WHITE PAPER – Carcinoma of the Pancreas and Stereotactic Radiosurgery

I. Introduction

This white paper will focus on carcinoma of the pancreas with sections one through six (**I-VI**) comprising a general review of pancreatic cancer. More information from the National Cancer Institute can be found at **cancer.gov**. Section seven (**VII**) will provide a literature review on stereotactic radiosurgery for the pancreas and section eight (**VIII**) will provide clinical indications and treatment guidelines on stereotactic radiosurgery for the pancreas. **Please Note:** This section is only available to members of the Radiosurgery Society®.

II. Definition and Incidence

Adenocarcinoma of the pancreas is a highly fatal disease, with almost all patients presenting of the disease dying from it. The only known cures are in patients who undergo complete surgical excision of the tumor and this occurs in less than 10% of all diagnosed cases. About 60-80% of all patients presenting with pancreatic adenocarcinoma are inoperable at presentation, although not necessarily metastatic. Standard care for locally advanced disease without signs of distant metastasis is chemotherapy with or without loco regional radiation.

In the United States, pancreatic cancer is the fourth leading cause of cancer-related death in both men and women. Because it is usually diagnosed at an advanced stage, the survival rate is poor compared with that of other types of cancer. Unfortunately, overall pancreatic cancer incidence and mortality rates have changed very little throughout the past three decades. It is estimated that 43,920 men and women (22,090 men and 21830 women) will be diagnosed with and 37,390 men and women will die of cancer of the pancreas in 2012[1]. Worldwide, pancreatic cancer is the eighth leading cause of cancer deaths in men (138,100 deaths annually) and the ninth in women (127,900) deaths annually[2].

II. Etiology and Pathogenesis

Despite the high mortality rate associated with pancreatic cancer, its etiology is poorly understood. Hereditary factors have been proposed[3,4], including familial pancreatitis and inherited genetic syndromes including BRCA associated Hereditary Breast and Ovarian Cancer Syndrome and Peutz-Jeghersrs. Non

hereditary conditions like chronic pancreatitis and diabetes ahs been associated with increased risk of pancreas cancer[5]. Environmental factors including obesity, smoking, coffee consumption and iatrogenic causes like gastrectomy and cholecystectomy have had conflicting association with increased incidence of pancreas cancer[6].

III. Prognostic Factors

Cancer of the exocrine pancreas is rarely curable and has an overall survival (OS) rate of less than 4%. The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of the disease accounts for fewer than 20% of cases. For those patients with localized disease and small cancers (<2 cm) with no lymph node metastases and no extension beyond the capsule of the pancreas, complete surgical resection can yield actuarial 5-year survival rates of 18% to 24%[7]. Improvements in imaging technology, including spiral computed tomographic scans, magnetic resonance imaging scans, positron emission tomographic scans, endoscopic ultrasound examination, and laparoscopic staging can aid in the diagnosis and the identification of patients with disease that is not amenable to resection.[8] In a case series of 228 patients, positive peritoneal cytology had a positive predictive value of 94%, specificity of 98%, and sensitivity of 25% for determining unresectability[9]. For patients with advanced cancers, the OS rate of all stages is less than 1% at 5 years with most patients dying within 1 year.[10,11]

No tumor-specific markers exist for pancreatic cancer; markers such as serum CA 19-9 have low specificity. Most patients with pancreatic cancer will have an elevated CA 19-9 at diagnosis. Following or during definitive therapy, the increase of CA 19-9 levels may identify patients with progressive tumor growth.[12] The presence of a normal CA 19-9, however, does not preclude recurrence.

IV. Pathology:

The commonly used term "pancreatic cancer" usually refers to a ductal adenocarcinoma of the pancreas (including its subtypes), which represents about 85 percent of all pancreatic neoplasms. Of the several subtypes of ductal adenocarcinoma, most share a similar poor long-term prognosis, with the exception of colloid carcinomas, which have a somewhat better prognosis. The more inclusive term "exocrine pancreatic neoplasms" includes all tumors that are related to the pancreatic ductal and acinar cells and their stem cells (including pancreatoblastoma), and is preferred. More than 95 percent of malignant neoplasms of the pancreas arise from the exocrine elements. Neoplasms arising from the endocrine

pancreas (i.e. pancreatic neuroendocrine [islet cell] tumors) comprise no more than 5 percent of pancreatic neoplasms.

