A Phase I Trial of Neoadjuvant SBRT with Elective Nodal Radiation for Resectable Pancreas Cancer

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BACKGROUND

Pancreatic cancer (PDA) is a highly lethal malignancy with a high rate of local and regional relapse, even among patients with resectable disease. Prior data from randomized trials have indicated improved local control when adding radiation in the adjuvant setting, however adjuvant therapy following pancreaticoduodenectomy is difficult to complete, and does not offer the possibility of downstaging. Therefore recent approaches have incorporated traditionally adjuvant therapy into the up front time period.

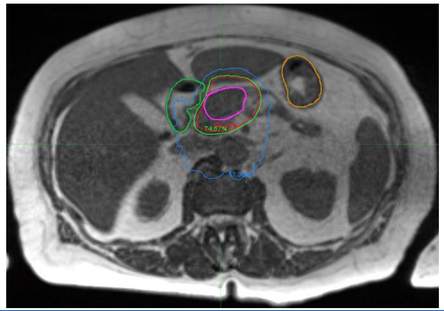
METHODS

We performed a phase I trial using a 4+4 dose escalation design. Eligible patients were >18 years of age, ECOG 0-2, and had exocrine PDA of the pancreatic head. Patients with resectable PDA as defined by the National Comprehensive Cancer Network were treated with stereotactic body radiation therapy (SBRT) and concurrent capecitabine to the primary tumor and regional lymph nodes prior to planned surgery. Primary tumor dose was escalated in 5 Gy increments from 25 Gy in 5 fractions up to 35 Gy in 5 fractions. Elective nodal radiation (ENI) was delivered to a dose of 25 Gy in 5 fractions for all dose levels to the at risk nodal basins. The primary outcome was toxicity defined as grade ≥3 non-hematologic toxicity attributable to SBRT.

DOSE ESCALATION RULES

Number of Dose-limiting toxicities (DLTs)	Rule
0/4	Escalate next cohort to higher dose level*
1/4	Assign next cohort to same dose level
≥2/4	Assign next cohort to lower dose level**

* If Dose level I proves toxic ≥2/4 DLTs then the trial will be stopped.
** If Dose level III is non-toxic (0/4 DLTs) then the next cohort will also be assigned to dose III



RESULTS

Patient Characteristics

Table 1 Patient characteristics

Age (median, range)	72 (63-84)
Sex	
Male	10
Female	6
KPS (median, range)	90 (90-100)
Clinical stage (AJCC)	
IA	1 (6.3%)
IB	6 (37.5%)
IIA	7 (43.8%)
IIB	2 (12.5%)
Clinical T stage	
T1	1 (6.3%)
T2	7 (43.8%)
T3	9 (56.3%)
Clinical N stage	
N0	14 (87.5%)
N1	2 (12.5%)
Resection	
Yes	13 (81.3%)
No	3 (18.7%)
Neoadjuvant chemotherapy	
FOLFIRINOX	4
Gemcitabine/Abraxane	1
Adjuvant chemotherapy	
FOLFIRINOX	1
Gemcitabine	5
Gemcitabine/Abraxane	1
No chemotherapy	4
Initial CA 19-9 (median, range)	150 (2-1958)

Abbreviations: KPS = Karnofsky performance status.

Toxicities

SBRT acute toxicities (grade)*

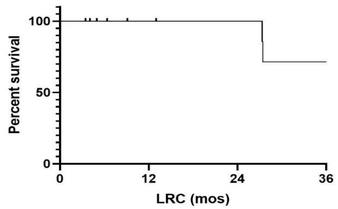
	1	2	≥3
Nausea	7	2	0
Fatigue	3	0	0
Biliary obstruction	0	1	0
Vomiting	2	0	0
Diarrhea	1	0	0

Post-surgical complications (grade)

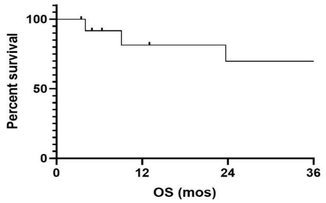
	1 (A)	2 (B)	3 (C)	4	5
DGE	0	3	1		
PPH	0	0	0		
Pancreatic fistula	0	0	0		
ASGS overall grade	7	4	1	1	0

Abbreviations: ASGS = accordion severity grading system for postoperative complications; DGE = delayed gastric emptying; PPH = postpancreactomy hemorrhage.
* Graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Locoregional Control

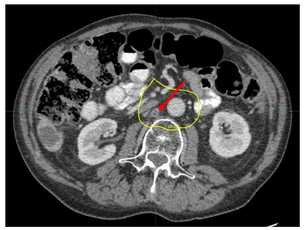


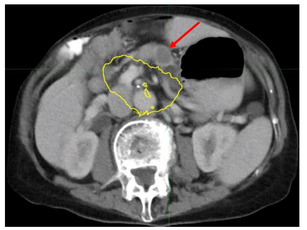
Overall Survival



OUTCOMES

- All (13/13) patients proceeding to surgery had R0 resections
- Median time from SBRT to surgery was 20 days (R; 15-42)
- Median OS was 19 months, and median LRC was 23 months
- 50% of patients developed metastatic disease
- Three total patients had locoregional failure, with 2 patients failing within the ENI volume





CONCLUSIONS

- Neoadjuvant chemo-radiation with ENI was well tolerated for patients with resectable PDA
- Dose escalation up to 35 Gy in 5 fractions was completed without dose limiting toxicity
- No patients had a delay to surgery or an increase in postoperative toxicity
- Lymph node positivity and metastatic disease were common
- Further work will be required to determine patient selection, appropriate target volumes, and optimal dose to reduce the risk of local and regional recurrence in this population

Work now published in the *International Journal of Radiation Oncology, Biology, Physics*:

PMID 32942002

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