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Technical Note

Implementation of a stereotactic body radiotherapy program for unresectable pancreatic cancer in an integrated community academic radiation oncology satellite network

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ABSTRACT

Background: With increasing interest in stereotactic body radiotherapy (SBRT) for unresectable pancreatic cancer, quality improvement (QI) initiatives to develop integrated clinical workflows are crucial to ensure quality assurance (QA) when introducing this challenging technique into radiation practices.
Materials/Methods: In 2017, we used the Plan, Do, Study, Act (PDSA) QI methodology to implement a new pancreas SBRT program in an integrated community radiation oncology satellite. A unified integrated information technology infrastructure was used to virtually integrate the planned workflow into the community radiation oncology satellite network (P – Plan/D – Do). This workflow included multiple prospective quality assurance (QA) measures including multidisciplinary evaluation, prospective scrutiny of radiation target delineation, prospective radiation plan evaluation, and monitoring of patient outcomes. Institutional review board approval was obtained to retrospectively study and report outcomes of patients treated in this program (S – Study).
Results: There were 12 consecutive patients identified who were treated in this program from 2017 to 2020 with a median follow-up of 27 months. The median survival was 13 months, median local failure free survival was 12 months and median progression free survival was 6 months from SBRT. There were no acute or late Common Terminology Criteria for Adverse Effects (CTCAE) version 5 toxicities $\geq$ Grade 3.
Conclusion: We report the successful implementation of a community pancreas SBRT program involving multiple prospective QA measures, providing the groundwork to safely expand access to pancreas SBRT in our community satellite network (A – Act).

1. Introduction

Exocrine pancreatic cancer is a deadly malignancy with over 57,000 cases expected in the United States in 2020 [1]. At initial presentation, 1/3 of patients present with locally-advanced disease that is not amenable to surgical resection [2,3], and nearly all of these patients progress on systemic therapy with median survival <12 months [4–8], While conventionally fractionated radiation has long been studied in locally-advanced pancreatic cancer [6,9–13], enthusiasm for long-course chemoradiation has been tempered by results of the LAP07 trial [14], where concurrent chemoradiation failed to improve survival compared to chemotherapy alone.

Stereotactic body radiotherapy (SBRT) has emerged as a technique to deliver ablative radiation doses to pancreatic tumors while minimizing time off of systemic chemotherapy. However, pancreas SBRT is a challenging procedure requiring careful patient selection and subspecialized expertise. For example, initial results

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of a Phase I clinical trial using single fraction SBRT for locally-advanced pancreatic cancer showed potential for increased gastrointestinal toxicity with long term follow-up, prompting pursuit of less extreme hypofractionated regimens [15–19]. A subsequent Phase II trial using 5 fraction SBRT to a dose of 33 Gy showed high rates of tumor control with low rates of serious adverse events [20]. SBRT for pancreatic cancer has also been evaluated pre-operatively for borderline resectable pancreatic adenocarcinoma in an ALLIANCE cooperative group trial with preliminary results recently reported in abstract form at the 2021 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancer Symposium [21]. As interest in SBRT for pancreatic cancer has grown, the American Society of Radiation Oncology (ASTRO) has provided consensus guidelines for pancreas SBRT [22]. Despite the emergence of SBRT as a promising treatment for pancreatic cancer, there are hurdles to safely implement this technique in community-based practices due to the complexities of radiation planning and delivery.

We report a quality improvement (QI) initiative using Plan, Do, Study, Act (PDSA) methodology to establish a new community-based SBRT program for unresectable pancreatic cancer in an integrated academic community satellite network. The PDSA is a well-established method to improve quality in healthcare (and other industries), whereby PDSA cycles are used to drive improvement in processes [23]. Often a central element of QI initiatives, the PDSA methodology has been utilized to improve care delivery for a number of cancers [24–26]. A prospective multidisciplinary workflow was established to maintain quality assurance (QA). Oncologic and toxicity outcomes were monitored in and reported herein to validate this QI initiative.

2. Materials and Methods

Approval was obtained from the University of Texas, M.D. Anderson Institutional Review Board to retrospectively report procedures and outcomes (2020–0514) of patients treated in this PDSA initiative.

