Trials and technology to advance gastrointestinal oncology: imagination, imaging and the intertwined imperfections.

In this edition of the Gastrointestinal Oncology Scan, we would like to first acknowledge Dr. Raldow who will be rotating off of the GI section after completing a 3-year term as an associate section editor. Dr. Raldow has consistently been an insightful and diligent member of the editorial team, and we sincerely thank her for her service and dedication. Also, Dr. Jeffrey Olsen will be completing his term as GI section editor and we thank him for his mentorship and leadership as section editor for the past 3 years. We are pleased to announce that Dr. Michael Chuong will transition from GI associate section editor to serve in this role. We are excited for Dr. Chuong to lead the GI section and ensure that the Red Journal continues to feature GI studies of the highest quality. We are also delighted to welcome Dr. Eric Miller from The Ohio State University, and Dr. Jonathan Ashman from Mayo Clinic Scottsdale to the GI editorial team. Both were selected based on exception performance as Red Journal reviewers, and we are grateful to have such a talented addition to the editorial team. Dr. Olsen would like to thank Dr. Sue Yom and the entire editorial team at the International Journal of Radiation Oncology Biology and Physics for the opportunity to have contributed to the mission of the journal, facilitating publication of high impact studies which ultimately raise the level of care provided to our patients.

In this edition of Oncoscan, we present several high impact upper GI studies relevant to our field. For gastric and gastro-esophageal junction (GEJ), the Neo-PLANET trial demonstrated safety and encouraging pathologic complete response with camrelizumab and chemoradiation (CRT) as neoadjuvant treatment for gastric and GEJ tumors. ESPAC 5 evaluated neoadjuvant therapies versus surgical resection alone in borderline resectable pancreatic head adenocarcinoma. While the trial demonstrated superior outcomes with neoadjuvant therapy, it raises important questions regarding practice bias. The SMART pancreas trial prospectively demonstrated that ablative 5-fraction stereotactic MR-guided adaptive radiation therapy for pancreatic cancer did not cause grade ≥3 or higher gastrointestinal toxicity definitely attributed to radiation therapy. These studies highlight the critical role of radiation oncologists in accurately evaluating the value of emerging therapies and treatment modalities while overcoming historical biases in clinical trial design and standard practice.

Neo-PLANET
Summary

Tang et al report the primary outcomes from the single arm phase II Neo-PLANET trial[1], which assessed neoadjuvant camrelizumab with CRT for patients with locally advanced stomach or GEJ adenocarcinoma. Patients with resectable cT3-4aN+M0 disease age 18-75 years, with performance status ECOG 0-1 were eligible. All patients underwent endoscopic ultrasound, or CT/MRI imaging, and staging laparoscopy to exclude peritoneal metastasis before enrollment. Neoadjuvant treatment consisted of induction chemotherapy with oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily on days 1-14 for a 21-day cycle (XELOX). CRT was initiated within 1 week after completion of induction XELOX, with radiotherapy prescribed to 45 Gy in 25 fractions utilizing IMRT. The clinical target volume (CTV) included gross primary and nodal disease, with elective nodal coverage. A 5-10 mm expansion was performed to comprise the planning target volume (PTV). Concurrent capecitabine (850 mg/m^2 twice daily) was given on each day of radiotherapy. An additional cycle of XELOX was given 2-3 weeks after CRT completion, with re-evaluation for resection 1-3 weeks later. Camrelizumab 200 mg every 3 weeks was given starting with initiation of induction chemotherapy for 5 cycles total until 3

weeks prior to surgery. Patients with resectable disease underwent gastrectomy with D2 lymph node dissection. Adjuvant XELOX for 4 cycles was recommended 4-6 weeks after surgery. The primary endpoint was pathologic complete response (pCR) rate (ypT0), with secondary endpoints of tpCR (ypT0N0) rate, major pathologic response (MPR) rate defined as <10% residual cells at the primary tumor, R0 resection rate, downstaging, progression free survival (PFS), and overall survival (OS). Biomarker analysis included correlation of clinical outcomes with PD-L1 expression, tumor mutational burden status (TMB), and microsatellite instability (MSI) status.

