9-15-2020

Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy (MRgRT) with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer

Michael Chuong
Baptist Health Medical Group; Miami Cancer Institute, michaelchu@baptisthealth.net

Kathyrn Mittauer
Miami Cancer Institute, KathrynM@baptisthealth.net

Matthew Hall
Baptist Health Medical Group; Miami Cancer Institute, matthewha@baptisthealth.net

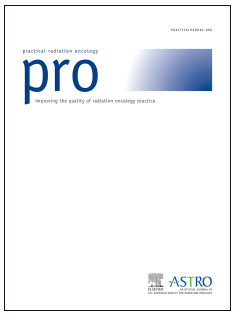
Rupesh Kotecha
Baptist Health Medical Group; Miami Cancer Institute, rupeshk@baptisthealth.net

Diane Alvarez
Miami Cancer Institute, dianeal@baptisthealth.net

See next page for additional authors

Citation

Practical Radiation Oncology (2020) [Epub ahead of print] Published online: September 15



Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy (MRgRT) with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer

Michael D. Chuong, MD, John Bryant, BS, Kathryn E. Mittauer, PhD, Matthew Hall, MD, MBA, Rupesh Kotecha, MD, Diane Alvarez, MSc, Tino Romaguera, PhD, Muni Rubens, MBBS, MPH, PhD, Sonia Adamson, MSN, APRN, AOCNP, Andrew Godley, PhD, Vivek Mishra, PhD, Gustavo Luciani, CMD, Alonso N. Gutierrez, PhD, MBA

PII: S1879-8500(20)30218-6

DOI: https://doi.org/10.1016/j.prro.2020.09.005

Reference: PRRO 1282

To appear in: *Practical Radiation Oncology*

Received Date: 16 March 2020

Revised Date: 3 September 2020

Accepted Date: 8 September 2020

Please cite this article as: Chuong MD, Bryant J, Mittauer KE, Hall M, Kotecha R, Alvarez D, Romaguera T, Rubens M, Adamson S, Godley A, Mishra V, Luciani G, Gutierrez AN, Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy (MRgRT) with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer, *Practical Radiation Oncology* (2020), doi: https://doi.org/10.1016/j.prro.2020.09.005.

Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy (MRgRT) with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer

Authors and affiliations:
Michael D. Chuong, MD[1], John Bryant BS[2], Kathryn E. Mittauer, PhD[1], Matthew Hall, MD, MBA[1], Rupesh Kotecha, MD[1], Diane Alvarez, MSc[1], Tino Romaguera, PhD[1], Muni Rubens, MBBS, MPH, PhD[1], Sonia Adamson, MSN, APRN, AOCNP[1],Andrew Godley, PhD[1], Vivek Mishra, PhD[1], Gustavo Luciani, CMD[1], Alonso N. Gutierrez, PhD, MBA[1]

[1]Department of Radiation Oncology, Miami Cancer Institute, Miami, Florida
[2]Herbert Wertheim College of Medicine, Florida International University, Miami, Florida

Corresponding author:
Michael D. Chuong, M.D.
Miami Cancer Institute
Department of Radiation Oncology
Miami, FL 33176
Phone: 786-527-8175
Fax: 786-814-4395
Email: michaelchu@baptisthealth.net

Running title: Ablative 5-fraction pancreas MR-guided RT

Conflict of interest:
Dr. Chuong reports grants, personal fees and non-financial support from ViewRay, personal fees and non-financial support from Sirtex, personal fees and non-financial support from Accuray, outside the submitted work. Dr. Gutierrez reports personal fees and non-financial support from ViewRay, outside the submitted work. Dr. Kotecha reports personal fees and non-financial support from Elekta, other from Novocure, outside the submitted work. Dr. Mittauer reports personal fees and non-financial support from ViewRay, other from MR Guidance, LLC, outside the submitted work.

Financial support:
No financial support was provided for this research.

Statistical analysis:
Muni Rubens, MBBS, MPH, PhD
munir@baptisthealth.net

Data sharing statement:
Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy (MRgRT) with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer

Running title: Ablative 5-fraction pancreas MR-guided RT

Abstract

Purpose: Radiotherapy (RT) dose escalation using stereotactic body radiation therapy (SBRT) may significantly improve both local control (LC) and overall survival (OS) for patients with inoperable pancreas cancer. However, ablative dose cannot be routinely offered because of the risk of causing severe injury to adjacent normal organs. Stereotactic magnetic resonance (MR)-guided adaptive radiation therapy (SMART) represents a novel technique that may achieve safe delivery of ablative dose and improve long-term outcomes.

Methods and Materials: We performed a single institution retrospective analysis of 35 consecutive pancreatic cancer patients treated with SMART in mid-inspiration breath hold on an MR-LINAC. Most had locally advanced disease (80%) and received induction chemotherapy (91.4%) for a median 3.9 months prior to SBRT. All were prescribed 5 fractions delivered in consecutive days to a median total dose of 50 Gy (BED_{10} 100 Gy_{10}), typically with a 120-130% hotspot. Elective nodal irradiation was delivered to 20 (57.1%) patients. No patient had fiducial markers placed and all were treated with continuous intrafraction MR visualization and automatic beam triggering.

Results: With median follow-up of 10.3 months from SMART, acute (2.9%) and late (2.9%) grade 3 toxicities were uncommon. One-year LC, distant metastasis-free survival, progression-free survival, cause-specific survival, and OS were 87.8%, 63.1%, 52.4%, 77.6% and 58.9%, respectively.