2.1. Clinical workflow

The workflow developed to implement this program is summarized in Fig. 1 (P – Plan). Key clinical resources and procedures used in this program are shown in Table 1 (D – Do). Briefly, all patients were evaluated by multidisciplinary tumor board and deemed appropriate for SBRT in accordance to criteria provided in the Supplemental Appendix. Patients underwent upper gastrointestinal endoscopy to rule out tumor bowel involvement and 2–3 gold fiducials were placed at the periphery of the tumor under ultrasound guidance. Patients were *nils per os* (N.P.O.) 3 h prior to CT-simulation. At time of CT-simulation, iodinated intravenous contrast was administered during time of image acquisition with 3 contrast enhanced scans using breath hold (DIBH) for motion management. DIBH scans were evaluated for reproducibility of setup and to generate an internal gross tumor volume (iGTV) and internal tumor vessel interface (iTVI) defined as the circumference of arterial or venous blood vessels in contact with the iGTV. Contours of normal structures, iGTV, iTVI and final planning target volumes (PTVs) were prospectively reviewed for QA with radiation oncologists of the M.D. Anderson main campus Gastrointestinal Radiation Oncology (GRO) section prior to radiation planning. PTV doses were chosen by GRO group consensus based upon multiple clinicopathologic factors including tumor extent, patient performance status and normal tissue anatomic considerations. The final radiation plan was prospectively reviewed by the M.D. Anderson GRO Section and radiation physicists for QA prior to delivery. Daily SBRT

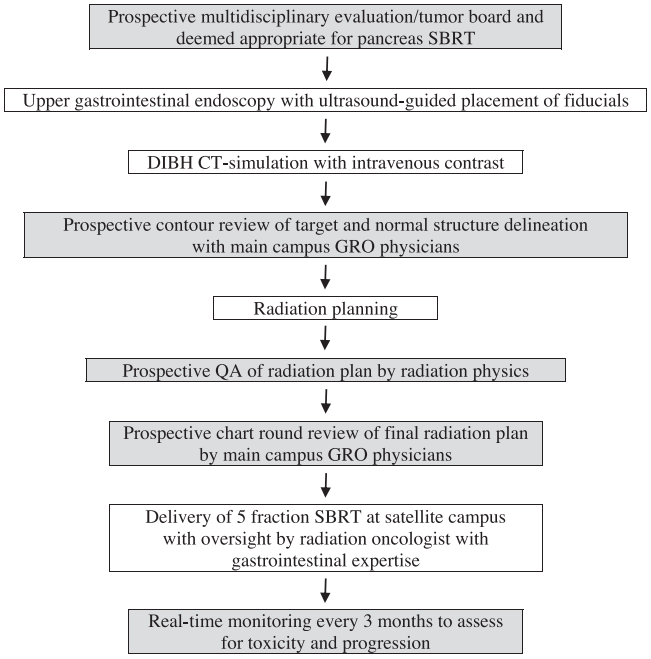

Fig. 1. Multidisciplinary workflow for integrated SBRT program for pancreatic cancer in community-based satellites. Grey boxes demarcate the multiple quality assurance measures undertaken for pancreas SBRT in the program. DIBH, deep inspiratory breath hold; GRO, gastrointestinal radiation oncology.

treatments were monitored by a board certified radiation oncologist with gastrointestinal expertise. Daily kilovoltage (kV) imaging was used for initial alignment to fiducials followed by cone beam CT-scans (CBCT) verification on a Truebeam™ (Varian Medical Systems Inc., Palo Alto, CA) linear accelerator (LINAC). On the CBCT, the covering radiation oncologist verified alignment of fiducials and reproducibility of bowel anatomy such that bowel structures did not fall into the 36–40 Gy isodose lines. Megavoltage (MV) films were then taken daily for final verification of setup. Bowel ulcer prophylaxis with a proton pump inhibitor (pantoprazole or omeprazole) was prescribed to patients from the first day of radiation taken daily for 6 months. Patients were evaluated every 3 months to assess tumor control and adverse events.