Among 36 patients enrolled, all had nodal involvement, with 30/36 patients (83%) having T4a disease, and 19/36 (53%) patients having tumors located at the GEJ. PD-L1 expression was assessed in 27/36 patients (75%) with 9/27 (33%) having a combined positive score (CPS) of 1 or more. MSI status was assessed in 33/36 patients (92%) with all tumors MSI-low. All patients received neoadjuvant therapy, and 32/36 completed neoadjuvant treatment as planned. One patient discontinued camrelizumab due to progression, and 3 discontinued due to adverse effects. Thirty-three patients underwent resection, with all achieving R0 resection. The rate of pCR, tPCR, and MPR in the full analysis set was 12/36 (33%, 95% CI 19-51%), 12/36 (33%, 95% CI 19-51%), and 16/36 (44%, 95% CI 28-62%), respectively. With a median follow-up time of 26 months, the 2-year PFS and OS rates were 67% and 76%, respectively. Grade $\geq$3 toxicity occurred in 28/36 (78%) of patients, with the most common toxicities reported including lymphopenia in 27/36 (75%) and leukopenia in 2/36 (5.6%). No grade 5 toxicity was observed. No correlation was observed between PD-L1 expression and pCR rate, although PD-L1 density was noted to significantly increase after neoadjuvant therapy.

Discussion

The combination of perioperative therapy and D2 gastrectomy is currently considered a standard treatment for locally advanced gastric and GEJ cancers. However, there is controversy regarding the optimal treatment regimen and the impact of pCR and R0 resection on survival outcomes. It has been demonstrated that CRT can alter the tumor immune microenvironment[2] by increasing the expression levels of immune checkpoints that subsequently elicit immune therapeutic responses to tumors[3]. The CheckMate-577 study demonstrated a survival benefit of adjuvant nivolumab after chemoradiation and resection of esophageal and GEJ tumors with residual microscopic disease[4].

However, the efficacy and safety of perioperative immunotherapy plus concurrent CRT in locally advanced gastric cancer remains poorly understood. Is immunotherapy more effective in the early stages of gastric and GEJ tumors when the tumor is still in situ? Does radiation induce neoantigen expression and enhance the immune response? The Neo-PLANET (NCT03631615)[1] phase II trial highlights the potential synergistic effect of combining neoadjuvant immunotherapy and CRT for locally advanced adenocarcinoma of stomach or gastroesophageal junction using the PD-1 antibody camrelizumab. This combination resulted in a pCR rate of 33.3% (95% CI, 18.6–51.0), MPR rate of 44.4% (95% CI, 27.9–61.9), and R0 resection rate of 91.7% in 36 patients with resectable, T3-4N+M0 adenocarcinoma of stomach or GEJ.

This small, single institution study indicates that CRT in addition to camrelizumab appears safe. However, the pCR rate is similar to previously reported CRT studies without immune therapy,[5–7] although cross study comparisons are limited given heterogeneity in patient populations. Importantly, before widespread clinical implementation is feasible, additional evidence based guidance on the use of ICI therapy in perioperative treatment of gastric and GEJ cancers,

patient selection criteria (with the exception of MSI high status) and treatment scheduling are needed.

ICI administration is not without challenges and associated immune-related adverse events can be severe and long-lasting. These issues must be addressed as ICI becomes integrated into treatment strategies for gastric and GEJ cancers. Establishing combination effectiveness will likely require long-term monitoring of survival in resource intensive clinical trials. KEYNOTE-585[8] and MATTERHORN[9] trials focus extensively on the role and potential of ICI, reflecting the global trend toward this treatment modality. However, radiotherapy is not incorporated in either trial. If pCR and MPRs are surrogates for survival outcomes, developing reliable surrogate biomarkers to assess the impact of ICI after combination of radiation and chemotherapy is paramount. Furthermore, maximizing upfront therapy potentially with radiation and immunotherapy could allow for organ preservation strategies, which have not been explored yet in gastric adenocarcinomas.

ESPAC 5
Summary

ESPAC5 was a multicenter, randomized, phase 2 feasibility trial evaluating neoadjuvant therapy prior to surgical resection for borderline resectable pancreatic head adenocarcinoma. Patients deemed candidates for chemotherapy, radiation therapy and surgery were screened at 16 centers in the UK and Germany. The four treatment groups included neoadjuvant gemcitabine plus capecitabine for two 3-week cycles, neoadjuvant FOLFIRINOX for four 2-week cycles, neoadjuvant CRT to 50.4 Gy in 28 fractions with concurrent capecitabine, and surgery alone. Patients that received neoadjuvant treatment underwent restaging contrast-enhanced CT imaging 4-6 weeks post-therapy. Those without progression underwent surgical exploration within 2 weeks. Postoperative therapy was at the treating physician's discretion. The primary objectives were to determine patient recruitment rate (defined as randomized patients relative to time in months a center was open for study) and surgical resection (number of patients with R0 or R1 resection). The study was powered to compare resection rate in patients receiving neoadjuvant therapy versus immediate surgery; no criteria was prespecified to establish superior resection rate in this feasibility study. Successful recruitment was defined as meeting the target accrual goal of 100 patients. Secondary objectives included determining R0 resection rate, toxicity, postoperative complication rate, 30-day post-operative mortality rate, response rate per RECIST 1.1, disease-free survival from date of surgery, local disease-free survival from surgery, overall survival from randomization, and quality of life per EORTC QLQ-C30.