Conclusions: To our knowledge, this is the first report of 5-fraction pancreas SMART delivered on an MR-LINAC. We observed minimal severe treatment-related toxicity and encouraging early LC. Prospective confirmation of feasibility and long-term clinical outcomes of dose intensified SMART is warranted.

Introduction

Pancreas cancer has a dismal prognosis with 5-year overall survival (OS) of <5% despite aggressive management(1). While the impact of non-ablative radiation therapy (RT) on OS for locally advanced pancreas cancer (LAPC) continues to be debated, randomized data demonstrate improved local control (LC) with chemoradiation (CRT) versus chemotherapy alone(2). This is meaningful as up to one-third of patients may die from local progression rather than distant metastases(3).

A growing body of literature suggests that escalation of the biologically effective dose (BED) may improve LC, which may improve OS for inoperable patients(4-10). Furthermore, published guidelines recommend that dose escalation be considered if appropriate resources such as motion management and daily image guidance are available to ensure safety(11). However, delivery of ablative dose (e.g. [BED_{10}] ≥100 Gy_{10}) to the majority of gross disease using computerized tomography (CT) guidance is not attempted for most patients due to the proximity of tumor to luminal gastrointestinal (GI) organs at risk (OARs)(12).

Magnetic resonance-guided radiation therapy (MRgRT) represents a novel solution to deliver ablative dose to larger volumes of gross disease regardless of proximity to OARs in up to 5 fractions because of several key features: 1) superior soft tissue visualization compared to CT(13), 2) real-time continuous intrafraction assessment of internal structures, 3) automatic beam gating based on target position, and 4) daily on-table adaptive replanning(14-16). A multi-institutional retrospective analysis of stereotactic MR-guided adaptive radiation therapy (SMART) using cobalt-60 (Co-60) demonstrated encouraging survival with no high-grade toxicity among patients who received dose escalation(5). These outcomes are supported by a recent single institution report of 5-fraction SMART, mostly delivered using Co-60(17).

The first MR-LINAC became clinically operational in 2017, offering improved dosimetry with multi-field IMRT compared to Co-60 and achieving comparable plan quality to a conventional c-arm linac(18,19). Higher dose conformality made feasible by the MR-LINAC

increases the potential for higher target doses previously not achieved with the first generation MRgRT Co-60 machines.

To the best of our knowledge, we report the first clinical experience of 5-fraction SMART for initially inoperable pancreas cancer exclusively on an MR-LINAC.

Methods and Materials

Patient details and clinical evaluation

After obtaining institutional review board approval, a retrospective analysis was performed of 35 consecutive non-metastatic patients with biopsy-proven pancreas adenocarcinoma who were treated with SMART on the ViewRay MRIdian Linac (Oakwood Village, OH) between October 2018 and November 2019 at a single institution.

No minimum distance between tumor and GI luminal organs was required for patients to be considered for SMART. Duodenal invasion based on endoscopic evaluation was a contraindication. Patients were offered SMART regardless of tumor size or number of involved regional lymph nodes. No patient had previously received abdominal RT.

All underwent endoscopic ultrasound (EUS) and CT scans of the chest, abdomen, and pelvis for initial staging. The majority also had either diagnostic MRI abdomen and/or positron emission tomography (PET) scans. Staging and resectability was determined according to the National Comprehensive Cancer Network guidelines(20).

Nearly all (91.4%) received induction chemotherapy for a median 3.9 months (range, 2-12.3 months) prior to SMART, most commonly with FOLFIRINOX (5-fluorouracil, irinotecan, leucovorin, oxaliplatin) (60%) and otherwise gemcitabine-based regimens. Three patients did not receive induction chemotherapy due to suboptimal performance status. No patient received concurrent chemotherapy.

RT treatment planning and delivery

Simulation was performed without delay for fiducial marker placement since MR guidance provides direct visualization of the tumor obviating the need for a surrogate marker. Patient geometry was supine and typically with both arms down at sides to improve patient comfort and beam angles were avoided that would treat through the arms(18). Simulation included a planning 0.35 T mid-inspiration breath hold, balanced steady-state free precession sequence (TrueFISP) MR scan (17-25 sec) acquired on the MRIdian Linac immediately followed by a planning CT scan. No immobilization device was used since daily 3D and 2D MR imaging was performed for inter/intra-fraction motion management, respectively.

The target and OAR contours were delineated on the TrueFISP MR simulation scan and exported to the MRIdian treatment planning system (TPS). The simulation CT was also exported to MRIdian TPS and deformably registered to the simulation MR scan for electron density information for dose calculation purposes. For some cases, bulk density assignment to the vertebral bodies as bone, external as water, and any abdominal gas as air was utilized to account for changes in anatomy between simulation CT and MR imaging. Intravenous (IV) or oral contrast was not given because the tumor and normal anatomy were well-visualized on the MR simulation scan and diagnostic imaging was fused as needed to define the target volumes.

The MRIdian Linac utilizes a step-and-shoot IMRT treatment delivery as has been previously described(21,22). Table 1 lists the OAR constraints used for initial planning and on-table adaptive replanning. A 12-18 beam, step-and-shoot IMRT plan was created with a 2.0 mm^3 resolution Monte Carlo dose calculation and magnetic field corrections. All plans underwent a measurement-based verification quality assurance (QA) using criteria of 2%/2mm distance-to-agreement (DTA) for a γ-analysis pass rate of 90%.

