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Stereotactic Body Radiotherapy for Unresectable Locally Advanced Pancreatic Cancer: A Retrospective Observational Study from a Regional Cancer Center in South Asia—A Case Series

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Abstract

Introduction Concurrent chemoradiation is the treatment of choice for unresectable locally advanced pancreatic cancer (LAPC). Recent progress toward an effective chemotherapeutic regime has seen improvement in systemic control; however, local control remains a significant issue. One strategy to improve local control and survival is stereotactic body radiotherapy (SBRT).

Objectives This study aims to describe the clinical and treatment characteristics of patients with unresectable LAPC treated with SBRT and to assess the outcome.

Material and Methods This is a retrospective observation study of case series involving patients treated with SBRT from January 2015 to December 2023 with unresectable LAPC. Data were recorded from the electronic medical records of the hospital-based cancer registry, and overall survival was calculated using the Statistical Package for the Social Sciences software.

Result We enrolled four patients in this study. This group consisted of four patients with unresectable LAPC who were treated with the FOLFORINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) chemotherapy regime followed by SBRT. For most patients, the radiotherapy dose was 30 to 40 Gy five times per week. These patients exhibited no acute or late toxicity, with 5 to 18 months overall survival.

Conclusion Chemotherapy followed by SBRT is an effective treatment in unresectable LAPC besides chemoradiation.

Keywords
- unresectable pancreatic cancer
- SBRT
- locally advanced
- chemotherapy

Introduction

Pancreatic cancer is one of the most aggressive neoplasms and has poor prognosis.[1] Despite aggressive multimodality treatment, 5-year survival remains less than 5%,[2] and median survival is approaching 13.6 months.[3] According to GLOBOCAN 2020 estimates, pancreatic cancer represents a significant global burden of disease. It is the 12th most prevalent cancer (2.6% of total cancers) and the 7th most common cause of cancer death (4.7% of total cancers).[1] Today, surgical resection

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of early disease can result in a cure.[4] For locally advanced diseases, multimodality treatment (chemotherapy/surgery/radiation) improves survival, local control (LC), and quality of life.[5] However, at diagnosis, only 20% of patients are resectable. At the same time, it has been reported that 30 to 50% of the patients present with unresectable locally advanced disease.[6] Usually, patients with unresectable disease will receive concurrent chemoradiation. External beam radiotherapy (EBRT) delivered in daily fractions for 5 to 6 weeks using three-dimensional (3D) conformal or intensity-modulated radiotherapy (IMRT) remains the most common treatment.[7] The limitations of this 3D technique include a large treatment field encompassing the primary and nodal areas, which increases the toxicity rate. Although more modest, LC post-chemoradiation is still low at approximately 40 to 55%, with median survival of 5 to 14 months.[8,9] The recent success of effective chemotherapeutic regimes such as FOLFIRINOX and gemcitabine plus nab-paclitaxel has led to reconsidering local therapy.[10,11] Even with better control on a systemic level, local progression remains a significant issue. This calls for a shift in treatment paradigm from generalized local chemoradiation to novel forms of radiotherapy focusing on the primary with minimal margins (stereotactic body radiotherapy [SBRT])[12] Indian data regarding SBRT for unresectable pancreatic cancer remains spare. We present a retrospective series of four patients with unresectable locally advanced pancreatic cancer (LAPC) treated at a tertiary cancer center, discussing their clinical characteristics and treatment outcomes after chemotherapy followed by SBRT.