Of the 478 patients screened for eligibility, 86 were assigned to a treatment group and included in the intention-to-treat analysis: gemcitabine and capecitabine (19 patients), mFOLFIRINOX (20 patients), CRT (16 patients), and immediate surgery (31 patients). The overall recruitment rate was 2.16 patients per month (25.92 per year). Planned pre-operative therapy was completed by 17 (100%) of patients in the gemcitabine plus capecitabine group, 15 (79%) in the mFOLFIRINOX group, and 12 (86%) in the CRT group. Of the 51 (59%) patients that underwent resection, 21 (68%) were in the immediate surgery group and 30 (55%) in the pooled neoadjuvant groups (p=.33). Three (14%) and seven (23%) patients had R0 resection in the immediate surgery and neoadjuvant therapy groups, respectively (p=.49) with rates of 18%, 18%, and 37% for the gemcitabine and capecitabine, mFOLFIRINOX, and CRT groups, respectively. Rates of pathologic lymph node involvement included 90% in the immediate surgery group compared with 64%, 73%, and 25% in the gemcitabine and capecitabine, mFOLFIRINOX, and CRT groups, respectively.

Surgical complications were similar between immediate surgery (50%) and neoadjuvant (38%) groups (p=.54). At restaging, no patients had a complete response, six (13%) had a partial response and seven (15%) had progressive disease. There were no deaths within 30 days of surgery. Adjuvant therapy was given to 17 (81%) and 26 (87%) patients in the immediate surgery and neoadjuvant groups, respectively. After a median follow-up of 12.2 months, 1-year overall survival was 39% for immediate surgery and 76% for combined neoadjuvant groups (p=.0052). 1-year overall survival was 78% for gemcitabine plus capecitabine, 84% for mFOLFIRINOX, and 60% for chemoradiotherapy groups (p=.0028). 1-year disease-free survival was 33% for immediate surgery and 59% for neoadjuvant therapies combined (p=.043). Grade 3 or higher toxicities were reported by 2 (7%) patients in the immediate surgery group and 17 (34%) patients in the neoadjuvant groups. There were no clinically significant differences in baseline and follow-up visits by quality-of-life questionnaire scores.

Discussion

The goal of a phase II trial is to assess whether a treatment regimen has sufficient "signal" of benefit to warrant further investigation in a definitive phase III trial[10]. As compared to larger phase III trials that have the potential to define new standards of care, phase II trials tend to be smaller in size and powered for intermediate secondary endpoints, rather than overall survival. Accordingly, ESPAC-5 was a modest-sized trial comparing four treatment strategies in borderline resectable pancreatic cancer with primary endpoints of recruitment rate and resection rate.

Notably, the target accrual of 100 patients over 4 years was not reached, despite opening the trial at 16 centers in 2 countries. Thirteen hospitals recruited 5 or fewer patients (median 3.5). This challenge emphasizes the difficulty of enrolling patients to trials of upfront surgery versus neoadjuvant therapy in pancreatic cancer, given patient preference and ingrained practice patterns despite the absence of level 1 evidence. Given the small numbers enrolling at most sites, there is potential for both selection bias and technical variation in delivery of treatment, which could limit interpretation of study findings. Future trials may employ the randomization paradigm of trials such as STABLEMATES (NCT02468024)[11], where patients are informed of their treatment randomization prior to agreeing to participate in the trial. Those who refuse randomization remain on an observational arm. While this may help overcome patient and perhaps even physician treatment preference and bias, the generalizability of the trial findings may be criticized[12].

There were no significant differences in resection rate with numerically more patients in the upfront surgery arm undergoing surgery (68% vs. 55%). This was due to progression of cancer precluding operative management in patients randomized to neoadjuvant therapy. However, only 14% (3/21) undergoing resection in the surgery arm had an R0 resection. This alone should discourage the use of upfront surgery in borderline resectable pancreas cancer.