GTV was defined as gross tumor within the pancreas and involved locoregional lymph nodes as seen on diagnostic imaging and simulation CT/MR scans; this was uniformly expanded by 3 mm to create the planning target volume (PTV). A 3-5 mm expansion of the GI OARs was performed to create planning organ at risk volumes (PRVs). Any overlapping portion

of the GTV or PTV by the PRVs was strictly constrained to 35 Gy to facilitate meeting OAR constraints while the remainder was dose-escalated to 50 Gy (n=30; 85.7%) although several patients in our early experience were prescribed 40 Gy (n=1; 2.9%) or 45 Gy (n=4; 11.4%) because of initial uncertainty about patient tolerability. Grossly involved lymph nodes were prescribed the same dose as the primary tumor. The dosimetric hotspot was optimized to be ≥120-130% of the prescription dose and encompassed as much of the PTV outside of the PRV as possible provided that OAR constraints were met.

Real-time tissue tracking on sagittal image acquisition every 250 milliseconds was performed to automatically gate the treatment delivery(23). The tracking region of interest (ROI) was defined daily from the gross target volume (GTV). Beam delivery was automatically paused when >3-5% of the tracking ROI was displaced by >3 mm from its prescribed location. Treatment was delivered for all patients in mid-inspiration breath hold to optimize duty cycle efficiency(24).

Our initial practice was to treat gross disease only and not elective nodal regions. After it was apparent that treatment was tolerated well we eventually adopted the routine use of ENI; this decision was influenced by patterns of failure data indicate that ENI may reduce locoregional failures(6,25). As such, ENI was delivered to the more recently treated 20 patients (57.1%) and the electively treated region gradually evolved to include a 5-10 mm radial expansion around the celiac axis, superior mesenteric vein (SMV), and superior mesenteric artery (SMA); up to the proximal 10-15 mm of these vessels was also included. Instead of routinely creating a clinical target volume (CTV), electively treated regions were typically included within the GTV to minimize the number of structures, expedite daily adaptive replanning, and reduce time patients were in the treatment unit. As such, electively treated regions were usually prescribed the same dose as gross disease.

On-table adaptive workflow

Our on-table adaptive MRgRT workflow was based on prior publications(15,26). Target volumes were rigidly registered from the simulation MR to the daily volumetric MR scan frame of reference and OARs underwent deformable registration. The target volumes were not modified since a change in gross tumor was not expected over the course of 5 fractions. OAR contours within 3 cm radially of the PTV and 2 cm cranial/caudal of the PTV were edited to reflect the anatomy of the day (Figure 1)(15). The optimization target volume assigned to the ablative prescription dose was updated to exclude the GI PRVs of the day.

After recontouring structures based on the current day's MRI anatomy, calculation of the initial plan using the current day's contours was performed to understand the predicted dose to targets and OARs. A predicted plan was created for all 175 fractions since visual assessment of the daily images alone has been shown to not be adequate for decision making about the indication for adaptation(26). Plan reoptimization was performed to meet dose constraints and/or improve target coverage; priority was always to ensure that OAR constraints were met even at the expense of target coverage. If all constraints were met on the predicted dose and the target coverage was not improved for the reoptimized plan, then the predicted plan was used. Plan prediction and reoptimization did not account for prior dose delivered. Prior to treatment, plan fidelity was verified through a secondary Monte Carlo QA dose calculation.

Follow-up and outcomes assessment

Patients were followed with CT/MRI scans and CA19-9 assessment starting 4-6 weeks after SMART and every 2-3 months thereafter, or sooner as clinically indicated. No patient was prescribed a proton pump inhibitor (PPI) after SMART. Chemotherapy was typically not started after SMART unless there was evidence of disease progression.

Toxicity was defined according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). We evaluated the highest grade toxicity experienced by each patient, with acute toxicity being considered to have occurred during or within 90 days after the start of

SMART. All toxicity was prospectively evaluated upon each clinic encounter and recorded in the patient's electronic medical record.

Statistical analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) (27) and statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, North Carolina). Wilcoxon rank sum test was used to compare time from initial setup to treatment delivery completion, time to deliver treatment, and in-room time between initial and more recently treated patients. Follow-up time was determined from the first day of SMART until the date of last patient contact or death. All clinical outcomes were assessed from the date of SMART initiation and were determined using the Kaplan-Meier method. LC was defined as lack of progression of the primary pancreas tumor or within regional lymph nodes according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, distant metastasis-free survival (DMFS) was defined as time to distant recurrence, and progression-free survival (PFS) was defined as the time from first delivered SMART fraction to local recurrence, distant recurrence, or death. Cause-specific survival (CSS) was defined as the time to death due to pancreas cancer whereas OS was defined as the time to death from any cause.

Results

Table 2 describes patient and tumor characteristics. A total of 35 consecutive patients were evaluated with median age of 67 years (range: 34-89 years), most frequently with tumors in the head of pancreas (88.6%) and with locally advanced disease (80%). Median CA19-9 at initial diagnosis was 102.5 U/mL (range, 0.9-1,517.5 U/mL) and this decreased to a median of 47.0 U/mL (range, 1.2-216.6 U/mL) at a median 5 weeks prior to SMART.

The median follow-up for all patients was 10.3 months (range: 2.2-17.9) and 12.5 months for 21 patients (60%) who were alive at time of analysis (range: 4.5-14.2). All patients

had at least 3 months of follow-up except for one who died 2.2 months after SMART; 15 patients (42.9%) were followed for at least 12 months from SMART.