V. Staging

The preferred staging system for all pancreatic cancers (exocrine and neuroendocrine) is the tumor-node-metastasis system of the combined American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC). The goal of the staging workup is to delineate the extent of disease spread and identify patients who are eligible for resection with curative intent. Abdominal CT provides an assessment of local and regional disease extent, which determines resectability, and also evaluates the possibility of distant metastatic spread. The reliability of CT as a staging tool for pancreatic cancer is highly dependent upon technique. Triple-phase contrast-enhanced thin-slice (multidetector row) helical computed tomography (MDCT) with three dimensional reconstructions is the preferred method to diagnose and stage pancreatic cancer. MRI, PET Endoscopic Ultrasound and Staging Laparoscopy may add additional diagnostic value.[13, 14]

Complete surgical resection is the only potentially curative modality of treatment for pancreatic cancer. An initial assessment of resectability can usually be made based upon the preoperative triple-phase staging contrast-enhanced CT scan. Local unresectability is usually (but not always) due to vascular invasion, particularly of the superior mesenteric artery (SMA). Although practice is variable across institutions, many surgeons would consider a pancreatic cancer to be categorically unresectable if any of the following are present:

- Extrapancreatic involvement, including extensive peripancreatic lymphatic involvement, nodal involvement beyond the peripancreatic tissues, and/or distant metastases.
- Direct involvement of the superior mesenteric artery (SMA), inferior vena cava, aorta, celiac axis, or hepatic artery, as defined by the absence of a fat plane between the low density tumor and these structures on CT scan.
- There are fewer consensuses on the definition of "borderline" resectable pancreatic cancer.

The seventh edition (2010) AJCC TNM[15] staging of exocrine Pancreas tumors is shown in the table below.

TNM staging system for exocrine and endocrine tumors of the pancreas

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ*		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

VI. Treatment Options

Surgical resection offers the only chance of cure, but only 15 to 20 percent of cases are potentially resectable at presentation. Furthermore, prognosis is poor, even for those undergoing complete (R0) resection.[7, 16] Reported five-year survival rates following pancreaticoduodenectomy for node-negative and node-positive disease is 25 to 30, and 10 percent, respectively. Systemic chemotherapy, radiation therapy (RT), and a combination of chemotherapy and RT have all been applied following surgery in an effort to improve cure rates. Although the benefit of adjuvant therapy has become clearer in recent years,

the optimal choice of treatment modality (chemotherapy with or without RT) remains intensely controversial.[17–20] Eligible patients should be encouraged to enroll in clinical trials evaluating the potential benefits of chemotherapy and/or chemoradiotherapy as well as new therapies.

Treatment for Stage I and II Pancreatic Cancer

Approximately 20% of patients present with pancreatic cancer amenable to local surgical resection, with operative mortality rates of approximately 1% to 16%.[21–25] Using information from the Medicare claims database, a national cohort study of more than 7,000 patients undergoing pancreaticoduodenectomy between 1992 and 1995 revealed higher in-hospital mortality rates at low-volume hospitals (<1 pancreaticoduodenectomy per year) versus high-volume hospitals (>5 per year) (16% vs. 4%, respectively, $P < 0.01$). [26] Complete resection can yield 5-year survival rates of 18% to 24%, but ultimate control remains poor because of the high incidence of both local and distant tumor recurrence.[7, 27–29] The role of postoperative therapy (chemotherapy with or without chemoradiation therapy [CRT]) in the management of this disease remains controversial because much of the randomized clinical trial data available are statistically underpowered and provide conflicting results.[30–32]

Three phase III trials examined the potential overall survival (OS) benefit of postoperative adjuvant 5-fluorouracil (5-FU)–based CRT. A small randomized trial conducted by the Gastrointestinal Study Group (GITSG) in 1985 demonstrated a significant but modest improvement in median-term and long-term survival over resection alone with postoperative bolus 5-FU and regional split course radiation given at a dose of 40 Gy.[31] An attempt by the European Organization for the Research and Treatment of Cancer to reproduce the results of the GITSG trial failed to confirm a significant benefit for adjuvant CRT over resection alone;[33] however, this trial treated patients with pancreatic as well as periampullary cancers (with a potential better prognosis). A subset analysis of the patients with primary pancreatic tumors indicated a trend towards improved median, 2-year, and 5-year OS with adjuvant therapy compared with surgery alone (17.1 months, 37% and 20% vs. 12.6 months, 23% and 10%, $P = .09$ for median survival). An updated analysis of a subsequent European Study for Pancreatic Cancer (ESPAC 1) trial examined only patients who underwent strict randomization following pancreatic resection. The patients were assigned to one of four groups (observation, bolus 5-FU chemotherapy, bolus 5-FU CRT, or CRT followed by additional chemotherapy). With a 2 × 2 factorial design reported, at a median follow-up of 47 months, a median survival benefit was observed for only the patients who received

postoperative 5-FU chemotherapy. These results were difficult to interpret, however, because of a high rate of protocol nonadherence and the lack of a separate analysis for each of the four groups in the 2 x 2 design.[34, 35]

