

## RAPID COMMUNICATION

# PHASE II STUDY TO ASSESS THE EFFICACY OF CONVENTIONALLY FRACTIONATED RADIOTHERAPY FOLLOWED BY A STEREOTACTIC RADIOSURGERY BOOST IN PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER

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**Purpose:** To determine the efficacy of concurrent 5-fluorouracil (5-FU) and intensity-modulated radiotherapy (IMRT) followed by body stereotactic radiosurgery (SRS) in patients with locally advanced pancreatic cancer.

**Methods and Materials:** In this prospective study, all patients (19) had pathologically confirmed adenocarcinoma and were uniformly staged. Our treatment protocol consisted of 45 Gy IMRT with concurrent 5-FU followed by a 25 Gy SRS boost to the primary tumor.

**Results:** Sixteen patients completed the planned therapy. Two patients experienced Grade 3 toxicity (none had more than Grade 3 toxicity). Fifteen of these 16 patients were free from local progression until death. Median overall survival was 33 weeks.

**Conclusions** Concurrent IMRT and 5-FU followed by SRS in patients with locally advanced pancreatic cancer results in excellent local control, but does not improve overall survival and is associated with more toxicity than SRS, alone. © 2005 Elsevier Inc.

**Body stereotactic radiosurgery, Intensity modulated radiation therapy, Image guided radiotherapy, Pancreatic cancer, Phase II.**

## INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, resulting in more than 30,000 annual deaths (1). Despite aggressive combined modality treatment approaches, the overall 5-year survival remains less than 5%.

Although surgery is the only potentially curative option, the majority of patients have unresectable or metastatic disease at presentation (2). Therefore, most patients with pancreatic cancer are treated either with chemotherapy alone or with combined chemoradiotherapy.

The Gastrointestinal Tumor Study Group demonstrated that treatment with 5-fluorouracil (5-FU) and concurrent radiotherapy resulted in superior survival compared with radiotherapy alone (3). A follow-up Gastrointestinal Tumor Study Group study comparing 5-FU/continuous radiother-

apy with chemotherapy alone (streptozocin, mitomycin, and 5-FU) also showed a survival benefit in the combined modality arm (4).

We have previously demonstrated the feasibility and safety of administering a single fraction of 25 Gy to patients with locally advanced pancreatic cancer (5). In this prior study, patients were treated with a single fraction of 15 Gy, 20 Gy, or 25 Gy using the CyberKnife (Accuray Inc., Sunnyvale, CA) stereotactic radiosurgery system. We observed minimal acute gastrointestinal (GI) toxicity and achieved our primary clinical endpoint of local control in all patients who received 25 Gy.

In the current study, our goal was to assess the efficacy of combining systemic 5-FU concurrently with conventionally fractionated radiotherapy followed by a stereotactic radiosurgery (SRS) boost in patients with locally advanced pancreatic cancer.

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Table 1. Patient information and SRS parameters

Patient	Gender	Age	Tumor location	Vol tx (cc)	Maximum dose ( $D_{max}$ )
1	M	59	Head of pancreas	64.8	3486 cGy
2	F	50	Head of pancreas	60.4	3906 cGy
3	M	64	Head of pancreas	34.1	3571 cGy
4	M	61	Head of pancreas	NA	NA
5	F	82	Body of pancreas	NA	NA
6	M	69	Head of pancreas	58.6	4385 cGy
7	F	61	Head of pancreas	49.4	3571 cGy
8	F	54	Body of pancreas	57.2	3906 cGy
9	M	59	Body of pancreas	92.2	3623 cGy
10	F	51	Body of pancreas	32.4	3731 cGy
11	F	78	Body of pancreas	45.7	3732 cGy
12	M	53	Head of pancreas	57.2	3570 cGy
13	F	78	Head of pancreas	50.6	3845 cGy
14	M	52	Head of pancreas	74.1	3246 cGy
15	F	81	Head of pancreas	13.9	3522 cGy
16	F	51	Head of pancreas	61.6	3204 cGy
17	M	79	Head of pancreas	NA	NA
18	M	79	Head of pancreas	34.0	3906 cGy
19	F	76	Body of pancreas	28.4	3846 cGy

Abbreviation: Vol tx = tumor volume.

## METHODS AND MATERIALS

All patients signed a Stanford Institutional Review Board approved consent form and had pathologically confirmed adenocarcinoma. They were uniformly evaluated and staged at the Stanford Gastrointestinal Multidisciplinary Tumor Board as previously described (5).

Patients were treated with 45 Gy in 1.8-Gy fractions to the pancreas tumor and regional lymph nodes using an intensity-modulated radiotherapy (IMRT) technique. Either 5-FU by protracted venous infusion (200 mg/m<sup>2</sup>/day) or capecitabine (1000 mg/m<sup>2</sup> by mouth, Monday-Friday) was given concurrently. Within 1 month after this therapy, 25 Gy stereotactic radiosurgery (SRS) was administered as a boost to the primary tumor.