Treatment planning and delivery

The median GTV and PTV for all patients were 65.6 cc and 99.8 cc, respectively. The median GTV and PTV of patients who did not receive ENI were 28.44 cc (range: 6.1-66.9 cc) and 43.2 cc (range: 11.3-68.6 cc), respectively, while for patients treated with ENI, they were 102.0 cc (range: 55.1-284.3 cc) and 141.0 cc (range: 77.1-368.1 cc), respectively.

The median number of fractions that met criteria for adaptive replanning was 5 (range: 1-5). Across all fractions, 169 (96.6%) were adapted online and all 5 fractions were adapted online for 33 patients (94.3%).

Table 3 displays the target volume coverage in total dose for the initial plan on the simulation anatomy versus on-table adaptive plans on the daily anatomy. Ablative dose was delivered to most of the target volumes on the initial plans as demonstrated by the median GTV and PTV D_{80} (52.5 Gy, 46.2 Gy) and D_{90} (50.8 Gy, 39.8 Gy), respectively. Furthermore, the prescribed dose covered a median 80.5% of the PTV on the initial plans. Despite the need to adapt most fractions we were able to maintain excellent high dose coverage (median D_{80}: 49.6 Gy, 44.7 Gy and median D_{90}: 47.5 Gy, 40.5 Gy) to most of the GTV and PTV, respectively. The prescription dose covered a median 70.4% of the PTV across all delivered fractions. Figure 2 illustrates differences in GTV and PTV coverage across 5 adapted fractions due to interfraction GI OAR changes for a patient prescribed 50 Gy.

The median time from initial setup to treatment delivery completion was 83 minutes (range: 56-108 minutes) for all patients. While not statistically significant, this was longer for the initial 17 patients compared to the more recent 18 patients (86 vs. 79.5 minutes; p=0.141) possibly reflecting our improved proficiency with the MR-LINAC over time, which had been operational in our department for only 6 months when we treated the first patient in this study.

Treatment was delivered over a median 20 minutes (range: 11-36 minutes) for all patients and was similar for the initial 17 patients compared to the more recent 18 patients (20 vs. 18 minutes; p=0.235) despite the transition to ENI that resulted in large target volumes.

We recently installed a monitor in the treatment room to show patients their real-time sagittal cine MR images and required breath hold position throughout each fraction(28). The intent was to provide visual biofeedback as a means to decrease the number of breath holds and treatment times as compared to only audio coaching through headphones, which was used for the initial 28 patients. The median in-room time for the 9 patients treated with versus without the monitor was 67 versus 85 minutes; p=0.032).

Therapy after SMART

Approximately half of patients did not resume chemotherapy after SMART (48.6%), most without evidence of disease progression. Thirteen received chemotherapy due to disease progression while 5 received maintenance chemotherapy due to medical oncologist preference.

Three patients received irreversible electroporation (IRE) at a median 11 months (7.3-11.1 months) after SMART. IRE was used to manage regional progression outside of the PTV in 2 patients; neither had distant metastasis. A third patient with stable disease had IRE despite lack of tumor progression, with intra-operative biopsy prior to IRE being negative for invasive adenocarcinoma.

Five patients underwent a Whipple procedure performed at a median 2 months (range: 1-9 months) after completing SMART, 3 with borderline resectable and 2 with locally advanced tumors. All resected patients received induction FOLFIRINOX (n=4) or gemcitabine/nab-paclitaxel (n=1). The prescribed radiation dose was 50 Gy (n=4) or 40 Gy (n=1). Four patients had negative margins and 4 had negative lymph nodes. One had a complete response, 2 had a near complete pathologic response, and 2 were noted to have a marked pathologic response. None of these patients has evidence of tumor recurrence after median 10.8 months follow-up.

Tumor control and survival

Three patients had local progression although only 1 occurred within the PTV (45 Gy prescription without ENI). The other 2 patients (50 Gy prescription with ENI for both) progressed regionally outside of the PTV, one within a lymph node and another along the SMA abutting the PTV. The 1-year LC was 87.8% (95% confidence interval [CI] 79.4-93.8%) and the median time to local progression was 7.4 months (range: 2.5-9.8 months) (Figure 3a). Thirteen patients developed distant metastasis after a median 3.0 months (range: 1.0-11.8 months). The 1-year DMFS was 63.1% (95%: 55.7-69.5%) (Figure 3b). The 1-year PFS and median PFS were 52.4% (95% CI 45.1-58.2%) and 7.9 months, respectively (Figure 3c). Of the 13 patient deaths, 6 were not related to pancreas cancer: cardiac arrest (n=2), sepsis (n=2), head trauma related to a fall (n=1), and pneumonia (n=1). The 1-year OS and median OS were 58.9% (95% 51.6-65.1%) and 9.8 months, respectively (Figure 3d). The 1-year CSS and median CSS were 77.6% (95% 72.7-84.8%) and 9.8 months, respectively (Figure 3e).

Toxicity

Acute grade 2 toxicity (nausea, anorexia) occurred in 3 patients (8.6%). Acute grade 3 toxicity (diarrhea) was reported in 1 patient (2.9%). One patient (2.9%) had late grade 2 duodenal bleeding that did not require transfusion. Late grade 3 toxicity (bile duct stenosis) occurred in 1 patient (2.9%) without evidence of disease progression that required percutaneous drainage. No grade 4-5 events were observed.