2.2. Radiation treatment planning

SBRT was planned largely in accordance to the Alliance for Clinical Trials in Oncology Group A021101 trial (supplemental appendix) [21]. Briefly, 5 fraction SBRT plans were developed using 6 MV photons with volumetric arc therapy (VMAT) using either the Pinnacle version 3 (Philips Healthcare, Amsterdam, Netherlands) or RayStation® version 9A (RaySearch Laboratories, Stockholm, Sweden) planning systems. A minimum of 25 Gy was prescribed to PTV1 that included the iGTV and iTVI with 3 mm volumetric expansion. Additional simultaneous boosts to the iGTV/iTVI excluding the bowel were delivered to PTV2 and/or PTV3 to a dose of 33–40 Gy.

2.3. Oncologic and toxicity outcomes

All consecutive patients 2017–2020 were analyzed for oncologic outcomes using the Kaplan-Meier method (S – Study). Common Terminology Criteria for Adverse Events (CTCAE) version 5 was used to rate severity of radiation-related side effects. Acute radiation side effects were defined as occurring during or within

Table 1
Key clinical resources for implementation of pancreas stereotactic body radiotherapy (SBRT) program. CBCT, cone beam CT-scan; EMR, electronic medical record; IR, interventional radiology; IV, intravenous; MV, megavoltage; LINAC, linear accelerator.

Clinical Resources
Integrated information technology infrastructure (EMR, RT planning system)
Multidisciplinary Tumor Board/Evaluation
Pancreatic fiducials for image guidance placed endoscopically or by IR
Upper GI endoscopic ultrasound to rule out bowel involvement
Board certified radiation oncologist, radiation physics and radiation therapy team with pancreas SBRT training/familiarity
CT-sim/LINAC Features
Volumetric arc therapy or non-coplanar SBRT with 6 MV photon energy
Surface guidance for setup
On board daily volumetric imaging (CBCT or CT on rails)
Iodinated IV-contrast for CT-simulation
Deep inspiration breath hold or respiratory gating for motion management

90 days of radiation treatment and late radiation side effects were defined as occurring more than 90 days from initiation of radiation.

3. Results

There were 12 consecutive patients treated in this QI initiative from 2017 through 2020 with baseline clinicopathologic shown in Table 2. All patients had histologically proven exocrine pancreatic carcinoma and the majority of patients received systemic gemcitabine and nab-paclitaxel or FOLFIRINOX prior to radiation. Two patients were treated with SBRT for Stage IV disease due to an induced oligometastatic state after initial systemic therapy. The dosimetric radiation plan parameters are shown in the Supplemental Appendix.

The median follow-up of patients from time of SBRT was 27 months. The median survival was 13 months, median progression free survival 6 months and median local control 12 months from SBRT (Fig. 2). All patients presented with abdominal pain prior to SBRT with improvement in 58% (N = 7) and stable pain in 42% (N = 5). One patient whose initial T4 disease encased the superior mesenteric artery and celiac axis was converted to resectability after FOLFIRINOX and SBRT resulting in margin negative resection with 5% viable tumor cells.

There were no CTCAE $\geq$ grade 3 adverse side effects related to radiation therapy. The majority of patients (83%) reported no acute side effects. One patient reported acute CTCAE grade 2 abdominal pain that resolved with narcotics and another patient reported acute Grade 2 nausea/vomiting requiring anti-emetics and IV fluid administration. With long-term follow-up, no late radiation side effects were identified.

Table 2
Baseline patient characteristics of all consecutive patients treated with SBRT for pancreatic adenocarcinoma. ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; FOLFIRINOX, folinic acid, 5-fluorouracil, ironotecan, oxaliplatin.

Characteristic	Value
Age, years, median (range)	68 (59–83)
Sex	
Female	7 (58%)
Male	5 (42%)
ECOG Performance Status	
0	2 (17%)
1	7 (58%)
2	3 (25%)
Histology	
Adenocarcinoma	12 (100%)
AJCC Group Stage	
IB	1 (8%)
III	8 (67%)
IV	3 (25%)
AJCC T-Stage	
T2	3 (25%)
T3	1 (8%)
T4	8 (67%)
Resectable	
Yes	2 (17%)
No	9 (75%)
Borderline	1 (8%)
Chemotherapy Prior to SBRT	
Gemcitabine nab-paclitaxel	7 (58%)
FOLFIRINOX	3 (25%)
None	2 (17%)

4. Discussion

We report the results of a planned QI PDSA initiative used to establish a community-based pancreas SBRT program in an integrated academic community satellite network. This involved developing a robust workflow (P – plan) and rigorous prospective multidisciplinary QA of procedures during implementation (D – Do). Analysis of initial outcomes (S – Study) from show acceptable oncologic outcomes with no major adverse effects highlighting the importance of prospective QA involving patient selection, target delineation, radiation plan evaluation and treatment delivery. This QI initiative has set the groundwork to improve community access to pancreas SBRT and to facilitate clinical trials aiming to refine the role of SBRT for pancreatic cancer (A – Act).

