Cureus

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Abstract
Published 02/11/2022

Incidence and Clinical Predictors of Local Failure in Patients with Localized Pancreatic Cancer Treated with Multi-Agent Chemotherapy followed by Stereotactic Body Radiation Therapy

Colin Hill [1], Shuchi Sehgal [2], Wei Fu [1], Chad Hu [3], Todd McNutt [4], Sarah Han-Oh [5], Joseph Herman [6], Jeffrey Meyer [1], Amol Narang [1]

1. Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, USA 2. School of Medicine, Philadelphia College of Osteopathic Medicine, Philadelphia, USA 3. Statistics, Johns Hopkins University School of Medicine, Baltimore, USA 4. Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, USA 5. Radiation Oncology & Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, USA 6. Radiation Oncology, Northwell Health Cancer Institute, New Hyde, USA

Corresponding author: Colin Hill, chill48@jhmi.edu

Categories: Radiation Oncology
Keywords: local failure, stereotactic body radiotherapy, pancreatic cancer

How to cite this abstract
Hill C, Sehgal S, Fu W, et al. (February 11, 2022) Incidence and Clinical Predictors of Local Failure in Patients with Localized Pancreatic Cancer Treated with Multi-Agent Chemotherapy followed by Stereotactic Body Radiation Therapy. Cureus 14(2): a715

Abstract

Objective: With improved systemic control from the use of multi-agent systemic therapy, local intervention has become increasingly important in patients with borderline resectable (BR) or locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC). In the pre-operative setting, stereotactic body radiation therapy (SBRT) can theoretically increase the rate of margin negative and decrease the rate of local recurrence. In the unresectable setting, SBRT can help improve local progression-free survival (LPFS) and thereby minimize complications from local progression. However, in either scenario, optimal dose and field design have not been well characterized. A better understanding of the incidence and predictors of local failure can help inform these considerations. Herein, we report on patterns of failure and clinical predictors of local failure in a modern series of BR/LA patients treated with SBRT at a high-volume institution.

Methods: Consecutive BR/LA PDAC patients treated with upfront multi-agent chemotherapy followed by five fraction SBRT administered at our institution between 2015 and 2018 were retrospectively reviewed. SBRT was delivered on consecutive weekdays. Active breathing control (ABC) was primarily used for motion management, with a minority of patients (3.2 %) treated using a free-breathing approach. Daily on-board cone-beam computed tomography (CT) was used for set-up, with daily alignment to endoscopically placed fiducials. The target volume generally incorporated gross disease and the full circumference of involved vasculature at the level of gross disease. Multiple breath-hold CTs were acquired at simulation to define a "patient-specific" margin that accounted for breath-hold variation, with a further 2mm expansion to generate the planning tumor volume (PTV). Patterns of initial failure were collected and are descriptively presented. Local recurrence after surgery was defined as evidence on imaging of disease arising in the post-op surgical bed, including local vasculature and locoregional nodal basins. In the unresectable setting, local progression was defined as growth of the primary tumor. Univariate (UVA) and multivariable analyses (MVA) were performed to determinate predictors of local progression-free survival. Kaplan-Meier survival analysis was performed to characterize local progression-free survival (LPFS), stratified by specific variables of interest.

Results: Over the time period, 156 BR/LA PDAC patients were treated at our institution with upfront chemotherapy followed by SBRT, with 92 patients (59.4%) having LA disease at diagnosis. Upfront chemotherapy entailed FOLFIRINOX in 117 patients (75%), and Gemcitabine/Abraxane in 37 patients (23.7%). Greater than four months of upfront chemotherapy were administered to 126 patients (80.8%). The median dose of SBRT delivered was 33 Gray (Gy) in five fractions (30-36 Gy). The median gross tumor volume (GTV) and PTV, respectively, were 57.4 and 87.3 cubic centimeters (cc). The median percentage of the GTV and PTV receiving 33 Gy was 97% and 88%, respectively. After chemotherapy and radiation, 130 patients (84%) were surgically explored with 106 patients (68%) successfully undergoing gross resection. Of patients who underwent gross resection, 97 patients (92%) were margin negative, 63 patients (59%) were node-negative and 8 patients (8%) demonstrated a pathologic complete response (pCR). Median local progression free survival (LPFS) after SBRT was 14.1 mo. (95% CI: 12.1 to NR). Of 106 patients taken to surgery, first failure was local in 16 patients (15%), distant in 46 patients (43%), and synchronous in 18 patients (17%). Therefore, out of 106 patients taken to surgery, 32% experienced local failure as a component of first failure, and 43% of all failures included a component of local failure. Of the 50 patients that were unresectable, first failure was local in 3 patients (6%), distant in 15 patients (3%), and synchronous in 10 patients (20%). Therefore, out of 50 unresectable patients, 26% experienced local failure as a component of first failure, and 46% of all failures included a component of local failure. On UVA, tumor

grade at biopsy, duration of neoadjuvant chemotherapy, greater than four months of neoadjuvant chemotherapy, ability to undergo gross resection, and receipt of adjuvant chemotherapy were all significant predictors ($p<0.05$) of LPFS, but only CA 19-9 greater than 90 U/mL, defined as a time-dependent covariate, remained significant on MVA (HR 2.24, 95% CI 1.31-3.84, $p<.05$). Among patients who survived without local failure 3 months after SBRT, Kaplan-Meier analyses showed improved LPFS in patients who successfully underwent resection (15.9 vs. 11.8 mo., $p<0.01$); among all the patients who had SBRT, LPFS was longer in patients who had greater than four months of induction chemotherapy (15.4 vs. 11.3 mo., $p<0.02$). Interestingly, stage of disease at diagnosis did not impact LPFS (15.5 mo. for LA vs. 13.3 mo for BR, $p=0.49$).

Conclusion: In patients with BR/LA pancreatic cancer treated with upfront chemotherapy and SBRT and who underwent gross total resection, margin negative rate was high (>90%). Despite this, local failure remained a common pattern of initial failure. In the unresectable setting, local failure was also a common pattern of initial failure. These findings highlight the need to further optimize radiation therapy in this population, perhaps through escalation of radiation dose and/or modification of field design.