Discussion

The proximity of OARs creates a formidable challenge in achieving significant tumor dose intensification to inoperable pancreas cancers while sparing especially the stomach and bowel, as to not cause serious harm to the patient. The importance of limiting high dose to GI

luminal organs was illustrated by the early pancreas SBRT experiences that reported significant toxicities(29-31). For example, a Dutch phase II trial of 45 Gy in 3 fractions (BED_{10} = 112.5_{10}) that used PTV margins up to 10 mm and without high-quality on-board CT imaging reported that 94% of patients had at least grade 2 pain at 3 months after treatment and multiple patients developed severe GI ulceration or perforation likely because at least 67% of the prescribed dose was delivered to the stomach or duodenum(30). Consequently, prioritization of OAR constraints over target volume coverage is strongly recommended(32).

The outcomes of SBRT to 24-36 Gy in 3-5 fractions (BED_{10} = 37.5-79.2 Gy_{10}) have been modest, although both LC and OS worsen with longer follow-up beyond at least 1 year(33-37). For example, a phase II trial by Quan et al. of sequential gemcitabine/capecitabine and 36 Gy in 3 fractions (BED_{10} 79.2 Gy_{10}) reported 1-year LC and OS of 78% and 54% although 2-year LC and OS decreased to 52% and 10%, respectively, among nonsurgical patients.

There has recently become greater enthusiasm in radiation dose escalation for inoperable pancreas cancer to potentially improve clinical outcomes(4-8,10,17). Investigators from MD Anderson Cancer Center (MDACC) reported that LAPC patients, typically treated in 28 fractions with daily CT guidance, had higher median survival (17.8 vs. 15.0 months; *p*=0.03) and local-regional relapse free survival (10.2 vs. 6.2 months; p=0.05) when a biologically effective dose (BED_{10}) >70 Gy_{10} was prescribed (Table 4)(4). Dose intensification was considered, typically with fractionation over multiple weeks to mitigate toxicity, if there was ≥1 cm between tumor and luminal GI structures. This is uncommon and highlights the need for technologies that can safely achieve dose escalation for a broader population.

MRgRT is a novel technique that facilitates dose escalation in the abdomen beyond what has been historically feasible using CT(5,17,22,38). SMART delivered with Co-60 was tolerated remarkably well in an analysis by Rudra et al. of 44 pancreas patients, with 25 receiving dose escalation to 40-67.5 Gy over 5-15 fractions(5). The minority received 5 fractions although it was not specified how many received at least 50 Gy (BED_{10} 100 Gy_{10}); it

was likely a small number given the median prescribed BED_{10} was 77.6 Gy_{10}. Similar to the MDACC analysis, BED_{10} >70 Gy_{10} was associated with improved outcomes. Earlier this year, a retrospective analysis of SMART prescribed to 50 Gy in 5 fractions without ENI was published by investigators at Washington University in St. Louis that included 44 inoperable pancreas cancer patients, most (86%) treated on a Co-60 system(17). With median follow-up of 16 months from pancreas cancer diagnosis, outcomes included 2-year LC, PFS, and OS of 59.3%, 13.9%, and 37.9%, respectively. Treatment was very well tolerated with limited grade 3 toxicity.

To the best of our knowledge the current study represents the first reported outcomes of ablative 5-fraction pancreas SMART delivered only on an MR-LINAC. With median follow-up of 10.3 months from SMART our early outcomes are encouraging. While we cannot draw conclusions about the impact of ENI on our 1-year LC of 87.8%, which is encouraging compared to other studies(4,34-37), it is notable that only 1 patient had disease progression within the PTV while the others progressed regionally outside of the PTV. Furthermore, the use of ENI was not associated with significant toxicity. While our 1-year OS of 58.9% is similar to other pancreas SBRT studies that prescribed non-ablative doses, nearly half of deaths were not related to pancreas cancer or to treatment-related toxicity. Lastly, grade 3 toxicity occurred in only 2 patients, which likely was achieved by interfraction anatomic changes being visualized daily on MRI and on-table adaptive replanning being able to account for these changes.

There are several aspects of our treatment approach worth emphasizing. First, there was no need to refer patients for fiducial marker placement, which could otherwise delay simulation up to several weeks. There was only a median 1 day between consultation to simulation and a median 13 days from consultation to delivery of first fraction for patients in our study. Whether decreasing the interval to start of RT impacts long-term outcomes remains unknown; in the short-term this can mitigate patient anxiety especially since some patients are referred for RT with local progression while on chemotherapy. Second, treatment was delivered in consecutive days and we did not prescribe a prophylactic PPI. Third, continuous intrafraction

tissue tracking permitted breath hold delivery, eliminating the need for an internal target volume (ITV) and thereby reducing the volume of normal tissue exposed to high dose. Direct intrafraction visualization of the tumor and in-plane OARs abutting the high dose gradient enabled not only greater confidence throughout the ablative dose delivery, but also allowed for treatment halting and repeat 3D MR imaging to adjust for the intrafraction motion detected on 2D MR imaging. The need for intrafraction dose assessment and reoptimization is currently unclear and this should be explored in future studies(28). Fourth, we found that both tumor and normal anatomy are visualized well on the MR simulation and daily treatment breath hold scans without contrast. This has improved patient satisfaction by avoiding diarrhea, the need to check renal function, and obtain IV access. We have also been able to free up nursing resources and decrease the time needed on the CT simulator for these patients. Fifth, most patients were treated to elective nodal regions, which is unconventional and frankly controversial(6,9,25). The role of ENI remains debated and because of potentially severe toxicity, at least using CT image guidance, some have recommended against it(11). Electively treated regions typically received an ablative dose prescription, and although this was tolerated well the long-term effects of this need to be closely evaluated. Lastly, ablative dose covered most of the targets as demonstrated by the median GTV and PTV D_{80} and D_{90} on the initial plans. Despite the need to adapt most fractions we were able to maintain ablative dose to most of the GTV and PTV, respectively. This is in distinct contrast to the strategy commonly employed for low dose SBRT using daily CT guidance in which dose escalation is confined to a restricted volume, for example only the tumor-vessel interface(9,35,39,40).

