Chi-square analysis. For surgical patients, we evaluated whether radiation modality influenced surrogates of surgical morbidity (hospitalization duration, unplanned hospital readmission rate within 30 days of discharge) and 30-/90- day mortality. The Kaplan Meier method was used to analyze OS for all patients in addition to surgical only and non-surgical only patients.

Results: A total of 13,645 patients were identified (surgery, n = 4,078; no surgery, n = 9,567). Most (73.8%) received multiagent chemotherapy while a minority (10.8%) received single agent chemotherapy. Median radiation dose was 50 Gy and median number of fractions was 28. A significant increase in IMRT utilization occurred during the study period (2003: 13.2%; 2007: 40.6%; 2012: 64.9%). IMRT was more commonly used for females (versus males), in urban (versus rural) areas, in academic (versus community) centers, and in certain geographic regions, but did not differ by primary payer. Overall IMRT (versus 3D) utilization among surgical patients was 50.3% (vs. 49.7%) and among non-surgical patients was 50.1% (vs. 49.9%) ($p=0.026$). For surgical patients, 3D was associated with a higher rate of hospital readmission (5.7 vs. 4.5%, $p<0.0001$) and higher 30-day mortality (3.8 vs. 2.7%, $p=0.041$), neither of which was significantly different based on year of diagnosis. Hospitalization length and 90-day mortality were similar. For all patients, IMRT was associated with longer OS (median 19.6 vs. 16.7 months, $p<0.0001$). For non-surgical patients only, IMRT was associated with longer OS (median 15.3 vs. 12.6 months, $p<0.0001$) although no significant OS difference was found among surgical patients only (32.2 vs. 33.4 months, $p=0.971$).

Conclusion: IMRT utilization has increased significantly in the United States over the past decade and now appears to be used more frequently than 3D. For surgical patients, IMRT may decrease surgical morbidity, presumably by reducing normal tissue dose, but does not appear to affect OS compared to 3D. While higher OS was found in non-surgical patients who received IMRT compared to 3D, further analysis is ongoing to clarify the significance of this association.

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MEK Inhibitor GSK1120212-Mediated Radiosensitization of Pancreatic Cancer Cells Involves Inhibition of DNA Double-Strand Break Repair Pathways

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Purpose/Objective(s): There is an urgent need for the development of novel therapies for pancreatic adenocarcinoma (PAC). About 90% of PAC expresses oncogenic mutant KRAS that constitutively activates its downstream Raf-MEK-ERK pathway, conferring resistance to both radiation and chemotherapy. MEK1/2 inhibitors have recently shown promising anti-tumor responses in preclinical studies and clinical trials in KRAS and BRAF mutant selected patients. MEK1/2 inhibitors are also currently being tested in combination with radiation therapy in phase I trials. In the current study, we have evaluated the radiosensitizing potential of a novel MEK1/2 inhibitor GSK1120212 (GSK212) and evaluated whether MEK1/2 inhibition alters DNA repair mechanisms in multiple PAC cell lines.

Materials/Methods: Radiosensitization was evaluated by clonogenic assay. DNA double-strand break (DSB) repair was assessed by comet assay, nuclear foci formation (gH2AX, DNA-PK, 53BP1, BRCA1, and RAD51), and also by functional GFP-reporter assays for homologous recombination (HR) and non-homologous end-joining (NHEJ). Expression and activation of DNA repair pathways were measured by immunoblotting.

Results: GSK212 blocked ERK1/2 activity and radiosensitized multiple KRAS mutant PAC cell lines, but not an immortalized small intestinal epithelial cell line, FHs74Int. Prolonged pre-treatment with GSK212 for 24-48 hours resulted in the highest degree of radiosensitization, compared with shorter time courses. GSK212 treatment resulted in delayed resolution of DNA damage as measured by comet assays and persistent gH2AX nuclear foci at 24 hours after radiation. GSK212 treatment also resulted in altered kinetics of BRCA1, RAD51, DNA-PK, and 53BP1 nuclear foci resolution after radiation. Using functional reporters, GSK212 caused downregulation of both HR and NHEJ repair activity. Moreover, GSK212-mediated MEK1/2 inhibition suppressed the expression and activation of a number of DSB repair pathway intermediates including BRCA1, DNA-PK, RAD51, RRM2, and Chk-1 in irradiated PAC cells.

Conclusion: The novel MEK1/2 inhibitor GSK212 confers radiosensitization to KRAS oncogene driven PAC cells by suppressing major DNA-DSB repair pathways. Together with other studies, these data provide support for the combination of MEK1/2 inhibition and radiation in the treatment of pancreatic cancer.