Although a secondary endpoint, there was a sizeable improvement in 1-year overall survival with neoadjuvant therapy versus upfront surgery (39% vs. 76%, p=.0052). Among neoadjuvant treatment strategies, initial chemotherapy had better survival as compared to CRT (p=.0028). This led the authors to conclude that the preferred management strategy for borderline resectable pancreas cancer is "short course" chemotherapy without radiation. We agree that the two most important treatments for borderline resectable pancreas cancer are surgery and chemotherapy, and NCCN guidelines recommend starting with neoadjuvant chemotherapy. It is notable, however, that despite CRT alone being generally considered a sub-optimal treatment approach for a disease with such high competing risks of distant metastasis like pancreatic cancer, CRT was associated with the most significant improvements in locoregional surrogates

of response such as R0 resection and pathologic lymph node involvement. Additionally, survival outcomes of 39% with upfront surgery compared with 60% for CRT provide a signal of the independent effect of CRT upon survival for patients with borderline resectable pancreatic cancer, further supporting the continued consideration for pre-operative radiotherapy as a component of neoadjuvant therapy. Because the patients randomized to CRT in ESPAC-5 did not also receive neoadjuvant chemotherapy, it is unclear from this study whether the combination of radiotherapy with neoadjuvant chemotherapy would confer an additional benefit. Further study is needed to assess relative benefit from neoadjuvant chemotherapy or CRT, sequencing, and the optimal dose fractionation regimen.

SMART
Summary

The SMART trial (NCT03621644) was a multi-center open-label single-arm phase II prospective study of ablative stereotactic magnetic resonance (MR)-guided adaptive radiation therapy (SMART) for pancreatic cancer. Patients with either borderline resectable (BRPC), locally advanced pancreas cancer (LAPC) or medically inoperable per institutional criteria were eligible for enrollment after ≥3 months of any chemotherapy without disease progression. Other key eligibility criteria included adenocarcinoma histology and CA 19-9 ≤500 U/mL after chemotherapy. There was no maximum tumor size. The primary endpoint was the incidence of acute grade ≥3 gastrointestinal (GI) toxicity definitely related to SMART as determined by an independent Clinical Events Committee comprised of pancreatic cancer experts not otherwise involved in the design or conduct of the study.

One-hundred thirty-six patients (LAPC 56.6%, BRPC 43.4%) were enrolled across 13 sites in the United States, Italy, and Israel between January 2019 to January 2022. Most tumors were in the head of pancreas (69.9%), mean tumor size was 3.1 cm, and mean CA 19-9 prior to enrollment was 71.7 U/mL. The mean interval from completing chemotherapy until starting SMART was 1.3 months. Most patients received FOLFIRINOX (81.7%) either alone or sequentially with other chemotherapy.

All were treated on a 0.35 Tesla (T) MR-guided radiation delivery system (MR-linac 98.5%, MR-cobalt 1.5%) with a prescribed dose of 50 Gy in 5 fractions (biologically effective dose (BED)10=100 Gy). The gross tumor volume (GTV) included the primary tumor and any clinical involved locoregional lymph nodes. The study protocol was amended in April 2019 to allow for an optional clinical target volume (CTV) that was required to be prescribed the same dose as the GTV; its design was as per the discretion of the treating physician. The planning target volume (PTV) was 3 mm.

Continuous intrafraction cine-MR imaging, automatic beam gating, and on-table adaptive replanning were mandatory. On-table adaptive replanning (utilized for 93.1% of the 680 delivered fractions) was required if the predicted dosimetry indicated: 1) violation of any GI organ-at-risk (OAR) constraint, 2) <85% coverage of the GTV by the 95% isodose line, 3) favorable anatomic shift between the GTV and OARs such that adaptive replanning would improve target coverage. Prospective central quality assurance (QA) review was not required of the plans or contours prior to treatment. SMART was not delivered with concurrent systemic therapy. Chemotherapy after SMART was permitted at the discretion of the treating physician. Surgery was permitted within 90 days of SMART, and occurred in nearly one-third of patients (n=44), half (n=23) of whom underwent vascular resection that was venous only (65%), arterial only (13%), or arterial and venous (22%).

Median follow-up was 16.4 months from diagnosis and 8.8 months from SMART, with all patients having at least 90 days of follow-up after SMART except 6 who died within 90 days. The primary endpoint was met since no patient had acute grade ≥3 GI toxicity definitely related to SMART; the incidence of acute grade ≥3 GI toxicity probably/possibly related to SMART was 8.8%. Clavien-Dindo grade ≥3 surgical complications were reported in 20.5% of resected patients; grade 5 adverse events occurred in 3 patients who underwent vascular resection >5 weeks after SMART. 1-year local control and 1-year overall survival from SMART were 82.9% and 65.0%, respectively.