Study limitations include that this is a retrospective analysis and subject to underreporting of toxicities although toxicities were evaluated prospectively at the time of each patient encounter. Patient numbers are small, although are similar to most published prospective or retrospective pancreas SBRT studies. Our results would benefit from more extended follow-up to better understand late toxicity and long-term clinical outcomes. Still, we

believe that our median follow-up of 10.3 months is long enough to provide meaningful comparison to other studies, especially given that the median survival for LAPC patients is approximately 12-16 months(4). In addition, whereas other analyses with longer follow-up measured outcomes from the time of diagnosis(17,36), which then is routinely followed by at least several months of chemotherapy, our analysis began from the initiation of SMART. Lastly, while most fractions were adapted the cumulative dose was not assessed with respect to clinical outcomes.

In conclusion, 50 Gy in 5 consecutive fractions delivered using an MR-LINAC to inoperable pancreas cancer and elective nodal regions with daily on-table adaptive replanning can achieve excellent early LC and with limited severe toxicity. Our experience supports enrollment to an ongoing phase II trial of 5-fraction ablative SMART prescribed to 50 Gy in 5 fractions (NCT03621644).

References

1. Li D, Xie K, Wolff R, et al. Pancreatic cancer. *Lancet* 2004;363:1049-57.
2. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The lap07 randomized clinical trial. *JAMA* 2016;315:1844-53.
3. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. Dpc4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009;27:1806-13.
4. Krishnan S, Chadha AS, Suh Y, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. *Int J Radiat Oncol Biol Phys* 2016;94:755-65.
5. Rudra S, Jiang N, Rosenberg SA, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. *Cancer Med* 2019;8:2123-2132.
6. Zhu X, Ju X, Cao Y, et al. Patterns of local failure after stereotactic body radiation therapy and sequential chemotherapy as initial treatment for pancreatic cancer: Implications of target volume design. *Int J Radiat Oncol Biol Phys* 2019;104:101-110.
7. Reyngold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: Techniques and results. *Radiat Oncol* 2019;14:95.

8. Ma SJ, Prezzano KM, Hermann GM, et al. Dose escalation of radiation therapy with or without induction chemotherapy for unresectable locally advanced pancreatic cancer. *Radiat Oncol* 2018;13:214.
9. Bernard V, Herman JM. Pancreas sbrt: Who, what, when, where, and how. *Practical Radiation Oncology*.
10. Arcelli A, Guido A, Buwenge M, et al. Higher biologically effective dose predicts survival in sbrt of pancreatic cancer: A multicentric analysis (paula-1). *Anticancer Res* 2020;40:465-472.
11. Oar A, Lee M, Le H, et al. Australasian gastrointestinal trials group (agitg) and trans-tasman radiation oncology group (trog) guidelines for pancreatic stereotactic body radiation therapy (sbrt). *Pract Radiat Oncol* 2019.
12. Murphy JD, Christman-Skieller C, Kim J, et al. A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:1420-6.
13. Mittauer K, Paliwal B, Hill P, et al. A new era of image guidance with magnetic resonance-guided radiation therapy for abdominal and thoracic malignancies. *Cureus* 2018;10:e2422.
14. Noel CE, Parikh PJ, Spencer CR, et al. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. *Acta Oncol* 2015;54:1474-82.
15. Bohoudi O, Bruynzeel AME, Senan S, et al. Fast and robust online adaptive planning in stereotactic mr-guided adaptive radiation therapy (smart) for pancreatic cancer. *Radiother Oncol* 2017;125:439-444.
16. Boldrini L, Cusumano D, Cellini F, et al. Online adaptive magnetic resonance guided radiotherapy for pancreatic cancer: State of the art, pearls and pitfalls. *Radiat Oncol* 2019;14:71.
17. Hassanzadeh C, Rudra S, Bommireddy A, et al. Ablative five-fraction stereotactic body radiation therapy for inoperable pancreatic cancer using online mr-guided adaptation. *Advances in Radiation Oncology* 2020.
18. Ramey SJ, Padgett KR, Lamichhane N, et al. Dosimetric analysis of stereotactic body radiation therapy for pancreatic cancer using mr-guided tri-(60)co unit, mr-guided linac, and conventional linac-based plans. *Pract Radiat Oncol* 2018;8:e312-e321.
19. Yadav P, Musunuru HB, Witt JS, et al. Dosimetric study for spine stereotactic body radiation therapy: Magnetic resonance guided linear accelerator versus volumetric modulated arc therapy. *Radiol Oncol* 2019;53:362-368.
20. Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic adenocarcinoma, version 1.2019. *J Natl Compr Canc Netw* 2019;17:202-210.
21. Fischer-Valuck BW, Henke L, Green O, et al. Two-and-a-half-year clinical experience with the world's first magnetic resonance image guided radiation therapy system. *Adv Radiat Oncol* 2017;2:485-493.
22. Green OL, Henke LE, Hugo GD. Practical clinical workflows for online and offline adaptive radiation therapy. *Semin Radiat Oncol* 2019;29:219-227.
23. Green OL, Rankine LJ, Cai B, et al. First clinical implementation of real-time, real anatomy tracking and radiation beam control. *Med Phys* 2018.