For the IMRT portion of the treatment, the areas treated included the pancreatic tumor and the regional lymph nodes (peripancreatic, celiac, superior mesenteric, porta hepatic, retroperitoneal). All patients underwent a pancreatic protocol computed tomography (CT) scan in the treatment position for delineation of all normal and target structures. General guidelines for dose limitations to normal structures included the following: 70% liver <15 Gy, 70% each kidney <15 Gy, 95% bowel <45 Gy, spinal cord <30 Gy. At least 95% of the GTC and CTV received at least 95% of the prescribed dose.

Stereotactic radiosurgery treatment was administered using the CyberKnife stereotactic radiosurgery system (Accuray Inc.). The radiation dose was prescribed to the isodose line that completely covered the pancreatic tumor. Of the patients who were treated with SRS on this study, half were treated using a mid-breath hold technique as previously described (5), and half were treated using the Synchrony (Accuray Inc.) respiratory tracking system. Synchrony uses a continuous respiratory tracking system in which detectors are placed onto the chest wall of the patient. The position of the internal fiducials is then correlated with the movement of the chest wall and the robot retargets the linear accelerator accordingly in real time.

Acute GI toxicity within the first 3 months after completion of therapy was scored according the Radiation Therapy Oncology

Group acute GI toxicity scale. At each follow-up visit, a pancreatic protocol CT scan was obtained and in some cases, a positron emission tomography (PET)-CT scan was also obtained. Laboratory values including CA 19-9, complete blood count, and a metabolic panel were also assessed at the same intervals.

## RESULTS

Between July 2003 and August 2004, 19 patients were enrolled onto this prospective study. Table 1 lists the characteristics of all patients enrolled on this protocol. The SRS tumor volumes ranged from 13.9 mL to 92.2 mL, and the maximum dose ( $D_{max}$ ) ranged from 2,250 Gy to 4,385 Gy. Three patients had evidence of distant progression before the SRS boost and therefore did not receive the planned SRS.

Table 2 lists the acute gastrointestinal (GI) toxicities for all patients who received the SRS boost. Most of the toxicities were nausea and anorexia of varying severities. Both patients who experienced Grade 3 toxicity developed gastroparesis requiring parenteral support (one at the end of IMRT before SRS and one after SRS). In addition to the acute toxicities listed, patients developed symptomatic (all medically managed) duodenal ulcers 4–6 months after SRS. Of the 16 patients completing all planned therapy, 13 had an elevated pretreatment CA 19-9. Eight

Table 2. GI toxicity as defined by the RTOG Acute Gastrointestinal Toxicity Scale

