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CT-guided online adaptive stereotactic body radiotherapy for pancreas ductal adenocarcinoma: Dosimetric and initial clinical experience

Albert Lee [a,b,*], Jared Pasetsky [a,b], Elizaveta Lavrova [a], Yi-Fang Wang [a], Geoffrey Sedor [a,b], Feng L. Li [a], Matthew Gallitto [a,b], Matthew Garrett [a], Carl Elliston [a], Michael Price [a], Lisa A. Kachnic [a,b], David P. Horowitz [a,b]

[a] Department of Radiation Oncology, Columbia University Irving Medical Center, New York, NY, United States
[b] Herbert Irving Comprehensive Cancer Center Minority Underserved NCORP, New York, NY, United States

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ABSTRACT

Purpose/Objectives: Retrospective analysis suggests that dose escalation to a biologically effective dose of more than 70 Gy may improve overall survival in patients with pancreatic ductal adenocarcinoma (PDAC), but such treatments in practice are limited by proximity of organs at risk (OARs). We hypothesized that CT-guided online adaptive radiotherapy (OART) can account for interfraction movement of OARs and allow for safe delivery of ablative doses.

Materials/Methods: This is a single institution retrospective analysis of patients with PDAC treated with OART on the Ethos platform (Varian Medical Systems, a Siemens Healthineers Company, Palo Alto). All patients were treated to 40 Gy in 5 fractions. PTV overlapping with a 5 mm planning risk volume expansion on the stomach, duodenum and bowel received 25 Gy. Initial treatment plans were created conventionally. For each fraction, PTV and OAR volumes were recontoured with AI assistance after initial cone beam CT (CBCT). The adapted plan was calculated, underwent QA, and then compared to the scheduled plan. A second CBCT was obtained prior to delivery of the selected plan. Total treatment time (first CBCT to end of radiation delivery) and active physician time (first to second CBCT) were recorded. PTV_4000 V95 %, PTV_2500 V9 5%, and D0.03 cc to stomach, duodenum and bowel were reported for scheduled (S) and adapted (A) plans. CTCAEv5.0 toxicities were recorded. Statistical analysis was performed using a two-sided T test and α of 0.05.

Results: 21 patients with unresectable or locally-recurrent PDAC were analyzed, with a total of 105 fractions. Average total time was 29 min and 16 s (16:36–49:40) and average active physician time was 19:41 min (9:25–39:34). All fractions were treated with adapted plans. 97 % of adapted plans met PTV_4000 V95.0 % >95.0 % coverage goal and 100 % of adapted plans met OAR dose constraints. Median follow up was 6.6 months. Only 1 patient experienced acute grade 3+ toxicity directly attributable to radiation. Only 1 patient experienced late grade 3+ toxicity directly attributable to radiation.

Conclusions: Daily CT-based OART was associated with significantly reduced dose OARs while achieving superior PTV coverage. Given the relatively quick total treatment time, radiation delivery was generally well tolerated and easily incorporated into the clinic workflow. Our initial clinical experience demonstrates OART allows for safe dose escalation in the treatment of PDAC.

Introduction

The role of radiation in the management of pancreatic ductal adenocarcinoma (PDAC) remains controversial [1,2]. However, the trials demonstrating no significant survival advantage utilized conventional radiotherapy with lower biologic effective doses (BED) [3]. There is retrospective data that suggest that dose escalation to a BED of at least 70 Gy may be beneficial in the treatment of PDAC [4,5]. Stereotactic body radiotherapy (SBRT) uses robust immobilization, motion management, and conformal dosimetry to deliver high doses per fraction to increase the BED of radiation treatments [6]. In practice, these high BED treatments are challenging to deliver clinically, given the proximity of

* Corresponding author at: Department of Radiation Oncology, Columbia University Irving Medical Center, New York, NY, United States.
E-mail address: awl2135@cumc.columbia.edu (A. Lee).

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dose-limiting luminal gastrointestinal structures [7].

