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Dosimetric evaluation of simultaneous integrated boost during stereotactic body radiation therapy for pancreatic cancer

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ABSTRACT

Stereotactic body radiation therapy (SBRT) provides a promising way to treat locally advanced pancreatic cancer and borderline resectable pancreatic cancer. A simultaneous integrated boost (SIB) to the region of vessel abutment or encasement during SBRT has the potential to downstage otherwise likely positive surgical margins. Despite the potential benefit of using SIB-SBRT, the ability to boost is limited by the local geometry of the organs at risk (OARs), such as stomach, duodenum, and bowel (SDB), relative to tumor. In this study, we have retrospectively replanned 20 patients with 25 Gy prescribed to the planning target volume (PTV) and 33∼80 Gy to the boost target volume (BTV) using an SIB technique for all patients. The number of plans and patients able to satisfy a set of clinically established constraints is analyzed. The ability to boost vessels (within the gross target volume [GTV]) is shown to correlate with the overlap volume (OLV), defined to be the overlap between the GTV + a 1(OLV1)- or 2(OLV2)-cm margin with the union of SDB. Integral dose, boost dose contrast (BDC), biologically effective BDC, tumor control probability for BTV, and normal tissue complication probabilities are used to analyze the dosimetric results. More than 65% of the cases can deliver a boost to 40 Gy while satisfying all OAR constraints. An OLV2 of 100 cm^3 is identified as the cutoff volume: for cases with OLV2 larger than 100 cm^3, it is very unlikely the case could achieve 25 Gy to the PTV while successfully meeting all the OAR constraints.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the U.S. with almost as many deaths as diagnoses in 2012.[1,2] Overall survival rates at 1 and 5 years are 26% and 6%, respectively. Although surgical resection provides the best opportunity for long-term survival, only 10% to 20% of patients are diagnosed with technically resectable disease.[3-5] Unfortunately, most patients with nonmetastatic disease present with locally advanced or borderline resectable disease at initial diagnosis. In such patients, involvement of local vasculature (portal confluence, superior mesenteric artery, and celiac axis) by tumor significantly increases the likelihood of a margin-positive resection, which portends generally poor clinical outcomes, similar to those of patients with unresected tumors.[6,7] Therefore, the role of radiotherapy (RT) in this cohort of patients with locally advanced disease is aimed at improving local control and downstaging to resectability.

In spite of a recent randomized trial showing a small but significant overall survival benefit following the addition of RT to gemcitabine relative to gemcitabine alone,[8] clinical outcomes and downstaging rates with RT remain modest. Indeed, a meta-analysis of prospective studies investigating the use of gemcitabine-based chemoradiation for locally advanced pancreatic cancer (LAPC) by Andriulli *et al.*[9] revealed that only 27% of patients were felt to be clinically downstaged to resectability, yet only 60% underwent margin-negative resection. Other studies have shown more modest downstaging rates of 5% to 14% following treatment of LAPC with chemoradiation.[8,10] As a result, current strategies are investigating escalated ablative doses of highly conformal radiation to the gross tumor volume (GTV) using stereotactic body RT

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(SBRT) to improve downstaging and local control. Given the high propensity for metastatic spread as site of first failure in LAPC, the shorter treatment time with SBRT also results in minimal delay before restarting systemic doses of chemotherapy. Schellenberg *et al.*[11] have reported on the use of a 25-Gy single fraction alone or following 45 Gy of standard fractionated chemoradiation with excellent local control rates (81% to 94%) and acceptable early and late gastrointestinal toxicities, yet rates of downstaging in this trial were not significantly different from those achieved using standard fractionated therapy. Ongoing prospective studies are using fractionated regimens of SBRT following induction and consolidative single-agent gemcitabine (NCT01146054), with preliminary reports suggesting promising local control rates, but modest rates of downstaging.