Grade 0	3
Grade 1	7
Grade 2	4
Grade 3	2

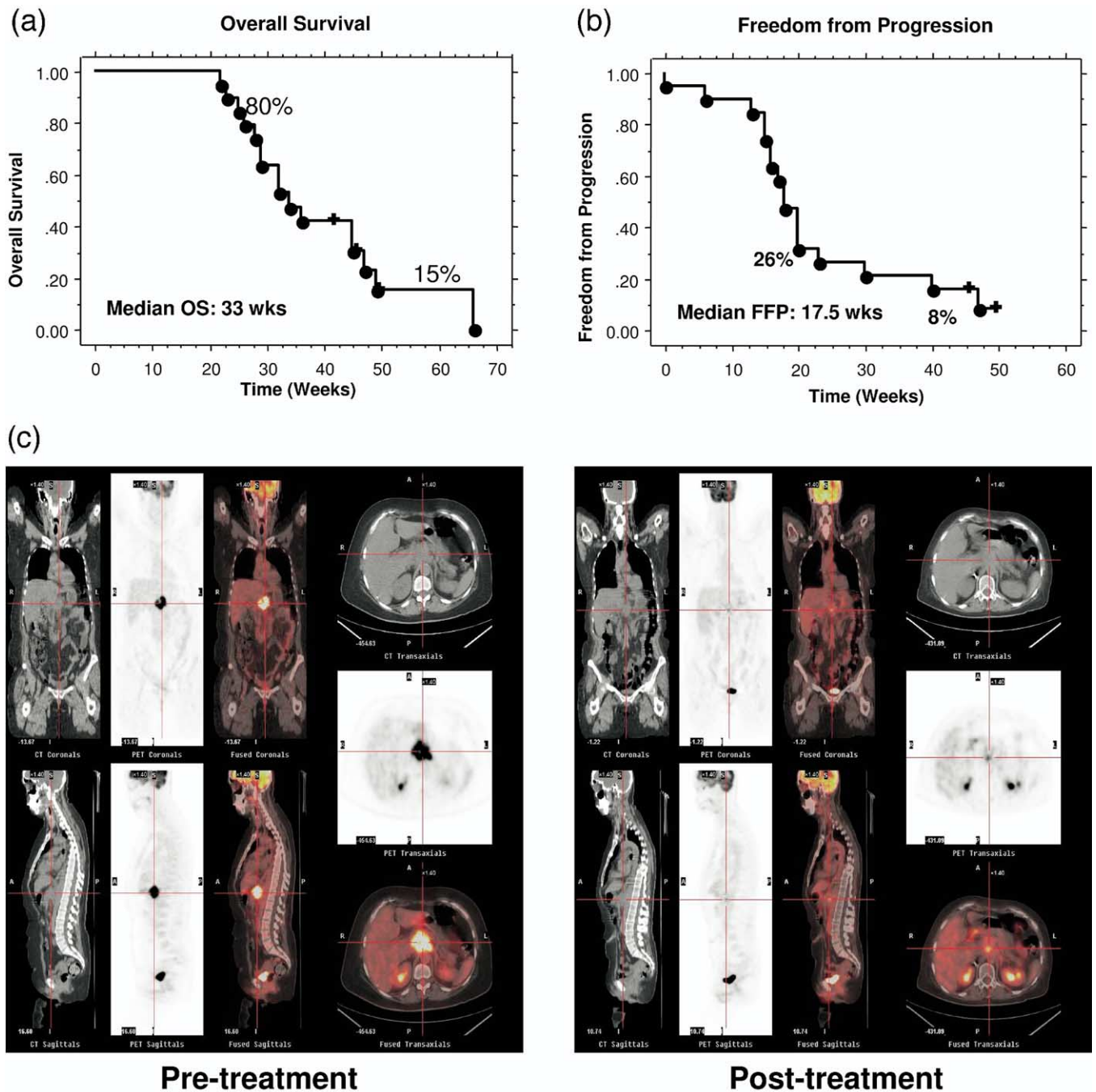


Fig. 1. (a) Kaplan-Meier estimates of overall survival (OS). Estimated OS was 80% at 6 months and 15% at 12 months. (b) Kaplan-Meier estimates of freedom from progression (FFP). Estimated FFP was 26% at 6 months and 8% at 12 months. (c) Example of tumor response by conventional computed tomography criteria compared to metabolic response by  $^{18}\text{F}$ -fluoro-2-deoxy-glucose positron emission tomography (FDG-PET) criteria.

of the 13 (62%) had a greater than 50% reduction in CA 19-9 after treatment. All 16 patients had follow-up pancreatic protocol CT scans to assess radiographic response. The median time to progression was 17.5 weeks after completion of therapy and the site of first progression in all cases was distant (liver). Fifteen of the 16 patients were free from local progression until death. One patient was scored as a local failure 34 weeks after SRS on the basis of an endoscopy report suggesting local

progression of the tumor even though the biopsy was negative. This event occurred after documented distant progression of the tumor (liver and lung). The median overall survival (OS) of the entire group was 33 weeks, and the median follow-up time was 23 weeks.

Figure 1a is a Kaplan-Meier curve showing the OS of all patients enrolled onto this study. The estimated 6-month survival was 80% and the estimated 1-year survival was 15%. Figure 1b shows the freedom from progression (FFP)

in this group. The estimated 6-month FFP was 26% and the estimated 1-year FFP was 8%.

By conventional CT criteria, all patients had stable disease at the primary site. In the last 4 consecutive patients, we obtained  $^{18}\text{F}$ -fluoro-deoxy-glucose positron emission tomography (FDG-PET) with concurrent CT scans before and 4–6 weeks after treatment. All of these patients had a complete or near complete response by metabolic imaging criteria, without a significant change in the size of the mass by conventional CT criteria. Figure 1c is an example of a pretreatment and posttreatment PET-CT scan. These results suggest that FDG-PET scanning may be a better method of assessing response to high-dose radiotherapy than CT scanning alone.

## DISCUSSION

Compared with our prior study using CyberKnife SRS alone (5), we observed more acute GI toxicity in this study in which patients with locally advanced pancreatic cancer were treated with conventionally fractionated radiation therapy (45 Gy) with concurrent 5-FU chemotherapy followed by a CyberKnife SRS boost (25 Gy, single fraction) to the primary tumor.

Although we achieved an excellent rate of local control (15 of 16 patients or 94%), we did not significantly impact OS because of the rapid progression of systemic metastases. In all cases, the site of first progression was

distant and the median FFP was 17.5 weeks from completion of therapy. Our median OS was 33 weeks, with 3 patients still alive at the time of this analysis.

Our study is comparable to other reports evaluating the use of external beam radiotherapy combined with intraoperative radiotherapy (6–10). Willett *et al.* recently updated the largest series in the literature (150 patients) of unresectable pancreatic cancer patients treated with this strategy (11). This study reported a 5-year survival rate of 4% with acceptable treatment-related toxicity.

Because of the rapid progression of systemic disease and increased GI toxicity observed in this study, our current practice has been to replace the 5-week course of IMRT with systemic chemotherapy (gemcitabine). Patients are given three weekly infusions of gemcitabine followed by SRS on week 4. Chemotherapy is then resumed on the same schedule until there is evidence of disease progression. This strategy allows more intensive systemic therapy to be administered earlier when disease burden is lower and does not require any “recovery” time from radiation therapy.

Achieving local control in pancreatic cancer will not likely translate into improved survival until more effective chemotherapy becomes available. The development of novel classes of chemotherapy and targeted agents holds much promise for improving treatment outcomes in this disease (12). Future research efforts should be directed toward this end.

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