Adaptive radiotherapy (ART) has been proposed for gynecologic as well as head and neck cancers to spare potential organs at risk (OARs) and improve target coverage [8,9]. Due to technical and workflow limitations, implementation of ART has been limited. With recent advances in technology, it is now possible to perform online adaptive radiotherapy (OART) where the plan is adapted to anatomic changes on each day of treatment [10]. There is a growing body of literature demonstrating the safety and feasibility of delivering high BED SBRT for PDAC using magnetic resonance (MR)-guided OART [11,12]. However, data regarding the use of computed tomography (CT)-guided OART to delivery pancreas SBRT is extremely limited [13]. Here, we report the largest clinical experience to date of pancreas SBRT utilizing CT-guided OART.

Materials/Methods

This is a single institution retrospective analysis of patients with PDAC treated with OART on the Ethos platform (Varian Medical Systems, a Siemens Healthineers Company, Palo Alto). Patients with different dose constraints or receiving re-irradiation were excluded. All patients were treated to 40 Gy in 5 fractions. For CT Simulation and all treatment/planning sessions, patients were supine and immobilized with an abdominal compression belt. CT simulation consisted of a contrast enhanced CT with a slice thickness of 1 mm with a 4D-CT acquisition with a slick thickness of 3 mm. Daily imaging for adaptive planning was 3-Dimensional and without IV contrast. Our target was an Internal Target Volume (ITV) accounting for respiratory motion. 3 mm expansion off the ITV created our Planning Treatment Volume (PTV). PTV overlapping with a 5 mm planning risk volume expansion on the stomach, duodenum and bowel received 25 Gy, with the rest of the PTV receiving 40 Gy. Initial treatment plans were created conventionally and peer-reviewed. For each fraction, PTVs and OARs volumes were recontoured with AI assistance after initial cone beam CT (CBCT). The adapted plan was calculated, underwent QA, and then compared to the scheduled plan. A second CBCT was obtained prior to delivery of the selected plan, and a shift was applied as necessary.

Treatment time

Total treatment time (first CBCT to end of radiation delivery) and active physician time (first to second CBCT) were recorded.

Dosimetric analysis

PTV_4000 V95 %, PTV_2500_eval, V95%, and D0.03 cc to stomach, duodenum and bowel were reported for scheduled (S) and adapted (A) plans. PTV_2500_eval was the volume of PTV_4000 subtracted from PTV_2500 to prevent under-coverage of our PTV_4000. The coverage goal for both PTVs was V95 % >95 % and the OAR constraint for duodenum, bowel and stomach was D 0.03 cc < 700 cGy [14]. Additional constraints, coverage goals and optimization inputs can be seen in supplemental Fig. 1. Statistical analysis was performed using a two-sided T test and α of 0.05.

Toxicities

CTCAEv5.0 toxicities were recorded, acute toxicity was within 3 months of completing RT while late toxicity was after 3 months.

Results

From October 2022 through July 2023, there were 22 patients with either primary or recurrent PDAC who were treated on the ETHOS machine with SBRT. One patient was excluded from our analysis because they were receiving a second course of radiation. Of the 21 patients who were included in this analysis, 11 (52 %) were male, with a median age of 68 (range 47–83). 19 of 21 patients had a KPS of 90 and median follow up time for the cohort was 198 days. Additional demographic data can be found in Table 1.

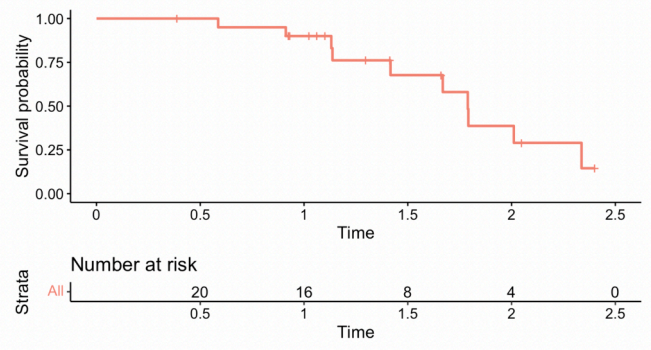

Fig. 1. Overall survival from diagnosis.