24. Bohoudi O, Bruynzeel AM, Senan S, et al. Sbrt for pancreatic cancer: In regard of bohoudi et al. *Radiother Oncol* 2018;127:511-512.
25. Kharofa J, Mierzwa M, Olowokure O, et al. Pattern of marginal local failure in a phase ii trial of neoadjuvant chemotherapy and stereotactic body radiation therapy for resectable and borderline resectable pancreas cancer. *Am J Clin Oncol* 2019;42:247-252.
26. Tyran M, Jiang N, Cao M, et al. Retrospective evaluation of decision-making for pancreatic stereotactic mr-guided adaptive radiotherapy. *Radiother Oncol* 2018;129:319-325.
27. Harris PA, Taylor R, Minor BL, et al. The redcap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
28. van Sornsen de Koste JR, Palacios MA, Bruynzeel AME, et al. Mr-guided gated stereotactic radiation therapy delivery for lung, adrenal, and pancreatic tumors: A geometric analysis. *Int J Radiat Oncol Biol Phys* 2018;102:858-866.
29. Koong AC, Le QT, Ho A, et al. Phase i study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1017-21.
30. Hoyer M, Roed H, Sengelov L, et al. Phase-ii study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol* 2005;76:48-53.
31. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2008;72:678-86.
32. Palta M, Godfrey D, Goodman KA, et al. Radiation therapy for pancreatic cancer: Executive summary of an astro clinical practice guideline. *Pract Radiat Oncol* 2019;9:322-332.
33. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009;115:665-72.
34. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2010;78:735-42.
35. Mellon EA, Hoffe SE, Springett GM, et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. *Acta Oncol* 2015:1-7.
36. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer* 2015;121:1128-37.
37. Quan K, Sutera P, Xu K, et al. Results of a prospective phase 2 clinical trial of induction gemcitabine/capecitabine followed by stereotactic ablative radiation therapy in borderline resectable or locally advanced pancreatic adenocarcinoma. *Pract Radiat Oncol* 2018;8:95-106.
38. Henke L, Kashani R, Robinson C, et al. Phase i trial of stereotactic mr-guided online adaptive radiation therapy (smart) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol* 2018;126:519-526.
39. Katz MHG, Ou FS, Herman JM, et al. Alliance for clinical trials in oncology (alliance) trial a021501: Preoperative extended chemotherapy vs. Chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *BMC Cancer* 2017;17:505.

40. Yang W, Reznik R, Fraass BA, et al. Dosimetric evaluation of simultaneous integrated boost during stereotactic body radiation therapy for pancreatic cancer. *Med Dosim* 2015;40:47-52.

Figure Legend:

Figure 1. Target volumes (top row) and isodose lines (bottom row) for a pancreas cancer patient prescribed 50 Gy in 5 consecutive fractions with daily magnetic resonance image guidance and on-table adaptive replanning

Figure 2. Dose-volume histograms for a patient prescribed 50 Gy that illustrates differences across 5 adapted fractions in coverage of the a) GTV and b) PTV.

Figure 3. Kaplan-Meier plots for a) local control, b) distant metastasis-free survival, c) progression-free survival, d) overall survival, e) cause-specific survival.

(Table 1. Organ at risk constraints for 5-fraction pancreas stereotactic magnetic resonance image-guided adaptive radiation therapy (SMART)

Organ at risk	Dose constraint
Stomach, duodenum, small bowel	V35 <0.5 cc V40 <0.03 cc
Large bowel	V38 < 0.5 cc V43 < 0.03 cc
Kidneys	Mean <10 Gy
Liver	Mean <15 Gy
Spinal cord	V25 < 0.03 cc

Table 2. Patient, tumor, and treatment characteristics

Characteristic	N (range)
Total number of patients	35
Age (yr), median	67 (34-89)
Gender	
Male	21 (60%)
Female	14 (40%)
Tumor location	
Head	31 (88.6%)
Body/tail	4 (11.4%)
ECOG performance status	
0	20 (57.1%)
1	12 (34.3%)
2	3 (8.6%)
Initial staging scans	
CT alone	8 (22.9%)
CT and MRI	14 (40%)
CT and PET	4 (11.4%)
CT, MRI, and PET	9 (25.7%)
Stage	
Locally advanced	28 (80%)
Borderline resectable	3 (8.6%)
Medically inoperable	4 (11.4%)
Clinical T stage	
1	0
2	7 (20%)
3	2 (5.7%)
4	26 (74.3%)
Clinical N stage	

0	25 (71.4%)
1	9 (25.7%)
2	1 (2.9%)
Clinical M stage	
0	35 (100%)
1	0
CA 19-9 (U/mL), median	
Initial diagnosis	102.5 (0.9-1,517.5)
Before SMART	47 (1.2-216.6)
Induction chemotherapy	
FOLFIRINOX	18 (51.4%)
gemcitabine/nab-paclitaxel	7 (20%)
FOLFIRINOX then gemcitabine/nab-paclitaxel	3 (8.6%)
gemcitabine alone	4 (11.4%)
none	3 (8.6%)
Induction chemotherapy duration (months), median	3.9 (2-12.4)
Radiation dose	
Total prescribed dose (Gy), median	50 (40-50)
Total prescribed fractions	5
Motion management	
Breath hold	30 (85.7%)
Free breathing gating	5 (14.3%)
Elective nodal irradiation	
Yes	20 (57.1%)
No	15 (42.9%)
On-table plan adaptation	
Adapted fractions per patient, median	5 (1-5)
Therapy after SMART	
Irreversible electroporation	3 (8.6%)
Pancreaticoduodenectomy	5 (14.3%)
Chemotherapy	18 (51.4%)

