3 in 4 patients (GI bleed)	Chuong et al 2013[4]
Duodenum/Stomach	33Gy in 5 fx	V15Gy<9cc; V20Gy<3cc;V33Gy<1cc	2% acute G3+ (ulcer); 8.5% Late G3+	Herman et al 2014[5]
Duodenum	45Gy in 6fx	V36<1cc	None>G2	Tozzi et al 2013[6]
Duodenum	25Gy in 5fx	V25<1cc	None>G2	Gurka et al 2013[7]
Duodenum/Stomach/Small Bowel	20-60GY in 3-5 fx	Mean<20Gy; V30<2cc, V35<0.5cc	7% G3+ (GI bleed)	Mellon et al 2015[8]
Stomach	45Gy in 3fx	V36<10%	None Acute/Late>G3	Shaib et al 2016[9]
Duodenum	45Gy in 3fx	<3cm^3 to receive >1.5Gy/fx	None Acute/Late>G3	Shaib et al 2016[9]

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Table 2. Pre-study and post- study dose constraints for dose escalated SBRT

Target	*Constraint Used for Planning*	*Adapted Constraint*
Duodenum	V20<20cc V35<1cc* Dmax<40Gy	V20<30cc V30<3cc V35<1cc V40<0.5cc
Small Bowel	V20<20cc V35<1cc* Dmax<40Gy	V20<15cc V30<1cc V35<0.1cc V40<0.5cc
Stomach	V20<20cc V35<1cc* Dmax<40Gy*	V20<20cc V30<2cc V35<1cc V40<0.5cc
Kidneys	V12<25%*	V12<25%
Liver	V12<50%*	V12<50%
Spinal Cord	V20<1cc*	V20<1cc

* Mandatory constraints

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