The United States Gastrointestinal Intergroup has reported the results of a randomized phase III trial (RTOG-9704) that included 451 patients with resected pancreatic cancers who were assigned to receive either postoperative infusional 5-FU plus infusional 5-FU and concurrent radiation or adjuvant gemcitabine plus infusional 5-FU and concurrent radiation.[36] The primary endpoints were OS for all patients and OS for patients with pancreatic head cancers. The median OS for the 388 patients with pancreatic head tumors was 20.5 months in the gemcitabine arm versus 16.9 months in the 5-FU arm; 3-year survival was 31% versus 22%, respectively (P = .09; hazard ratio = 0.82; confidence interval [CI], 0.65–1.03). OS for all patients was not reported in the publication; however, median survival estimates extrapolated from the presented survival curve were approximately 19 months for the gemcitabine group and 17 months for the 5-FU group.

Results have also been reported from CONKO-001, a multicenter phase III trial of 368 patients with resected pancreatic cancer who were randomly assigned to six cycles of adjuvant gemcitabine versus observation.[37] In contrast to the previous trials, the primary endpoint was disease-free survival (DFS). Median DFS was 13.4 months in the gemcitabine arm (95% CI, 11.4–15.3) and 6.9 months in the observation group (95% CI, 6.1–7.8; P < .001). However, there was no significant difference in OS between the gemcitabine arm (median 22.1 months, 95% CI, 18.4–25.8) and the control group (median 20.2 months, 95% CI, 17–23.4).[33]

Although the available data do not resolve the controversy of the optimal adjuvant therapy strategy for patients with resected pancreatic cancer, the results of CONKO-001 and RTOG-9704 suggest that a gemcitabine-containing regimen represents an appropriate choice for current management and may be considered as an acceptable standard.

There is no consensus regarding the overall optimal management of patients after resection of an exocrine pancreatic cancer, and the approach is different in Europe and in the United States. Largely based upon the ESPAC-1 trial, which showed that 5-FU containing chemotherapy prolongs survival, and results of the German CONKO trial showing a survival benefit from adjuvant genmcitabine, most European clinicians use chemotherapy alone after resection of a pancreatic neoplasm.[38] The American

approach more often includes chemoradiotherapy as well as adjuvant chemotherapy. Guidelines from the National Comprehensive Cancer Network support either approach. Off-protocol, a combination of concurrent chemoradiotherapy and chemotherapy for all patients with resected pancreatic cancer is commonly used and during the concurrent chemoradiotherapy portion, infusional 5-FU is preferred, and gemcitabine is used alone for the chemotherapy portion.

Treatment for Stage III Pancreatic Cancer

Patients with stage III pancreatic cancer have tumors that are technically unresectable because of local vessel impingement or invasion by tumor. These patients may benefit from palliation of biliary obstruction by endoscopic, surgical, or radiological means.[12]

Two major trials attempted to look at issues of combined modality therapy versus radiation therapy alone (the Gastrointestinal Tumor Study Group's GITSG-9173 trial, the Eastern Cooperative Oncology Group's E-8282 trial.[39, 40] The trials had substantial deficiencies in design or analysis. Until recently, the standard of practice has been to give chemoradiation therapy, and that was based on these studies.

Prior to the use of gemcitabine for patients with locally advanced or metastatic pancreatic cancer, investigators from the GITSG randomly assigned 106 patients with locally advanced pancreatic adenocarcinoma to receive external beam radiation therapy (EBRT) (60 Gy) alone or to receive concurrent EBRT (either 40 Gy or 60 Gy) plus bolus fluorouracil (5-FU).[39] The study was stopped early when the chemoradiation therapy arms were found to have better efficacy. The 1-year survival was 11% for patients who received EBRT alone compared with 38% for patients who received chemoradiation with 40 Gy and 36% for patients who received chemoradiation with 60 Gy. After an additional 88 patients were enrolled in the combined modality arms, there was a trend toward improved survival with 60 Gy EBRT plus 5-FU, but the difference in time-to-progression and overall survival (OS) was not statistically significant when compared to the 40 Gy arm.