From our cohort, 13 (62 %) patients were treated to the primary pancreatic lesion. Eight (38 %) patients were treated for a local recurrence with RT alone, all of whom had received surgery between 6 months and 9 years prior to this course of RT. Of the 13 patients that were treated to the primary pancreatic lesion, 2 patients were metastatic at diagnosis. One patient presented at diagnosis with multiple lung nodules, which remained stable for two years while the patient was on a clinical trial (NCT04104672). The second patient presented at diagnosis with multiple liver metastases. He enrolled on a clinical trial (NCT04543071) and had near resolution of hepatic disease on imaging. On both trials, radiotherapy to the primary pancreatic mass was permitted after discussion with the sponsors. Sites of metastatic disease were not treated.Of the 11 non-metastatic patients, 7 proceeded to surgery after RT, either Appleby or Whipple procedure. Histopathologic results can be found in Table 2. Eighteen of twenty-one patients were treated with various chemotherapy regimens before OART. Additional information about staging and treatments can be found in Table 1.

Each of the 21 patients was treated with 5 fractions of SBRT, totaling 105 fractions for which time and dosimetric data could be analyzed. After the adapted plan was generated, plan evaluation was performed by our physicians and physics teams. Overall, there were just 2/105 fractions where the scheduled plan was deemed non-inferior to the adaptive plan and the patient was treated with the scheduled plan. The adapted plan was selected for 103 of 105 (98 %) fractions. Median PTV_4000 vol was 53.59 cc (4.12–154.44 cc) and median PTV_2500 vol was 71.285 (6.85–177.28 cc).

Time

Three fractions were excluded from our time data analysis due to machine malfunction during the treatment that led to significant delays in total treatment time, leaving 102 remaining fractions for analysis, Table 3. Overall, the average active physician time was 19 min and 41 s (range 9:25–39:34) while the average total treatment time was 29 min and 16 s (range 16:36–49:40). Only 4 of 102 fractions (4 %) required more than 30 min of active physician time while 15 of 102 (15 %) were completed with less than 15 min of active physician time. Patient level analysis revealed that on average, no patient required more than 28 min of active physician time and no more than 38 min of total time.

Dosimetry

One-hundred and five fractions were available for dosimetric analysis for PTV_4000 V95% and D0.03 cc to stomach and bowel. Only 75 fractions were available for analysis for D0.03 cc to duodenum, excluding the 6 patients (30 fractions) that were receiving RT for a

recurrence post-Whipple. In one fraction for a single patient, the PTV target was greater than 3 mm away from the bowel, and thus the PTV_2500_eval V95% metric was not assessed in this fraction, leaving 104 fractions for analysis of this metric. Tables 4 and 5 describe the dosimetric coverage data included in this analysis.

Only 12 of 105 (11 %) scheduled plans met the PTV_4000 coverage goal, compared to 102 of 105 (97 %) of adapted plans. 91 of 93 (98 %) fractions where the scheduled plan that did not meet coverage goals, the adapted plan met coverage goals. Only 1 fraction had a scheduled plan that met the coverage goal with the adapted plan not meeting the coverage goal; the scheduled plan was selected for this fraction. On average, across 105 scheduled plans, the PTV_4000 V95% was 80.8 %, while adapted plans had an average of 98.2 % ($p < 0.001$). Additional analysis revealed that the 12 fractions where the scheduled plan met the PTV_4000 V95% coverage goal were limited to just 4 patients, meaning that 17 of 21 (81 %) patients did not have a single fraction where the scheduled plan met our primary coverage goal. Furthermore, of those 12 fractions where scheduled coverage for PTV_4000 met our goal, 10 would have failed to meet the bowel and/or duodenum OAR constraint.

For the PTV_2500_eval coverage goal, 49 of 104 (47 %) scheduled plans met the coverage goal, while all 104 (100 %) adapted plans met the coverage goal, which means that for 55 of 104 (53 %) fractions, the coverage goals would not have been met without treatment adaptation. On average, across 104 scheduled plans, the PTV_2500_eval V95% was 88.9 % while adapted plans had an average of 99.7 % ($p < 0.001$).