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Proton Reirradiation for Locally Recurrent Pancreatic Adenocarcinoma

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Purpose/Objective(s): Local recurrence following definitive treatment affects up to 25% of patients with pancreatic adenocarcinoma and is associated with significant morbidity. Retreatment options are limited. Proton radiation therapy (PRT) may confer an advantage in this setting by sparing dose to previously irradiated normal tissues and structures while improving local control and overall survival.

Materials/Methods: Between 8/2010-11/2014, 15 patients with locally recurrent pancreatic cancer were treated with proton reirradiation. Toxicity was graded using CTC v4.0 and acute toxicity was defined as occurring within 90 days from the start of PRT. Kaplan-Meier analysis was used to determine overall survival (OS), locoregional progression-free survival (LPFS) and distant metastasis-free survival (DMFS), which was defined from the start of PRT.

Results: Median follow-up was 9.6 months (1.1-38.4) from the start of reirradiation and 17.4 months from diagnosis of local recurrence (2.4-43.7). The mean age was 66 years (52-79). The median CTV size was 75 cc (15-236). Eleven patients received concurrent 5-fluorouracil or capecitabine-based chemotherapy. Median PRT dose was 59.4 Gy (RBE) (37.50-59.4) and the median prior radiation dose was 50.4 Gy (30-59.4). The median time from end of treatment of the prior course to the start of the PRT was 26.7 months (7-461.3). Of the 15 patients, 2 had stents, one biliary in the treatment field and one enteral, placed 3 days following the end of treatment for obstructive symptoms and progressive disease. Both of these patients notably had significant acute toxicities. The patient with an in-field stent developed grade 4 duodenal ulcers and the other patient died from a grade 5 small bowel perforation following stent placement. The other 13 patients tolerated radiation well with minimal grade 1 and grade 2 non-hematologic acute toxicities observed. Two patients had acute grade 3 anorexia and fatigue but recovered 1-2 months following the completion of radiation. There were no Grade 2 or higher late non-hematologic radiation-related toxicities. Three patients developed local progression in the treatment field; one had progressive disease identified at stent placement following the end of treatment, and the other two at 12.2 and 14 months following the completion of reirradiation. The median survival was 13.5 months (2.4-39.8) and OS at one year was 71.5% (95% CI 51.2-99.8). The LPFS and DMFS at one year was 78% and 52.2% respectively.

Conclusion: In these carefully selected patients, proton reirradiation was well-tolerated and resulted in prolonged overall survival, local-regional

progression-free, and distant metastasis-free survival, when compared to historical controls of locally recurrent pancreatic cancer. However caution should be exercised when combining reirradiation with stents.

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The Impact of Adjuvant Radiation Therapy on Survival in Patients With Surgically Resected Pancreatic Adenocarcinoma: A SEER Study From 2004 to 2010

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Purpose/Objective(s): Survival for patients with pancreatic adenocarcinoma remains poor. Patients who are able to undergo oncologic surgery for this disease have a better prognosis. However, the utility of adjuvant external beam radiation therapy (EBRT) in these patients remains controversial. We utilized the SEER database to study the role of radiation therapy in disease-specific outcomes in pancreatic cancer patients with various presentations of disease that underwent different oncologic surgeries. Our aim was to elucidate subsets of patients who may or may not benefit from adjuvant radiation therapy.

Materials/Methods: 6114 patients with pancreatic adenocarcinoma treated with oncologic surgery between 2004 and 2010 were extracted from the SEER database. Additional information was obtained for each patient, specifically: year of diagnosis, age (<60 or >=60), race (white, black, or other), type of surgery, site of tumor (head, body, or tail of pancreas), T stage, N stage, tumor grade, type of lymph node dissection and how many nodes were dissected, whether or not patients received radiation, and at last follow-up whether patients were dead from pancreatic cancer, or alive or dead from other causes. A Cox multivariate analysis was performed to provide an adjusted hazard ratio of dying from pancreatic cancer.

Results: The adjusted hazard ratio of dying from pancreatic cancer (HRDPC) favored the adjuvant EBRT arm (HRDPC=0.745, 95% CI 0.698-0.794, p<0.0001). Higher age, T stage, N stage, and grade were found to significantly increase the HRDPC in the overall population of pancreatic cancer patients. Race, type of surgery performed, location of the tumor, and extent of lymph node dissection did not significantly impact the HRDPC in this overall population. In the population receiving adjuvant EBRT, higher age, T stage, N stage, and grade were found to significantly increase the HRDPC. Race, type of surgery performed, location of the tumor, and extent of lymph node dissection did not significantly impact the HRDPC in the population receiving adjuvant EBRT. Interestingly, the HRDPC for the overall population was statistically significantly improved in 2009 and 2010 as compared to 2004. The HRDPC did not significantly improve in the adjuvant EBRT population with time.