In contrast, investigators from the ECOG randomly assigned 114 patients to radiation therapy (59.4 Gy) alone or with concurrent infusional 5-FU (1,000 mg/m2 daily on days 2 through 5 and days 28 through 31) plus mitomycin (10 mg/m2 on day 2) and found no difference in OS between the two groups.[40]

Whether chemoradiation therapy should be considered for patients with stage III pancreatic cancer became controversial with more modern results from the FFCD-SFRO study.[41] Patients with locally advanced pancreatic cancer were randomly assigned to receive either concurrent chemoradiation therapy followed by gemcitabine or gemcitabine alone. The trial was halted because of poor accrual after 109 of the planned 176 patients were enrolled. In a preliminary report with a median 16-month follow-up, patients who received chemoradiation followed by gemcitabine had a median survival of 8.4 months versus 14.3 months for the group who received gemcitabine alone (stratified log-rank, P = .014). However patients receiving concurrent therapy were treated with non standard chemotherapy regimen (cisplatin and 5FU) which could have contributed to additional toxicity.

More recently another ECOG study evaluated the role of radiation therapy with concurrent gemcitabine (GEM) compared with GEM alone in patients with localized unresectable pancreatic cancer.[42] Of 74 patients entered on trial and randomly assigned to receive GEM alone (Arm A n= 37) or GEM plus radiation (Arm B n= 34), patients in arm B had greater incidence of grades 4 and 5 toxicities (41% *v* 9%), but grades 3 and 4 toxicities combined were similar (77% in A *v* 79% in B). No statistical differences were seen in quality of life measurements at 6, 15 to 16, and 36 weeks. The primary end point was survival, which was 9.2 months (95% CI, 7.9 to 11.4 months) and 11.1 months (95% CI, 7.6 to 15.5 months) for arms A and B, respectively.

This trial demonstrated improved overall survival with the addition of radiation therapy to GEM in patients with localized unresectable pancreatic cancer, with acceptable toxicity.

The current standard therapy for Stage III pancreas Cancer would be Chemoradiation and Gemcitabine chemotherapy. The promising response rates with FOLFIRINOX combination chemotherapy in the metastatic setting has encouraged oncologists to use this instead of Gemcitabine in younger patients with good performance status.[43, 44]

Treatment for Stage IV Pancreatic Cancer

The low objective response rate and lack of survival benefit with current chemotherapy indicates clinical trials as appropriate treatment of all newly diagnosed patients with stage IV pancreatic cancer. Occasional patients have palliation of symptoms when treated by chemotherapy with well-tested older

drugs such as fluorouracil (5-FU). Gemcitabine has demonstrated activity in patients with pancreatic cancer and is a useful palliative agent.[45–47] A phase III trial of gemcitabine versus 5-FU as first-line therapy in patients with advanced or metastatic adenocarcinoma of the pancreas reported a significant improvement in survival among patients treated with gemcitabine (1-year survival was 18% with gemcitabine as compared with 2% with 5-FU, P = .003). When 5-FU was added to gemcitabine and compared with gemcitabine alone, the median survival of patients with advanced or metastatic disease (6.7 months vs. 5.7 months, respectively, P = .09) was not significantly improved. Another randomized phase III trial (CAN-NCIC-PA3) comparing gemcitabine alone versus the combination of gemcitabine and erlotinib (100 mg/day) in patients with advanced or metastatic pancreatic carcinomas showed that erlotinib modestly prolonged survival when combined with gemcitabine alone.[48] Differences in overall survival (OS) favored the erlotinib arm (hazard ratio = 0.82; 95% confidence interval, 0.69–0.99; P = .023). The corresponding median and 1-year survival rates for patients receiving erlotinib versus placebo were 6.24 months and 5.91 months, and 23% versus 17%, respectively. Other combinations to this including bevacizumab have been studied in this setting.[49]

More recently intensive FOLFIRINOX combination chemotherapy has shown substantial improvements in objective response rates and overall in metastatic pancreas cancer in comparison with gemcitabine at a cost of increased toxicity and decreased Quality of Life. In the PRODIGE study comparing 342 patients between FOLFIRINOX and Gemcitabine, improved response rates (31.6% vs. 9.4%; p,0.001), median overall survival (11.1months vs. 6.8 months ; p,0.001) and median progression free survival (6.4months vs. 3.3months; p<0.001).[50] Increased toxicity and poor Quality of life were also reported.[50,51,52]

The current standard treatment option in patients with metastatic pancreas cancer with good performance status would include FOLFIRINOX combination chemotherapy, while Gemcitabine based chemotherapy would remain the treatment of choice for most other patients.