Materials and Method

Study Design

A retrospective case series study was conducted at the Cancer Institute (WIA), Chennai, Tamil Nadu, India, from January 2015 to December 2023. Patient details were documented in the institution's hospital-based cancer registry. Patients are immobilized with the all-in-one board at our institute for patients receiving SBRT. Tumor localization was accomplished using four-dimensional computerized tomography (4DCT) and respiratory gating. We used a specialized wide-bore 16-slice 4DCT scanner (GE Lightspeed Xtra; GE Healthcare, Milwaukee, Wisconsin, United States). Patients were positioned supine with arms placed above the head, a setup we have found to be both comfortable and reproducible. We used the Varian real-rime position management (RPM) system (version 1.7.5; Varian Medical Systems, Palo Alto, California, United States) for motion management. This system includes an infrared camera and an RPM box with reflective markers to monitor and analyze respiratory patterns effectively. After 1 week of observing the patient's breathing patterns, we acquired two sets of images: free-breathing scout films and 4DCT images acquired with or without contrast during free breathing. The 4DCT acquires images in 2.5 mm slices from the mid-chest to the lower border of the pubic symphysis. The acquired images are exported to the GE workstation for reconstruction, and 10 phase-based bins, called 0 to 90% phases, are generated. The reconstructed images include maximum intensity projection (MIP) and average intensity projection (Av-IP). The MIP image displays the entire motion envelope of the tumor and is used to delineate the internal target volume (ITV).[13,14] An Av-IP image is an average image over all phases used for planning and dose calculation.[15]

Target volume and organs at risk (OARs) delineation are proposed according to the new guideline developed by the Australasian Gastrointestinal Trials Group, and we used the Trans-Tasman Radiation Oncology Group[16] guidelines to delineate the gross tumor volume (GTVp). As per the guidelines, we define the tumor–vessel interface as the area where the GTVp is involving or within 5 mm of the major vessels in the upper abdomen, including the celiac artery, superior mesenteric artery, common hepatic artery, left gastric artery, superior mesenteric vein (SMV), portal vein, splenic vein, or aorta. With a 4DCT, the clinical target volume usually equals the ITV. The ITV represents the composite tumor volume, including the motion envelope, as determined by a 4DCT scan. It is defined by contouring the tumor on the MIP data set and visually confirming that the tumor remains within the MIP-defined boundaries across all respiratory phases (0–90%) in axial, coronal, and sagittal views. The planning target volume (PTV) includes a 5-mm margin around the ITV to account for setup errors. If the PTV extends into or approaches a hollow viscous Planning organ at risk volume (PRV), adjustments are made to the dose coverage in that region to ensure compliance with dose constraints for hollow viscera.

The prescribed dose ranged from 30 to 40 Gy in five fractions per week. OAR was the liver, spinal cord, duodenum, stomach, small bowel, large bowel, and kidneys. The Eclipse treatment planning system (Version 15.5, Varian Medical Systems) generates volumetric-modulated arc therapy (VMAT) plans. Depending upon the site of the tumor, two full arc/partial arcs or semi-arcs are used to develop VMAT plans. Acurious BV algorithm was used for planning. Dose–volume histograms (DVHs) were reviewed for dose coverage and OARs.

We quantitatively assessed the treatment plan by analyzing the dose distribution and calculating key dosimetric indices for the PTV and OARs using the DVH. Conformity of the prescription dose was assessed using the conformity index (CI), which is defined as the ratio of the prescription isodose volume to the PTV. A CI value close to 1 indicates better dose conformity to the target. For OARs, we assessed the spinal cord (0.5 cm^3) (D0.5 cm^3) with a maximum dose of less than 20 Gy, the maximum dose to gastrointestinal structures (duodenum, small bowel, stomach, large bowel) is < 33 Gy (D0.5 cm^3). At the same time, we recorded the V12 $< 25\%$ for the combined kidneys. The homogeneity index (HI) is defined as the D5% to D95% ratio, where D5% and D95% are the minimum doses delivered to 5 and 95% of the PTV, respectively. A HI value closest to 1 indicates greater homogeneity within the target. ►**Fig. 1** shows the DVH of patients with pancreatic cancer.

Treatment is delivered using online image guidance with kilovolt cone-beam CT (CBCT) and VMAT. Before treatment delivery, the senior radiotherapy technician and physicist