The incorporation of a simultaneous integrated boost (SIB) during SBRT to the region of the vessels precluding resectability may have the potential to improve rates of downstaging by sterilizing the positive surgical margin, while providing adequate local control. An integrated boost technique also has potential logistical, dosimetric, and radiobiologic advantages over standard SBRT and even sequential boosting.[12,13] However, dose delivery is likely to be influenced by tumor, normal tissue, and patient-specific variables, including individual volumes and the dynamic geometric relationship between these volumes. Given the potential clinical significance of downstaging LAPC to margin-negative resection combined with the clinical successes seen to date with SBRT, this article investigates the dosimetric feasibility and potential clinical applicability of an SIB-SBRT–based treatment approach through a retrospective planning study.

Methods and Materials

Patient selection, contouring, and dose constraints

Under an institutional review board–approved protocol, 20 consecutive patients with locally advanced, unresectable or borderline resectable head of pancreas adenocarcinoma were identified. Patient computed tomography (CT) simulation images were used for the purpose of the retrospective planning study. All patients were simulated supine with arms up using Vac-Lok (CIVCO Medical Solutions, Coralville, IA) for immobilization with or without intravenous and oral contrast. The GTV was delineated by a single radiation oncologist with the assistance of available contrast CT, positron emission tomography–CT, and magnetic resonance imaging registered to the planning CT, and endoscopic reports. Organs at risk (OAR) including stomach, duodenum, bowel (SDB), kidneys, liver, and spinal cord were delineated according to the Radiation Therapy Oncology Group atlas for plan optimization and evaluation.[14] The planning target volume (PTV) was defined as a 4-mm isotropic expansion of the GTV, based on our clinical SBRT setup accuracy (using implanted fiducials and breath-hold treatment with a spirometer-assisted breath-hold device (SDX, Qfix). The margin was reduced in areas where the PTV was abutting critical normal structures, including SDB. The boost target volume (BTV) was contoured to include the pertinent vasculature (celiac, superior mesenteric artery, and splenoportal confluence) inside the GTV felt to be at greatest risk for positive margin after resection.

Patients were planned with coplanar volumetric modulated arc therapy (VMAT) using Eclipse (Varian, Palo Alto, CA), with AAA algorithm, version 10 and a calculation grid of 2.5 mm. The commissioned Trilogy machine (Varian, Palo Alto, CA) in Eclipse was equipped with Millennium 120 multileaf collimator in sliding window mode. Overall, 3 full arcs with 6 MV and different collimator angles (generally 225°, 135°, and 190°) were used for VMAT planning. A dose of 25 Gy was prescribed to the PTV, and a series of SIB boost doses (33, 40, 50, 60, 70, and 80 Gy) were used in the optimization of the BTV for all patients, all treated in 5 fractions. All plans were optimized so that 95% of the PTV received a minimum dose of 25 Gy and 95% of the BTV received 100% of the BTV prescription dose. Doses higher than 110% of the BTV prescription dose were penalized. For OARs, the dose constraints listed in the Table were used in all optimizations.[15] Only plans that met PTV coverage and all OAR constraints were considered to be valid plans for this study. As a reference, plans with a homogeneous 25-Gy PTV dose prescription were also created for each patient.

Iterative treatment planning process

Initial planning objectives placed the highest weight/priority on achieving both the BTV, as well as the PTV coverage (>95% of PTV receiving ≥25 Gy). Secondary objectives were to meet normal tissue dose constraints. Plans were then iteratively optimized at each BTV boost dose level by increasing the weight/priority of those normal tissue constraints not met on the previous optimization. This was performed until either all normal tissue dose constraints were met or deemed to be not achievable at the specified boost dose level. Following completion of the iterative optimizations for each patient at each specified BTV dose level, all patients underwent similar iterative optimizations at the next higher BTV dose. The percentage of cases that were able to meet all the normal tissue dose constraints at each BTV prescription dose level was determined via this successive optimization strategy.