Supportive care with palliative radiation, biliary stents, analgesics, celiac plexus blocks play a crucial role in the palliation of these patients.[53]

Recurrent Pancreatic Cancer

Chemotherapy and radiation therapy may occasionally produces objective antitumor response and palliation, but the low percentage of significant responses and lack of survival advantage warrant use of investigational therapies under evaluation for recurrent pancreatic cance.[47]

VII. SRS Literature Review

This section reviews the literature on treatment of pancreatic cancer with stereotactic radiosurgy (SRS) which is also called stereotactic body radiation therapy SBRT, and is further defined as a high dose of radiation per treatment with a small number of total treatments (to a maximum of five). There are unique concerns in regards to performing SRS of the pancreas. While the pancreas does not manifest any major clinical sequelae following radiation therapy, it is close to many other critical organs that are highly radiosensitive. The organs at risk needing consideration are the duodenum, liver, stomach, and bile duct. The liver is not usually problematic, since the volume of liver tissue receiving a significant dose of radiation is likely to be small. The common bile duct has the potential to stricture with radiation, but as most patients with pancreatic cancer have already received biliary stents, this has not been the source of significant side effects from SRS. If the bile duct is not already stented and is to receive a high dose of radiation, it is suggested that it be stented prophylactically. The hardest organs to avoid with SRS are the duodenum, and the stomach that directly abut the pancreas. Delivery of even moderate doses of radiation to small bowel is associated with a high risk of late stenosis, ulceration, bleeding and perforation.

The published series of the use of single or multiple fraction SBRT is shown in the following table:

Study (Author)	Treatment	Number of patients	Progression Free Survival (months)	Overall Survival (months)
Koong Phase I [54]	SRS 15-25 Gy	15	2	11 #
Koong Phase II [55]	RT 45 Gy + SRS 25 Gy	19	4.5	8 #
Schellenberg [56]	GEM+SRS 25 Gy +GEM	16	9	11.4 #
Chang (includes all of above patients) [57]	SRS 25 Gy +/- GEM EBRT	77	-	11.4 #
Hoyer [58]	SBRT 45 Gy	22	4.8	5.7#
Mahadevan [59]	SBRT 24-36 Gy + GEM	36	CA 19-9: 7.9 CT: 9.6	14.3 †
Polistina [60]	GEM + SBRT 30 Gy	33	NR	10.6#
Didolkar [61]	SBRT 15-30 Gy + GEM	85*	NR	18.6 # 8.6 †
Rwigema[62]	SRS 18-25 Gy	71^	NR	10.3 †
Mahadevan[63]	GEM- SBRT-GEM (24-36Gy)	39	15	20#
Goyal[64]	SBRT (24-30Gy)	20	11.43	14.37

Abbreviations: EBRT – external beam radiation therapy, GEM – gemcitabine, NR – not reported RT – radiation therapy, SBRT– stereotactic body radiation therapy, SRS – stereotactic radiosurgery.

From diagnosis; † From start of treatment; *includes recurrent patients; ^includes recurrent and positive margin patients some of which received post-SRS chemotherapy.

The first cases of SRS for pancreatic carcinoma were reported in 2000 from Stanford University and showed basic feasibility of single fraction SRS in the treatment of pancreatic cancer.[65] This study was followed by an initial phase I dose escalation study of SRS for pancreatic cancer also from Stanford University.[54]A totals of fifteen patients were enrolled and received doses of either15, 20, or 25 Gy to the primary tumor. Twelve of the patients had not received any prior radiation or chemotherapy. Five patients had acute toxicity which consisted of grade 2 nausea, pain, or diarrhea. The 6 patients who received 25 Gy had local control of their primary pancreatic tumor, but all 6 died to distant metastases as the site of first progression. The median survival for the cohort was 11 months. There was no grade 3 toxicity or higher. This study established the feasibility and dose parameters of single fraction SRS for the treatment of pancreatic cancer.

This same group then assessed efficacy of combining systemic 5-FU with conventionally fractionated radiotherapy (EBRT) followed by SRS boost in patients with locally advanced pancreatic cancer.[55] This phase II trial looked at chemoradiation with 5-FU and 45 Gy delivered in 1.8 Gy per day fractions to both the tumor and regional lymph nodes, followed by a 25 Gy SRS boost to the gross tumor (GTV). Fifteen

out of 16 patients who completed treatment were free from local progression until death, but all patients developed distant disease, with a median freedom from progression of 17.5 weeks. The median survival was 33 weeks. Two patients experienced grade 3 acute toxicity. There was more GI toxicity when combining SRS with conventional fractionated radiotherapy and although there was excellent local control there was no impact on overall survival because of rapid progression of systemic metastasis.