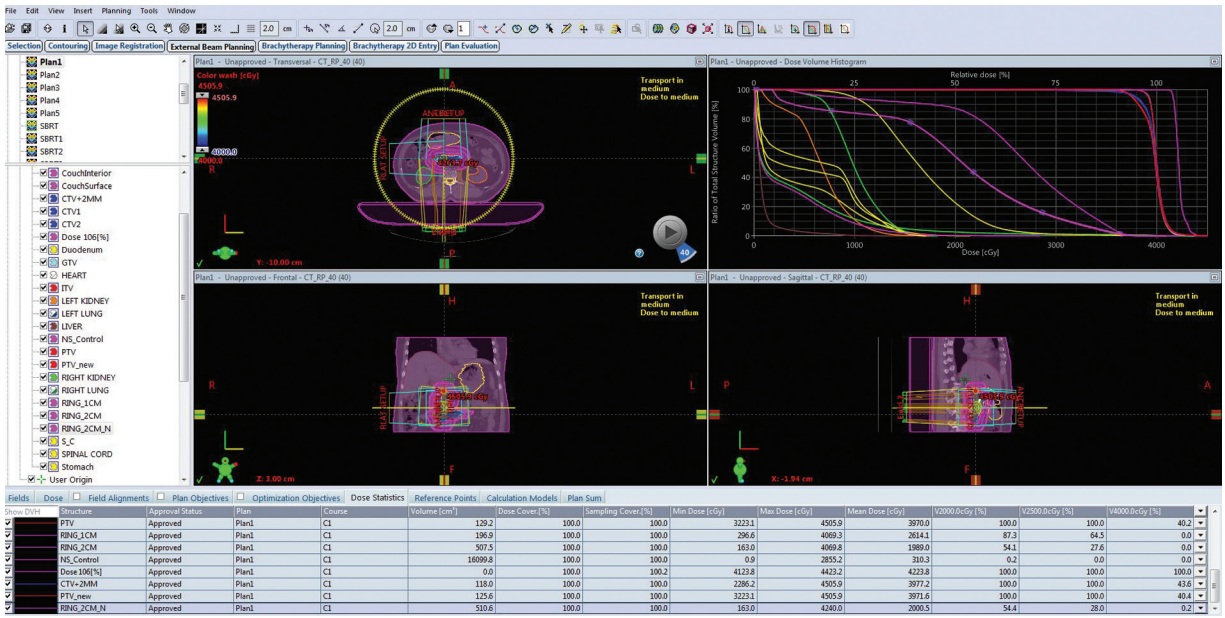

Fig. 1 Dose–volume histogram of the patient with unresectable locally advanced pancreatic cancer.

use online kilovolt CBCT for image matching. Both bony landmarks, such as the vertebral body and soft tissue positioning of the tumor, are used to match the planning CT with the verification images. Our institute's tolerance for CBCT image verification is 3 mm in the left-right, anterior-posterior, and cranial-caudal directions.

The response assessment was performed by triple-phase CT at the end of 3 months and was based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[17] Patients were followed at three monthly intervals.

Sample Size

This retrospective observation study of the case series involves four patients treated with SBRT.

Inclusion and Exclusion Criteria

The specific inclusion criteria include age of more than 18 years, LAPC that was confirmed in biopsy but not operable, and use of SBRT. Patients with metastatic disease or with any history of radiation treatment were excluded.

Primary and Secondary Outcome

The primary objective of this study was to measure the toxicity. The secondary objective was to assess the overall survival (OS).

Acute and Late Toxicity Observed

Acute and late toxicity was observed during and after radiation therapy (RT) as per the Radiotherapy Oncology Group toxicity criteria. Acute toxicity observed includes nausea, anorexia, vomiting, abdominal pain, increased bowel movement, hematemesis, melena, and blood-related toxicity like neutropenia, anemia, and thrombocytopenia. Late toxicity observed include obstruction, bleeding, and perforation.

Statistical Analysis

Statistical analysis was conducted using the Statistical Program for the Social Sciences (Released 2011, IBM SPSS Statistics for Windows, Version 20.0, IBM Corp., Armonk, New York, United States). OS was calculated from diagnosis to death or last follow-up.

Ethical Approval

The study was approved by the Institute Ethics Committee (IEC) of the Cancer Institute [(IEC/2024/Jan03); date of approval: January 03, 2024]. This study was retrospective; therefore, the need to obtain informed consent was waived. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and other guidelines, such as Good Clinical Practice guidelines and Indian Council of Medical Research (ICMR) rules for the conduct of clinical trials.