Table
Dose constraints for OARs

OAR	Metric	Constraint
Cord	$V_{8\ Gy}$	0.3 cm^3
Total kidneys	$D_{75\%}$	12 Gy
Liver-GTV	$D_{50\%}$	12 Gy
Stomach	$V_{15\ Gy}$	≤ 12 cm^3
	$V_{20\ Gy}$	≤ 9 cm^3
	$V_{33\ Gy}$	≤ 0.3 cm^3
	$D_{50\%}$	< 12 Gy
Duodenum	$V_{15\ Gy}$	≤ 12 cm^3
	$V_{20\ Gy}$	≤ 9 cm^3
	$V_{33\ Gy}$	≤ 0.3 cm^3
	$D_{50\%}$	< 12 Gy
Bowel	$V_{15\ Gy}$	≤ 12 cm^3
	$V_{20\ Gy}$	≤ 9 cm^3
	$V_{33\ Gy}$	≤ 0.3 cm^3
	$D_{50\%}$	< 12 Gy

Metrics to evaluate the treatment plans

To quantify the relationship of the OARs and target for each patient, overlap volumes were created and defined as the overlap between the expanded GTV (either GTV + 1 cm for OLV1 or GTV + 2 cm for OLV2) and the union of SDB. An example of the 2 volumes, OLV1 and OLV2 relative to GTV, is shown in Fig. 1.

To illustrate the ability of SIB plans to allow additional dose to the BTV, the "boost dose contrast" (BDC) was defined as the mean dose to the BTV divided by the mean dose to the PTV excluding the BTV (PTV-BTV).[16] The ideal BDC is thus the ratio of the BTV prescription dose and the PTV prescription dose. The ideal is typically not achievable, however, because delivery of a higher dose to the BTV within the PTV will unavoidably increase the dose to parts of the PTV, thereby increasing dose heterogeneity and causing the actual BDC to deviate from the ideal BDC. To take the SIB delivery of the boost dose into account, the "biologically equivalent dose contrast" (BEDC) was defined as the biologically equivalent dose (BED) calculated from the average BTV dose divided by the BED of the PTV-BTV dose. BED was calculated using the following standard equation. The α/β ratio of 10 was used for the target volumes.

$$\mathrm{BED} = \mathrm{nd}\left[1 + d/\left(\frac{\alpha}{\beta}\right)\right] \tag{1}$$

The integral dose is defined as the product of the mean dose to the body excluding PTV (Body-PTV) and the volume of the Body-PTV. The integral dose at each BTV boost dose level is normalized to that of the 25-Gy homogeneous dose plan for each patient. As the integral dose to the patient is expected to change with varying BTV doses, these changes were used as an additional evaluation criterion to assess the cost of delivering highly heterogeneous doses to the PTV.

To analyze further the potential benefit of maximizing dose to the BTV, tumor control probability (TCP) for each valid plan for 13 patients was estimated using a Poisson model.[17] The generic Poisson statistics predict that the probability to sterilize all tumor clonogens is as follows:

$$\mathrm{TCP} = \exp\left(-\mathrm{N}p_s\,(\mathrm{D})\right) \tag{2}$$

where N is the initial number of clonogens and p_s (D) is the cell survival fraction after a dose D. The Eq. (2) can be rewritten as

$$\mathrm{TCP} = \left(\frac{1}{2}\right)^{\exp\left[2\gamma_{50}\left(1-\frac{D}{D_{50}}\right)/\ln 2\right]} \tag{3}$$

in which D_{50} and γ_{50} are the 2 parameters describing the dose and normalized slope at the point of 50% probability of control. For the case of heterogeneous irradiation, the overall probability of tumor control is the product of the probabilities to sterilize all clonogens in each tumor subvolume described by the differential dose volume histogram (dDVH) as shown by

$$\mathrm{TCP} = \prod_i \mathrm{TCP}\,(\mathrm{D}_i, \mathrm{v}_i) \tag{4}$$