A key resource that facilitated this QI initiative was a fully integrated information technology (IT) infrastructure between main and satellite campuses that facilitated virtual integration of the workflow. The integration of the electronic medical record, medical imaging and radiation treatment planning system allowed for prospective QA of nearly every aspect of this QI initiative. The investment in this IT infrastructure made prior to the SARS-CoV-2 (COVID-19) pandemic has paid off in dividends, having paved the way for virtual QA that adheres to Center for Disease Control and Prevention (CDC) guidelines for social distancing [27].

A number of factors have renewed interest in SBRT for pancreatic cancer at both academic centers and the community setting. With the COVID-19 pandemic, strategies that reduce healthcare system exposure are crucial to combat pandemic spread, making strategies such as SBRT advantageous from a public health perspective [28]. Furthermore, locally-advanced pancreatic cancer patients have often received substantial amounts of immunosuppressive chemotherapy which places them at disproportionate risk of morbidity and mortality from COVID-19. Establishment of a telemedicine platform for select patients, including QA for SBRT patients, would help to mitigate this risk for immunocompromised patients [27]. Another factor contributing to interest in hypofractionated radiation treatment regimens is the impending imple-

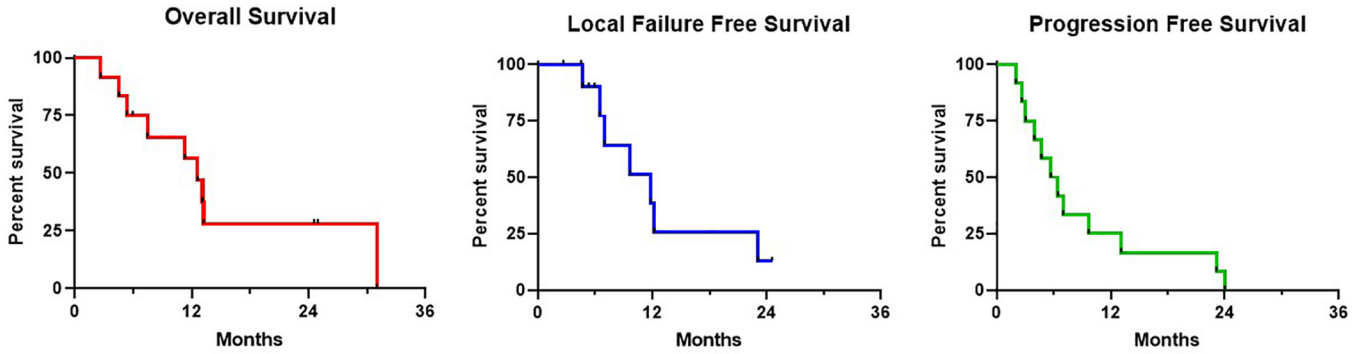

Fig. 2. Survival outcomes for patients treated as part of this QI initiative including overall, local failure free and progression free survival using Kaplan-Meier method.

mentation of episode-based reimbursement and the radiation oncology alternative payment model (APM) [29,30].While COVID-19 delayed the APM rollout, strategies such as pancreas SBRT that provide efficacy while reducing resource utilization are expected to provide a more favorable cost structure than other more resource intensive strategies such as long course chemoradiation. By implementing this in the community, we have also reduced financial burden for patients unable to travel to a major academic center to receive pancreas SBRT. While preliminary results of the Alliance A021101 trial presented in abstract form at the ASCO Gastrointestinal Cancer Symposium did not show clear evidence of SBRT superiority, the final report of this study will provide more clarity on the role of preoperative SBRT for pancreatic cancer if any [21].