Another phase II trial from the Stanford group aimed to integrate standard gemcitabine chemotherapy with SRS to address the high propensity of distant metastasis with pancreatic carcinoma. This study on the combined use of chemotherapy and SRS studied a trial of gemcitabine (1,000 mg/m2 on days 1, 8, and 15) followed by a single dose of 25 Gy SRS on day 29 for local control. Two weeks or more after SRS, gemcitabine was restarted at 1,000 mg/m2 per week and continued until disease progression.[56] Sixteen patients were enrolled and all 16 completed treatment with a median survival of 11.4 months, median time to progression was 9.7 months and one-year survival was 50%. Thirteen of 16 patients were locally controlled, but these patients developed metastases. None of the patients had sufficient response to undergo resection. Acute toxicity was mild, but late toxicity was severe including five late grade 2 duodenal ulcers, one grade 3 duodenal stenosis requiring stenting, and one grade 4 duodenal perforation requiring surgery. Combining radiosurgery with pre- and post-treatment gemcitabine is well tolerated and excellent local control was achieved, but late toxicities were more common. The same group tested this strategy using sequential gemcitabine after single fraction SBRT with similar results.[66] Their pooled results of SBRT in locally advanced pancreas cancer was subsequently published.[57]

Another phase II trial from Denmark studied SRS in twenty-two patients with locally advanced surgically non-resectable, pancreatic cancer.[58] The target consisted of gross tumor treated with a central dose of 45 Gy in 3 fractions. Of the twenty-two patients that were treated, only two achieved partial response. Six patients recurred locally, with the mean time to progression at 4.8 months, and 6 patients received gemcitabine after relapse. The median survival was 5.7 months with a one-year survival of 5%. Acute toxicity was pronounced with 4 patients having severe ulceration of the stomach or duodenum. One patient had a perforated gastric ulcer requiring surgery. Of note in this study, the gross tumor volumes (GTV) that were treated were much larger than those in the initial Stanford study. In addition there were larger margins used here and a larger total does of 45 Gy. There was no mention of respiratory motion compensation with the techniques used in this study as opposed to others with this capability.[67]

In other study Mahadevan *et al*. in 2010 studied SBRT in 36 locally advanced pancreas cancer patients followed by Gemcitabine chemotherapy. A tolerance based dose prescription was utilized based on the relation ship of the duodenum to the tumor; if closely involved patients received 24Gy in 3 fractions, if abutting the patients received 30Gy in 3 fractions and if the tumor did not involve the duodenum thy received 36Gy in 3 fractions. The overall local control was 85% with a median progression free survival of 9.6 months and median overall survival of 14.3 months. Grade 3 toxicity was seen in 3 patients.

Further studies utilizing SBRT for locally advanced pancreas cancer showing excellent tolerability, efficacy and toxicity profile has been published from Italy, University of Pittsburg and Case Western University as described in the Table above.

Recent focus in LAPC (Locally Advanced Pancreas Cancer) treatment has shifted to ideal sequencing of therapies. A Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) review of LAPC patients and a retrospective review from MD Anderson Cancer Center showed similar results with OS favoring induction chemotherapy and radiation therapy over starting with radiation.[68] Combining the results of the GERCOR study favoring induction chemotherapy and the evidence that SBRT produces excellent local control, the Harvard group hypothesized that an ideal combination may be induction chemotherapy, restaging and a short break for SBRT, followed by chemotherapy until progression - so called "sandwich" therapy. This would allow us to stratify the ~20% who would develop rapid-onset metastatic disease and prevent delays in potentially life-prolonging systemic therapy. From October 2007 to February 2010, 47 patients with LAPC were given two cycles of gemcitabine, followed by restaging. Patients without metastatic disease were given a third cycle while undergoing radiation planning. Patients were then treated with 24-36Gy in three fractions. Patients then received maintenance gemcitabine until progression.[63] 8 patients (17%) developed metastatic disease prior to undergoing SBRT. Median overall survival was 20 months in patients who proceeded to SBRT. The median overall survival of 20 months in patients receiving SBRT is slightly longer than the 8 to 14 month median survival typically seen in patients with LAPC and the 15 month median survival seen in the GERCOR trial. It is unclear if this benefit was due to optimization of chemotherapy and SBRT delivery or the removal of patients with rapid progression of metastatic disease from the treatment group.

VIII. Clinical Indications and Guidelines for SRS

This section is accessible only to society members – for more information about the Radiosurgery Society®, go to www.therss.org

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA: A Cancer Journal for Clinicians*. 2012;62(1):10–29.

2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA: A Cancer Journal for Clinicians*. 2011;61(2):69–90.