For the D0.03 cc constraint to duodenum, 21 of 75 (28 %) scheduled plans met the OAR constraint, while all 75 (100 %) adapted plans met the OAR constraint, which means that for 54 of 75 (72 %) fractions, the duodenum would not have been properly spared without treatment adaptation. On average, across 75 scheduled plans the D0.03 cc to duodenum was 749.9 cGy while adapted plans had an average of 611.2 cGy ($p < 0.001$).

For the D0.03 cc constraint to bowel, 38 of 105 (36 %) scheduled plans met the OAR constraint while all 105 (100 %) adapted plans met the OAR constraint, which means that for 67 of 105 (64 %) fractions, the bowel would not have been properly spared without treatment adaptation. On average, across 105 scheduled plans the D0.03 cc to bowel was 723.1 cGy while adapted plans had an average of 601.6 cGy ($p < 0.001$).

For the D0.03 cc constraint to stomach, 75 of 105 (71 %) of scheduled plans met the OAR constraint while all 105 (100 %) adapted plans met the OAR constraint, which means that 30 of 105 (29 %) fractions had a scheduled plan that did not meet OAR constraint with the adapted plan meeting the OAR constraint. On average, across 105 scheduled plans the D0.03 cc to stomach was 451.3 cGy while adapted plans had an average of 395.5 cGy ($p = 0.259$).

Further patient-level analysis revealed that on average, only one patient's scheduled plan would have met the PTV_4000 coverage goal while all 21 patients met all dosimetric goals on the average of their 5 treatments. Only 5 patients scheduled plans would have met the PTV_2500_eval coverage goal on average; 7 patients scheduled plans would have met the bowel constraint on average and 3 patients would have met the duodenum constraint.

Overall survival and local control

The median follow-up of our patients was 303 days.Median overall survival (OS) from diagnosis was 21.6 months. 6 month and 12 month OS for patients who went on to resection was 91.5 % and 89.5 %, respectively (Fig. 1). Local control at 6 months was 100 % and at 12 months was 90.9 % (Fig. 2).

Toxicity

In total, four patients developed acute grade 3+ toxicities. Only one patients side effect could be directly attributable to radiation treatment.

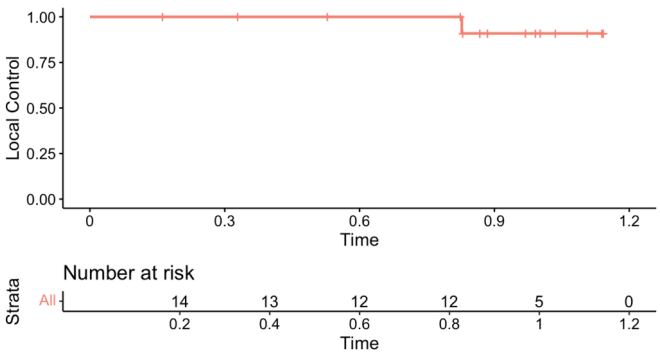

Fig. 2. Local Control from OART for resected patients.

One patient developed acute abdominal pain requiring admission and was found to have radiation enteritis, which improved with bowel rest, IV fluids, and pain medication. Another patient acutely developed ST elevation myocardial infarction (STEMI) and bilateral pulmonary emboli in the setting of metastatic progression. The other two patients developed toxicities post Whipple procedure that were unrelated to their radiation treatment.

Four patients developed late grade 3+ toxicities. Only one patient could be directly attributable to radiation treatment. This patient developed a pseudoaneurysm off the common hepatic artery (CHA), requiring stent placement. Two other patients experienced grade 5 toxicities in the setting of disease progression and death. One patient developed thrombosis involving the superior mesenteric vein (SMV), inferior mesenteric vein (IMV), and distal venous branches, but this happened just after restarting chemo and about 2 months after Appleby surgery. 13 (62 %) patients had acute grade 1 or 2 toxicity and 3 (14 %) of patients had no reported toxicity within 3 months.