Case Series

Patient 1: A 49-year-old male with no comorbidities presented with complaints of abdominal pain and radiation to the back for the past 40 days. The serum carcinoembryonic antigen of 958 ng/mL and serum cancer antigen (CA) 19–9 of 444.9 U/mL were found to be high in value. CT revealed a 3.8×3 cm size hypodense lesion in the pancreatic parenchyma of the body with exophytic extension into the preaortic space with the entire splenic vein showing enhancement with luminal narrowing; endoscopic ultrasound showed 2.6×2 cm hypoechoic lesion located in the body of the pancreas, with no venous flow in the splenic vein. Fine-needle aspiration cytology showed moderated differentiated adenocarcinoma. He was treated with six cycles of FOLFORINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) chemotherapy and

SBRT with a total dose of 30 Gy. CT scan after 3 months showed primary lesion static response with ascites and peritonitis, causing retreatment to six cycles of single-agent gemcitabine. The patient lived for a year.

Patient 2: A 46-year-old woman was brought to the hospital complaining of darkening urine and yellowing of the sclera for 1 week. The workup showed serum bilirubin of 13.1 mg/dL and CA 19–9 of 227 U/mL. CT triple phase showed a lesion of ill-defined hypodensity of size 2.1 × 5.5 × 2.6 cm head, uncinate process, body and tail pancreas with intrahepatic biliary radical dilatation (common bile duct [CBD] dilatation), and CT angiogram showed soft tissue mass in the head, uncinate process, and body of pancreas with intrahepatic biliary radical dilatation and encasing common hepatic artery and a short segment of the proximal splenic artery, encasing portal SMV confluence. She underwent endoscopic retrograde cholangiopancreatography (ERCP) and self-expanding metal stent placement. She was treated with three cycles of gemcitabine and capecitabine. As the lesion became more static, the patient was treated with nine cycles of FOLFORINOX chemotherapy. After the FOLFORINOX chemotherapy had a partial response, the patient was treated with SBRT with a total dose of 30 Gy. Post-SBRT, at 3 months, a CT scan showed stable disease and survived for 5 months.

Patient 3: A 37-year-old female without any comorbidity presented with complaints of intermittent abdominal pain for 1-month duration. Upon workup: CA 19–9 was 20.7 U/mL, endoscopic ultrasound showed a 3.6 × 3 cm mass lesion with vascularity in the head and neck of the pancreas with an enhancement of SMV portal confluence, few subcentimeter peripancreatic nodes, fine-needle aspiration of the mass showed adenocarcinoma, CT triple phase showed 4 cm hypodense pancreatic mass involving the SMV portal confluence and 1.3 cm mass lesion in the IVB segment of the liver, and positron emission CT showed increased metabolic activity in the head of the pancreas with increased metabolic activity in the subcapsular space-occupying lesion in segment four, which suggested metastasis. She was treated with palliative chemotherapy with six cycles of FOLFORINOX. Postchemotherapy positron emission tomography-CT (PET-CT) showed a residual lesion in the head of the pancreas and no uptake or subtle uptake in the liver. She was treated with SBRT to the pancreas with a total dose of 35 Gy. Post-SBRT, at 3 months, a CT scan showed stable disease. The patient survived for 12 months.

Patient 4: A 55-year-old female presented with complaints of jaundice of 1 week duration. Serum bilirubin was 8.77 and serum CA 19.9 was 3.8 U/mL. Endoscopic ultrasound showed a hypoechoic mass lesion of size 3.5 × 2.2 cm on the head of the pancreas with portal vein enhancement and dilated CBD/pancreatic duct. Contrast-enhanced CT showed a mass lesion in the head and uncinate process of the pancreas and less than 180-degree portal vein enhancement. Biopsy of the mass lesion revealed moderately differentiated adenocarcinoma. PET-CT showed a mass in the head of the pancreas encasing the SMV. The patient underwent ERCP and metallic stenting. She was treated with six cycles of FOLFORINOX. CT showed residual disease and was treated with SBRT with a total dose of 40 Gy. The patient completed six more cycles of FOLFORINOX. Post-SBRT, at 3 months, a CT scan showed partial response. The patient survived for 18 months.

No patients had acute or late toxicity. The median follow-up was 5 months, and the median OS was 12 months.