3. Olson SH, Kurtz RC. Epidemiology of pancreatic cancer and the role of family history. *J Surg Oncol*. 2012.

4. Klein AP, Hruban RH, Brune KA, Petersen GM, Goggins M. Familial pancreatic cancer. *Cancer J*. 2001;7(4):266–273.

5. Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br. J. Cancer*. 1999;80(11):1830–1837.

6. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int. J. Cancer*. 1989;43(3):415–421.

7. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann. Surg.* 1997;226(3):248–257; discussion 257–260.

8. Riker A, Libutti SK, Bartlett DL. Advances in the early detection, diagnosis, and staging of pancreatic cancer. *Surg Oncol*. 1997;6(3):157–169.

9. Merchant NB, Conlon KC, Saigo P, Dougherty E, Brennan MF. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. *J. Am. Coll. Surg.* 1999;188(4):421–426.

10. Mancuso A, Calabrò F, Sternberg CN. Current therapies and advances in the treatment of pancreatic cancer. *Crit. Rev. Oncol. Hematol*. 2006;58(3):231–241.

11. Lockhart AC, Rothenberg ML, Berlin JD. Treatment for pancreatic cancer: current therapy and continued progress. *Gastroenterology*. 2005;128(6):1642–1654.

12. Willett CG, Daly WJ, Warshaw AL. CA 19-9 is an index of response to neoadjunctive chemoradiation therapy in pancreatic cancer. *Am. J. Surg.* 1996;172(4):350–352.

13. John TG, Greig JD, Carter DC, Garden OJ. Carcinoma of the pancreatic head and periampullary region. Tumor staging with laparoscopy and laparoscopic ultrasonography. *Ann Surg*. 1995;221(2):156–164.

14. Minnard EA, Conlon KC, Hoos A, et al. Laparoscopic ultrasound enhances standard laparoscopy in the staging of pancreatic cancer. *Ann Surg*. 1998;228(2):182–187.

15. American Joint Committee on Cancer. Exocrine Pancreas. In: *AJCC CAncer Staging Manual*. 7th ed. Springer; 2007:157–164.

16. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. *Ann Surg*. 1996;223(3):273–279.

17. O'Reilly EM. Adjuvant therapy for pancreas adenocarcinoma: where are we going? *Expert Rev Anticancer Ther*. 2011;11(2):173–177.

18. Saif MW. Adjuvant therapy of pancreatic cancer: beyond gemcitabine. Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 20-22, 2011. *JOP*. 2011;12(2):106–109.

19. Shinohara ET, Mitra N, Fei W, Kirschner AN, Metz JM. Trends in the use of postoperative radiation therapy in patients with localized resectable pancreatic cancer. *Am. J. Clin. Oncol.* 2012;35(6):543–548.

20. Sultana A, Cox T, Ghaneh P, Neoptolemos JP. Adjuvant therapy for pancreatic cancer. *Recent Results Cancer Res.* 2012;196:65–88.

21. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. *Surgery*. 1999;125(3):250–256.

22. Hsu CC, Wolfgang CL, Laheru DA, et al. Early mortality risk score: identification of poor outcomes following upfront surgery for resectable pancreatic cancer. *J. Gastrointest. Surg.* 2012;16(4):753–761.

23. Venkat R, Puhan MA, Schulick RD, et al. Predicting the risk of perioperative mortality in patients undergoing pancreaticoduodenectomy: a novel scoring system. *Arch Surg*. 2011;146(11):1277–1284.

24. Nathan H, Wolfgang CL, Edil BH, et al. Peri-operative mortality and long-term survival after total pancreatectomy for pancreatic adenocarcinoma: a population-based perspective. *J Surg Oncol*. 2009;99(2):87–92.

25. DeOliveira ML, Winter JM, Schafer M, et al. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. *Ann. Surg.* 2006;244(6):931–937; discussion 937–939.

26. Spanknebel K, Conlon KC. Advances in the surgical management of pancreatic cancer. *Cancer J*. 2001;7(4):312–323.

27. Butturini G, Stocken DD, Wente MN, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. *Arch Surg*. 2008;143(1):75–83; discussion 83.

28. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J. Gastrointest. Surg.* 2006;10(9):1199–1210; discussion 1210–1211.

29. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann. Surg.* 2006;244(1):10–15.

30. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985;120(8):899–903.

31. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer*. 1987;59(12):2006–10.

32. Choti MA. Adjuvant therapy for pancreatic cancer--the debate continues. *N Engl J Med*. 2004;350(12):1249–1251.

33. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann. Surg.* 1999;230(6):776–782; discussion 782–784.

34. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *Lancet*. 2001;358(9293):1576–1585.

35. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350(12):1200–1210.

36. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA*. 2008;299(9):1019–1026.

37. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297(3):267–277.

38. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA*. 2010;304(10):1073–1081.

39. 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):1705–1710.

40. Cohen SJ, Dobelbower R, Lipsitz S, et al. A randomized phase III study of radiotherapy alone or with 5-fluorouracil and mitomycin-C in patients with locally advanced adenocarcinoma of the pancreas: Eastern Cooperative Oncology Group study E8282. *Int J Radiat Oncol Biol Phys*. 2005;62(5):1345–1350.

41. Barhoumi M, Mornex F, Bonnetain F, et al. [Locally advanced unresectable pancreatic cancer: Induction chemoradiotherapy followed by maintenance gemcitabine versus gemcitabine alone: Definitive results of the 2000-2001 FFCD/SFRO phase III trial]. *Cancer Radiother*. 2011;15(3):182–191.

42. Loehrer PJ Sr, Feng Y, Cardenes H, 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):4105–4112.

43. Levy A, Chargari C, Huguet F, Védrine L, Deutsch E. FOLFIRINOX in locally advanced pancreatic cancer: the starting point for questioning. *Pancreas*. 2012;41(6):973–974.

44. Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer*. 2012;12:199.

45. Rothenberg ML, Moore MJ, Cripps MC, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol*. 1996;7(4):347–353.

46. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403–2413.

47. Storniolo AM, Enas NH, Brown CA, et al. An investigational new drug treatment program for patients with gemcitabine: results for over 3000 patients with pancreatic carcinoma. *Cancer*. 1999;85(6):1261–1268.

48. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* 2007;25(15):1960–1966.

49. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J. Clin. Oncol.* 2009;27(13):2231–2237.

50. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med.* 2011;364(19):1817–1825.

51. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial. *J. Clin. Oncol.* 2012.

52. Peddi PF, Lubner S, McWilliams R, et al. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. *JOP*. 2012;13(5):497–501.

53. Kneuertz PJ, Cunningham SC, Cameron JL, et al. Palliative surgical management of patients with unresectable pancreatic adenocarcinoma: trends and lessons learned from a large, single institution experience. *J. Gastrointest. Surg.* 2011;15(11):1917–1927.

54. 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):1017–1021.

55. Koong AC, Christofferson E, Le Q-T, et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys*. 2005;63(2):320–323.

56. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys*. 2008;72(3):678–686.

57. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer*. 2009;115(3):665–672.

58. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol*. 2005;76(1):48–53.

59. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *International Journal of Radiation Oncology* Biology* Physics*. 2010;78(3):735–742.

60. Polistina F, Costantin G, Casamassima F, et al. Unresectable Locally Advanced Pancreatic Cancer: A Multimodal Treatment Using Neoadjuvant Chemoradiotherapy (Gemcitabine Plus Stereotactic Radiosurgery) and Subsequent Surgical Exploration. *Annals of Surgical Oncology*. 2010;17:2092–2101. Available at: [Accessed November 27, 2011].

61. Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J. Gastrointest. Surg.* 2010;14(10):1547–1559.

62. Rwigema J-CM, Parikh SD, Heron DE, et al. Stereotactic Body Radiotherapy in the Treatment of Advanced Adenocarcinoma of the Pancreas. *Am J Clin Oncol*. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20308870.

63. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. *International Journal of Radiation Oncology* Biology* Physics*. 2011.

64. Goyal K, Einstein D, Ibarra RA, et al. Stereotactic Body Radiation Therapy for Nonresectable Tumors of the Pancreas. *Journal of Surgical Research*. 2011. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0022480411006743 [Accessed November 27, 2011].

65. Murphy MJ, Adler JR Jr, Bodduluri M, et al. Image-guided radiosurgery for the spine and pancreas. *Comput. Aided Surg.* 2000;5(4):278–288.

66. 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. *International Journal of Radiation Oncology* Biology* Physics*. 2011.

67. Schweikard A, Glosser G, Bodduluri M, Murphy MJ, Adler JR. Robotic motion compensation for respiratory movement during radiosurgery. *Comput. Aided Surg.* 2000;5(4):263–277.

68. Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J. Clin. Oncol.* 2007;25(3):326–331.

69. Rwigema J-CM, Heron DE, Parikh SD, et al. Adjuvant Stereotactic Body Radiotherapy for Resected Pancreatic Adenocarcinoma with Close or Positive Margins. *J Gastrointest Cancer*. 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20809393 [Accessed November 27, 2011].