Conclusion: In the SEER database, patients receiving adjuvant EBRT after oncologic surgery are at decreased risk of dying from pancreatic cancer. Unfortunately, it was not possible to elucidate subsets of patients who may or may not share this benefit with the overall group based on prognostic factors or treatment approaches. Interestingly, the HRDPC decreased in 2009 and 2010 as compared to 2004 for the overall population – this is worthy of further investigations.

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CEA as a Predictor of Pathologic Tumor Response Following Long Course Neoadjuvant Chemoradiation Therapy for Rectal Cancer

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Purpose/Objective(s): To identify clinical predictive factors for tumor response for patients treated with long-course neoadjuvant chemoradiation therapy (CRT) for locally advanced rectal cancer.

Materials/Methods: From May 1999 to July 2012, patients who received long-course neoadjuvant CRT followed by surgical resection with curative-intent for locally advanced rectal cancer were included in this study. T- and N-level downstaging was assessed by comparing the clinical and postoperative pathologic stage and defined as a reduction of at least 1 T- or N-stage level. Tumor responses after neoadjuvant CRT were assessed using the AJCC tumor regression grading (TRG) system. Statistical analyses were performed to identify clinical factors associated with pathologic tumor response.

Results: In total, 143 patients met criteria for analysis. Median age at diagnosis was 57 (range 21-95 years) and the male/female ratio was 103/40. Tumor downstaging occurred in 88 patients (62%), and a pathologic complete response was observed in 29 patients (20%). The median serum carcinoembryonic antigen (CEA) at diagnosis was 3 (range 0.21-257 ng/mL). Only 39% of patients with a baseline ≥3 ng/mL had an AJCC TRG score of either 0 or 1 (complete regression and single cells/small groups of tumor cells, respectively) as compared to 59% of patients with a baseline CEA<3 ng/mL (p=0.026). Baseline CEA nearly trended toward significant for T-downstaging (p=0.089). There was no correlation of CEA with N-downstaging. Several variables showed a trend towards significance as predictors of N-downstaging including average hemoglobin during treatment (p=0.089), hyperlipidemia (p=0.11), use of a statin (p=0.10), and diabetes (p=0.12).

Conclusion: The baseline CEA at diagnosis is a significant predictive factor of pathologic tumor response after long-course neoadjuvant CRT for locally advanced rectal cancer. This knowledge is useful to predict clinical outcomes and may play a role in the selection of treatment options.

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Heart Dose and Outcomes in Radiation Treatment for Esophageal Cancer

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Purpose/Objective(s): Recent publications have suggested that radiation dose to the heart may be associated with worse outcomes in patients with lung cancer treated with chemoradiation. As esophageal cancer radiation treatment fields can also result in relatively high doses to the heart, we evaluated a single-institution database of patients treated for esophageal cancer for heart dose and outcomes data.

Materials/Methods: On an IRB approved study, 60 eligible patients with esophageal cancer were identified who were treated with definitive-intent radiation therapy to >45 Gy from 2005-15. Mean heart dose (MHD) was extracted from the radiation plan. Kaplan-Meier analysis was conducted to test for statistical associations between MHD and overall survival (OS), distant metastasis-free survival (DM-FS), and local-regional recurrence-free survival (LRR-FS). Parameters included MHD as a categorical variable (above/below median) as well as a continuous variable. Independent group testing of patient subgroups was performed using Mann-Whitney test.

Results: 14 (23%) had squamous cell carcinoma, 46 (77%) had adenocarcinoma. Pre-treatment staging included 1 stage IB, 2 IIA, 13 IIB, 34 IIA, 3 IIIB, 5 IIIC, and 2 IV at diagnosis, though both were treated with definitive intent. MHD was 3090 (269.1-4757.3). 31 were treated using 3D conformal (3D) technique and 29 were treated using IMRT. There was no statistically significant difference in median LRR-FS (32.1 vs. not reached, log-rank p=0.93), DM-FS (32.1 vs. not reached, log-rank p=0.93), or OS (not reached vs. 28.9 mo, log-rank p=0.79) for patients whose MHD was below the median vs those whose MHD was above the median. The lack of association with OS also held true when looking at MHD as a continuous variable (Chi-square p=0.45). MHD was found to be significantly higher