Table 3. Target volume coverage reported in total dose for initial plan on simulation anatomy versus on-table adaptive plans on daily anatomy

Target volume	Initial plan on simulation anatomy (total dose)			Adaptive plan on daily anatomy (total dose)		
	median	mean ± SD	range	median	mean ± SD	range
PTV D_{90}	39.8 Gy	43.9±6.3 Gy	32.7-53.0 Gy	40.5 Gy	40.9±6.0 Gy	26.8-68.1 Gy
GTV D_{90}	50.8 Gy	50.4±6.2 Gy	38.8-58.3 Gy	47.5 Gy	47.2±5.8 Gy	32.1-68.1 Gy
PTV D_{80}	46.2 Gy	45.9±5.6 Gy	37.4-54.9 Gy	44.7 Gy	44.7±5.4 Gy	25.6-63.3 Gy
GTV D_{80}	52.5 Gy	51.9±4.7 Gy	44.1-58.8 Gy	49.6 Gy	50.1±4.7 Gy	39.4-69.2 Gy
PTV Max	65.9 Gy	65.2±5.7 Gy	49.9-74.1 Gy	65.7 Gy	64.9±6.1 Gy	59.8-76.1 Gy
GTV Max	65.4 Gy	61.8±4.9 Gy	57.8-73.1 Gy	65.4 Gy	64.9±6.0 Gy	59.8-76.1 Gy
PTV Mean	52.7 Gy	52.0±3.9 Gy	42.7-58.3 Gy	50.5 Gy	50.4±4.7 Gy	43.8-67.6 Gy
GTV Mean	56.3 Gy	60.3±3.4 Gy	49.4-60.1 Gy	54.4 Gy	54.0±4.0 Gy	46.9-70.8 Gy

PTV = planning target volume; GTV = planning target volume; D_{80} = dose to 80% of volume; D_{90} = dose to 90% of volume; SD = standard deviation

Table 4. Selected studies of radiation therapy for patients with inoperable pancreas adenocarcinoma

Study	RT modality	Image guidance	Resectability	N	Total dose and # fx	BED_{10} (Gy_{10})	ENI used	Median PTV volume	Surgery after RT	Median FU (mo)	LC	OS	Acute grade 3+ toxicity
Hoyer et al. (36)	X-ray	Portal imaging	100% LA	22	45 Gy in 3 fx	112.4	No	GTV: 32 cc (7-102 cc)	0%	NR	6-mo: 57%	1-yr: 5%	Grade 2+: 79%
Herman et al. (30)	X-ray	CBCT	100% LA	49	33 Gy in 5 fx	54.8	No	71.4 (31.9-225.2 cc)	4 (8.2%)	13.9 (from dx)	1-yr: 78% 2-yr: NR	1-yr: 59% 2-yr: 18%	Grade 2+: 11%
Krishnan et al. (4)	X-ray	CBCT, CT-on-rails	100% LA	14 11 7 1 1 13	63 Gy in 28 fx 70 Gy in 28 fx 67.5 Gy in 15 fx 60 Gy in 10 fx 50 Gy in 5 fx 51.3-70.4 Gy in 13-39 fx	77.2 87.5 97.9 96.0 100.0 70.4-84.3	No	NR	2 (4.3%)	9.6 (from RT)	1-yr: 21% 2-yr: 17%	1-yr: 60% 2-yr: 22%	2.0% (diarrhea)
Quan et al. (33)	X-ray	CBCT	54.3% BR 45.7% LA	35	36 Gy in 3 fx	79.2	No	18.9 cc (5.5-65.2 cc)	12 (34.3%)	15.4 (from trial enrollment)	1-yr: 78% 2-yr: 52% (LA only)	1-yr: 54% 2-yr: 10% (nonsurgical LA only)	0%
Rudra et al. (5)	Cobalt-60	0.35T MRI	75% LA 16.7% BR	16 9	40-52 Gy in 5 fx 50-67.5 Gy in 10-15 fx	median 77.6 median 82.7	Yes (% NR)	73.3 cc (13.8-239.0)	2 (8.3%)	17 (from RT)	2-yr: 77% (BED_{10}>70)	2-yr: 49% (BED_{10}>70)	0% (BED_{10}>70)
Hassanzadeh et al.	Cobalt-60 (86%) X-ray (14%)	0.35T MRI	64% LA 14% BR	44	50 Gy in 5 fx	100.0	No	109 cc (25-419 cc)	3 (6.8%)	16 (from dx)	1-yr 84.3% 2-yr 59.3%	1-yr: 68.2% 2-yr: 37.9%	0%
Current study	X-ray	0.35T MRI	80% LA 8.6% BR	30 4 1	50 Gy in 5 fx 45 Gy in 5 fx 40 Gy in 5 fx	100.0 85.5 72.0	Yes (57.1%)	99.8 cc (11.3-368.1 cc)	5 (14.3%)	10.3 (from RT)	1-yr: 87.8%	1-yr: 58.9%	2.9% (diarrhea)

RT = radiation therapy; 0.35T = 0.35 Tesla; N = number of patients; BR = borderline resectable; LA = locally advanced; Fx = fraction; BED = biologically effective dose; ENI = elective nodal irradiation; FU = follow-up; dx = diagnosis; mo = months; LRC = locoregional control; OS = overall survival; PTV = planning target volume; NR = not reported; CBCT = cone-beam computed tomography; MRI = magnetic resonance imaging; BED_{10} = biologically effective $dose_{10}$