In summary, we report the successful implementation of a new SBRT pancreas program in an integrated academic satellite network using PDSA methodology that has improved community access to this treatment.

Declaration of Competing Interest

Dr. Chun reports being a consultant for AstraZeneca, PLC., and for Norton Healthcare, Inc. Dr. Reed reports being a consultant for Varian Medical Systems, Inc. Dr. Koong reports holding stock in Aravice, Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.02.004.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA A Cancer J Clin 2020;70(1):7–30.
[2] Stathis A, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. Nat Rev Clin Oncol 2010;7(3):163–72.
[3] Attard JA, Farrugia A, Pathanki A, et al. Treatment strategies for the optimal management of locally advanced pancreatic adenocarcinoma with curative intent: a systematic review. Pancreas 2020;49(10):1264–75.
[4] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817–25.
[5] Von Hoff DD, Ervin T, Arena FP, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. N Engl J Med 2013;369(18):1691–703.
[6] Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362(17):1605–17.
[7] 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(11):1806–13.
[8] Bernard V, Herman JM. Pancreas SBRT: who, what, when, where, and how. Pract Radiat Oncol 2020;10(3):183–5.
[9] Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: A randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil. The gastrointestinal tumor study group. Cancer 1981;48(8):1705–10.
[10] Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil–an Eastern Cooperative Oncology Group study. J Clin Oncol 1985;3(3):373–8.
[11] Loehrer Sr PJ, Feng Y, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an eastern cooperative oncology group trial. J Clin Oncol 2011;29(31):4105–12.
[12] Myint AS. The role of radiotherapy in the palliative treatment of gastrointestinal cancer:. Eur J Gastroenterol Hepatol 2000;12(4):381–90.
[13] Morganti AG, Trodella L, Valentini V, et al. Pain relief with short term irradiation in locally advanced carcinoma of the pancreas. J Palliat Care 2003;19(4):258–62.
[14] 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(17):1844–53.
[15] Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncolo Biol Phys 2008;72(3):678–86.
[16] Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. Cancer 2009;115(3):665–72.
[17] Schellenberg D, Kim J, Christman-Skieller C, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2011;81(1):181–8.
[18] 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(4):1017–21.
[19] Pollom EL, Alagappan M, von Eyben R, et al. Single- versus multifraction stereotactic body radiation therapy for pancreatic adenocarcinoma: outcomes and toxicity. Int J Radiat Oncol Biol Phys 2014;90(4):918–25.
[20] 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(7):1128–37.
[21] Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: alliance for clinical trials in oncology trial A021101. JAMA Surg 2016;151(8):e161137.
[22] 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(5):322–32.
[23] Taylor MJ, McNicholas C, Nicolay C, et al. Systematic review of the application of the plan-do-study-act method to improve quality in healthcare. BMJ Qual Saf 2014;23(4):290-8
[24] Macleod A, Campbell F, Macrae D, et al. Reducing wait time for administration of systemic anticancer treatment (SACT) in a hospital outpatient facility. BMJ Open Qual 2020;9(4).
[25] Bhatt N, Taufique Z, Kamen E, et al. Improving thyroid function monitoring in head and neck cancer patients: A quality improvement study. Laryngoscope 2020;130(11):E573–9.
[26] Martin Y, Braun LA, Janggen MA, et al. Offering patients a choice for colorectal cancer screening: a quality improvement pilot study in a quality circle of primary care physicians. BMJ Open Qual 2019;8(4):e000670.
[27] Maroongroge S, Smith B, Bloom ES, et al. Telemedicine for radiation oncology in a post-COVID world. Int J Radiat Oncol Biol Phys 2020;108(2):407–10.
[28] Noticewala SS, Koong AC, Bloom ES, et al. Radiation oncology strategies to flatten the curve during the coronavirus disease 2019 (COVID-19) pandemic:

experience from a large tertiary cancer center. Adv Radiat Oncol 2020;5(4):567–72.
[29] Howard DH, Torres MA. Alternative payment for radiation oncology. JAMA 2019. https://doi.org/10.1001/jama.2019.15888.
[30] Jones RT, Helm B, Parris D, et al. The Medicare access and chip reauthorization act of 2015 (MACRA) made simple for medical and radiation oncologists: a narrative review. JAMA Oncol 2019;5(5):723–7.