Neoadjuvant Stereotactic Body Radiation Therapy followed by Pancreatic Cancer Resection with Intra-Operative Electron Radiation Therapy (IOeRT) boost: Clinical Insights and Initial Outcomes

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Introduction

- Pancreatic cancer is an aggressive disease with limited treatment options and poor prognosis, making it one of the deadliest forms of cancer
- Resection remains the mainstay modality for curative intent treatment
- According to the best and latest adjuvant chemo trials (ESPAC-4, PRODIGE-24), the rate of R0 resections for initially resectable is only 40-60%.
- There is interest in delivery of neoadjuvant radiation therapy with SBRT to improve the RO resection rate
- SBRT allows delivery of highly conformal radiation in few treatments, however are limited due to GI luminal structures
- IOeRT allows for dose escalation to areas at high risk for recurrence
- Purpose of our study was to evaluate our outcomes of patients treated with Neoadjuvant Stereotactic Body Radiation Therapy followed by Pancreatic Cancer Resection with Intra-Operative Electron Radiation Therapy (IOeRT) boost

Methods

- We conducted a single-institution retrospective review of consecutive patients treated from February 2021 to October 2023, who underwent neoadjuvant SBRT followed by pancreatic resection with IOeRT.
- All cases were discuss in multi-disciplinary tumor board with GI Surgical Oncologist, Medical Oncologist and Radiation Oncologist
- Patients with borderline resectable (BR) and selected resectable patients were referred for pre-operative treatment
- All BR received neoadjuvant chemotherapy

Pre-operative SBRT

- Patients were immobilized per standard institutional protocol and underwent CT Simulation scan using 2-3 mm slice thickness. 4-dimensional CT was also performed
 - Gross tumor volume (GTV) was delineated using diagnostic triphasic CT, PET-CT and/or MRI
 - ITV was created after 4D-CT was reviewed.
 - An additional 3mm margin was added to create planning target volume (PTV) named PTV_high.
 - A clinical target volume (CTV) encompassing at risk nodes was delineated.
 - An additional 5mm margin was added to create PTV_low.
- Treatment plan was generated using volumetric modulated arc therapy and patients treated on Truebeam system (Varian).
- Dose fractionation included 35 40 Gy in 5 fractions to PTV_high and 25 Gy in 5 fractions to PTV_low.
- The highest isodose line of the prescribed dose was recommended to cover >95% of the PTV and 99% of the GTV/ITV.
 - Organs at risk (OARs) were delineated per consensus guidelines.
 - Dose constraints utilized per Timmerman tables and OARs were prioritized over GTV/ITV coverage.





CTV includes Triangle Volume" (TV), bordered by the celiac axis, superior mesenteric artery, common hepatic artery, portal vein, and superior mesenteric vein.

Surgery and IOERT Boost

- Following SBRT, patients underwent restaging imaging in order to confirm localized/resectable disease.
- Patients underwent Whipple or Distal pancreatomy 3 to 8 weeks following radiotherapy.
- IOeRT was delivered as follows:
 - after surgical removal of the tumor the mobile IOeRT accelerator (SIT) was mobilized.
 - A 40-80mm applicator was chosen which encompassed the tumor bed focused on areas of concern for recurrence.
 - The applicator was placed flush on the post-operative bed and organs at risk (stomach, small bowel, kidney) were confirmed to be out of field.
 - A 0.5 cm wet gauze bolus was placed in region to be irradiated.
 - The surgeon dictated the depth of coverage needed and physics and the treating radiation oncologist determined the proper energy and performed a monitor unit calculation.
 - After ensuring adequate coverage, 10-12 Gy was delivered using 6-8MeV electrons prescribing to the 80-95% isodose line under the supervision of Radiation Oncologist.



Results

- 14 patients with pancreatic cancer, treated between February 2021 and October 2023. Median follow-up was 16 months (range 7-32 months).
- Mean age: 66.7 years (range 44-81).
- Tumor location: 8 in the body and 6 in the head of the pancreas.
- Nine patients (64%) were borderline resectable and received neoadjuvant chemotherapy prior to SBRT, while five were (36%) resectable at diagnosis and received upfront SBRT.
- Twelve patients (85.7%) underwent R0 resection
- Two patients (14.2%) with BRCA2 had a complete pathological response (both received pre-op CHT and SBRT).

Table 1.				
Characteristics	N = 14			
Gender				
Male	10 (71%)			
Female	4 (29%)			
Genoma analysis				
BRCA 2	2 (14%)			
No BRCA	12 (86%)			
Neoadjuvant chemotherapy				
FOLFIRINOX	6 (42%)			
FOLFOX	2 (14%)			
Gemcitabine	1 (7%)			
Pre-op SBRT dose				
35Gy in 5 fractions	11 (79%)			
40Gy in 5 fractions	3 (21%)			
IORT Dose				
10Gy	13 (92%)			
12Gy	1 (7%)			
Surgery Type				
Whipple (pancreaticoduodenectomy)	6 (42%)			
Distal Pancreatectomy	8 (58%)			

SBRT Acute Toxicity (CTCAE v.5)

Toxicity	Grade	Number of Patients (%)	
Fatigue	Grade 1	6 (42.86%)	
	Grade 2	0	
Nausea	Grade 1	3 (21.43%)	
	Grade 2	3 (21.43%)	
Abdominal pain	Grade 1	3 (21.43%)	
	Grade 2	4 (28.57%)	

Surgical Complications (within 30 days)

Clavien-Dindo Grade	Number of Patients	Complications	Treatment Required
Grade 1	4 (28.57%)	Ileus, surgical site infection	Conservative management
Grade 2	4 (28.57%)	Hospital-acquired pneumonia (HAP), bacteremia, DVT, UTI	Anticoagulants, antibiotics
Grade 3	1 (7.14%)	Dehiscence requiring repeated surgical intervention	Surgical re-intervention
Grade 5	1 (7.14%)	Early post-operative complications (acute on chronic renal failure, Hospital Acquired Pneumonia)	Fatal outcome, post-operative complications

Late Complications (> 30 days)

One patient died from long-term postoperative complications (hepatic artery occlusion, biloma and biliary sepsis)

Oncologic Outcomes



Median PFS from surgery 13 months

Median OS from surgery 14 months

Oncologic Outcomes



Median PFS from start of any treatment 15 months



Median OS from start of any treatment 18 months

Recurrence Patterns in patients



Recurrence Status

Cause of Death (7 patients)

- Distant Metastases: 4 patients
- Early post-op sepsis: 1 patient
- Biliary sepsis: 1 patient
- Coronavirus: 1 patient

Conclusion

- Local control and margin-negative resection rates were high with preoperative SBRT and IOeRT in surgically resected pancreatic cancer patients.
- Distant recurrence was the predominant site of failure, with only one case of isolated locoregional recurrence.
 - Maximizing systemic therapy either in the neoadjuvant or adjuvant setting is necessary.
- Optimal patient selection is critical to maximize the benefits of this treatment strategy.