Discussion

This study represents the first reported outcomes of 5 fraction pancreas SBRT delivered on the Varian Ethos platform with OART. With a median follow up time of 198 days, early outcomes suggests that pancreas SBRT utilizing CT guided OART is safe and feasible. Daily adaptation improved PTV_4000 coverage from 80.83 % with the scheduled plan to 98.22 % with the adapted plan ($p < 0.001$). It also significantly decreased the average dose per fraction to the duodenum (749.92 cGy to 611.23 cGy, $p < 0.001$) and the rest of the bowel (723.92 cGy to 601.65 cGy, $p < 0.001$). If the scheduled plan had been used without daily adaptation, only one patient would have met PTV coverage goals and 14 patients (67 %) would not have met at least one OAR constraint.

Upon, further examination of the dosimetry data, if the constraints were made more generous, meaning PTV_4000 V95 % >90 % and D0.03 cc < 770 cGy for bowel and duodenum, there were still 57 of 105 (54 %) fractions where the scheduled plan would have failed to meet the PTV_4000 coverage goal AND either the bowel or duodenum OAR constraint. All 57 of those fractions had adapted plans that met our intended dosimetry goals. In other words, more than half of the scheduled plans would have significantly under-dosed our target while overdosing an OAR, and using the adapted plan allowed us to meet all planning goals.

These dosimetric improvements likely contributed to the relatively low rates of adverse events. Only one patient experienced grade 3+ toxicities acutely and one patient experienced grade 3+ toxicities late that could be directly attributed to radiation. Of note, the one patient that developed a late Grade 3+ toxicity developed a common hepatic artery pseudoaneurysm approximately 4 months after RT, leading to significant anemia and bleeding. While RT may have played a role in causing his pseudoaneurysm, he did have variant anatomy of his

common hepatic artery coming off the superior mesenteric artery, and he had undergone Whipple 2 years prior to RT. Another patient, discussed above had a thrombus that could have been related to radiation, but not definitely related. Our toxicity results are similar to recently published data on Stereotactic MR-guided on-table adaptive radiation therapy (SMART), reinforcing the safety of adaptive radiotherapy [15].

The total treatment time and active times from our initial experience demonstrate that OART can be easily incorporated into the clinical workflow, with treatments requiring less than 20 min of physician work and 30 min of total time on average. Compared to MR-guided ART where average total time has been reported around 83 min, our patients completed treatment in less than half the time, with no patient requiring more than 50 min.

Limitations of this study include the retrospective nature of this analysis. Although toxicities were evaluated prospectively, the toxicities may also be underreported given the lack of long term follow up and we plan to provide more concrete 1 year toxicity data along with outcomes data. Long term follow up would better elucidate late toxicities and provide insight into clinical outcomes Patients included in this analysis are small, but similar to many adaptive pancreas SBRT studies. As discussed above, we also utilize CT guided OART, which has less robust soft tissue contrast compared to MR guided OART. We believe in advocating for future research with a direct comparison of different adaptive modalities, to better understand if the improved soft tissue image quality leads to better dosimetric and toxicity outcomes, despite the increased physician time and treatment time. The final limitation of this analysis is that while at our institution we believe having two targets, of 40 Gy and 25 Gy and not treating nodes electively is appropriate, other studies in the space have treated up to 50 Gy, not included a dose-deescalated target or included elective nodes within the PTV. All of these differences make it difficult to compare our results to other RT data and we advocate for future prospective trials to standardize our target volumes and doses.

Conclusions

Daily CT-based OART was associated with significantly reduced dose OARs while achieving superior PTV coverage. Given the relatively quick total treatment time, radiation delivery was generally well tolerated and easily incorporated into the clinic workflow. Our initial clinical experience demonstrates OART allows for safe dose escalation in the treatment of PDAC.

CRediT authorship contribution statement

Albert Lee: Investigation, Methodology, Writing – original draft. **Jared Pasetsky:** Formal analysis, Visualization, Writing – original draft. **Elizaveta Lavrova:** Data curation. **Yi-Fang Wang:** Methodology, Data curation. **Geoffrey Sedor:** Formal analysis. **Feng L. Li:** Data curation. **Matthew Gallitto:** Methodology, Writing – review & editing. **Matthew Garrett:** Methodology. **Carl Elliston:** Methodology. **Michael Price:** Conceptualization, Writing – review & editing. **Lisa A. Kachnic:** Conceptualization, Supervision, Writing – review & editing. **David P. Horowitz:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100813.

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