►**Table 1** Shows the demographic features and treatment details of patients with unresectable LAPC. ►**Fig. 1** shows the DVH of unresectable LAPC patients.

Discussion

Pancreatic cancer is the most common exocrine cancer. Patients who may have their tumors resected have the

Table 1 Demographic features and treatment details of patients with unresectable locally advanced pancreatic cancer

	Age	Sex	CA 19–9 U/mL	Site	Size (cm)	Chemotherapy	SBRT dose/ Fractionation/BED	Overall survival (mo)
Patient 1	49	Male	444.9	Body	3.1 × 2.7 × 2,5	FOLFORINOX	30 Gy/5/48_{Gy10}	12
Patient 2	46	Female	227	Head Body UC	2.4 × 1.8 × 3.2	FOLFORINOX	30 Gy/5/48_{Gy10}	5
Patient 3	37	Female	20.7	Head Neck	3.4 × 2.3 v 3.5	FOLFORINOX	35 Gy/5/59.5Gy_{10}	12
Patient 4	55	Female	3.8	Head Body	4.5 × 4 × 4.5	FOLFORINOX	40 Gy/5/72_{Gy10}	18

Abbreviations: BED, biologically effective dose; CA 19–9, cancer antigen 19–9; FOLFORINOX, folinic acid, fluorouracil, irinotecan, oxaliplatin; SBRT, stereotactic body radiation therapy.

best chance for cure, while those with unresectable cancers are almost uniformly fatal.[18] Nearly all pancreatic cancer with unresectable disease results in 5-year OS rate of $< 5\%$. In contrast, the 5-year OS for resectable patients is significantly improved by 20%.

In patients with unresectable nonmetastatic pancreatic cancer, early data provide evidence that RT in combination with chemotherapy can offer a significant clinical benefit.[19] What is still unclear is how best to use these modalities relative to sequence, technique, and dosing. In the literature, SBRT has been shown to be well-tolerated and effective.[20–23] In borderline resectable cancer settings, SBRT achieves promising clinical outcomes and converts a large proportion of patients to resectable, which may yield long-term outcomes comparable to that of initially resectable patients.[24]

Downstaging of LAPC with FOLFORINOX has been described more recently in several publications. Hosein et al recently published their series of 18 LAPC patients; five underwent R0 resection initially and three patients later underwent R0 resection after further chemoradiotherapy, with an overall resection rate of 44%.[25] Faris et al also published one preliminary experience with FOFLFORINOX on an upfront basis, comparing it with standard-of-care chemotherapy in 22 LAPC patients with a 23% resectability rate.[26]

The STEP study[27] from Italy showed that SBRT is an effective and safe therapeutic option for treating LAPC patients with longer LC. The median OS was 11.6 months, and the 1-, 2-, and 3-year LC rates were 81.9, 69.1, and 58.5%, respectively.

de Geus et al study[28] showed that SBRT has a significantly better outcome than chemotherapy alone or combined with conventional EBRT. Before matching, the unadjusted median survival was 9.9 months (chemotherapy), 10.9 months (EBRT), 12.0 months (IMRT), and 13.9 months (SBRT), respectively.

In our series of four patients treated with FOLFORINOX chemotherapy followed by SBRT, the OS was between 5 and 18 months.

Currently, there is no consensus about the best dose-for-fraction regimen; the available literature recommends the scheme of five fractions with a minimum total dose of 33 Gy,[29,30] 35 Gy,[31] and 40 Gy.[32,33] Our study's dose fraction regimen ranged from 30 to 40 Gy in five fractions except in one patient.

The study's limitations are the small number of patients and the fact that this is a retrospective study.

Conclusion

Chemotherapy plus SBRT is an effective regimen for unresectable LAPC. In borderline operable disease, it provides an opportunity for resection and improves survival.

Institutional Review Board

Approved.

Authors' Contributions

A.M.N., P.V., G.S., R.A., P.J.S contributed to the Concepts design, definition of intellectual content, and manuscript review. A.M.N., P.V. contributed to the literature search, data acquisition, data analysis, manuscript preparation, manuscript editing. A.M.N. contributed to the statistical analysis and as guarantor.

Patient Consent

None.

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None.

Conflict of Interest

None declared.

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