Discussion

This phase II trial utilized stereotactic MR-guided on-table adaptive radiation therapy (SMART) in the treatment of locally advanced or borderline resectable pancreatic ductal adenocarcinoma (PDAC). Traditionally, radiation therapy for PDAC has utilized non-ablative doses to avoid damaging nearby organs, with significant toxicity previously published for ablative intent treatment delivered in 3-5 fractions[13,14]. The limitations of current CT-based technology in visualizing and avoiding radiation to sensitive organs have deterred radiation dose escalation, especially in hypofractionated PDAC treatment. However, recent studies have suggested that higher doses of radiation may improve tumor control[15].

The SMART study explored the potential benefits of dose escalation with an ablative prescription dose of 50 Gy in 5 fractions. The primary objective of the trial was to assess the incidence of acute grade 3 or higher GI toxicity definitely related to SMART, and the observed incidence of events definitely related was 0%. While some patients experienced severe complications, it is uncertain whether these were attributed to SMART. The study highlights the importance of caution when considering surgery, particularly with vascular resection, after ablative radiation therapy.

Strengths of the study include participation across multiple (international) sites and the large number of enrolled patients. However, there are limitations such as the variability in chemotherapy regimens prior to study enrollment and a CA 19-9 limit of 500 U/mL that may have influenced overall survival outcomes. Moreover, the inclusion of locally advanced and borderline resectable patients in addition to the frequent use of surgery after SMART adds complexity in interpreting the results. Further, the investigators permitted a CTV at the discretion of the prescribing physician. Without clear guidelines in the parameters for CTV contouring, it is not clear how to apply this trial's target coverage guidelines in clinical practice.

Adaptive radiation therapy also requires new contours of the patient anatomy for each fraction. The risk of inaccurate contours due to time constraints or peer coverage is inherent to this process. The wide range of experience in the centers participating on the trial as well as no central review prior to each adaptive treatment (which would not be practical or feasible) raises the question of whether outcomes may have been improved with more rigorous quality control or at more experienced centers. However, these data are likely representative of "real life" adaptive treatments compared to previously published single institution studies from high volume centers[16,17]. Longer follow-up and patient-reported quality of life outcomes are planned for future evaluation. Further research[18] is necessary to better understand the long-term treatment outcomes and potential benefits of this novel treatment approach, and how it compares to other ablative regimens[19]. Comparison to other adaptive platforms, such as CBCT guided adaptive radiation therapy utilized in the ongoing ARTIA-Pancreas trial[20], will also be warranted.

References

1. Tang Z, Wang Y, Liu D, et al. The Neo-PLANET phase II trial of neoadjuvant camrelizumab plus concurrent chemoradiotherapy in locally advanced adenocarcinoma of stomach or gastroesophageal junction. *Nat Commun*. 2022;13(1):6807. doi:10.1038/s41467-022-34403-5

2. McLaughlin M, Patin EC, Pedersen M, et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. *Nat Rev Cancer*. 2020;20(4):203-217. doi:10.1038/s41568-020-0246-1

3. Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. *Pharmacol Ther*. 2021;221:107753. doi:10.1016/j.pharmthera.2020.107753

4. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021;384(13):1191-1203. doi:10.1056/NEJMoa2032125

5. Ajani JA, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol Off J Am Soc Clin Oncol*. 2006;24(24):3953-3958. doi:10.1200/JCO.2006.06.4840

6. Ajani JA, Mansfield PF, Janjan N, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol*. 2004;22(14):2774-2780. doi:10.1200/JCO.2004.01.015

7. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *N Engl J Med*. 2012;366(22):2074-2084. doi:10.1056/NEJMoa1112088

8. Bang YJ, Van Cutsem E, Fuchs CS, et al. KEYNOTE-585: Phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. *Future Oncol Lond Engl*. 2019;15(9):943-952. doi:10.2217/fon-2018-0581

9. Janjigian YY, Van Cutsem E, Muro K, et al. MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. *Future Oncol*. 2022;18(20):2465-2473. doi:10.2217/fon-2022-0093

10. Torres-Saavedra PA, Winter KA. An Overview of Phase 2 Clinical Trial Designs. *Int J Radiat Oncol Biol Phys*. 2022;112(1):22-29. doi:10.1016/j.ijrobp.2021.07.1700

11. Timmerman R. *JoLT-Ca A Randomized Phase III Study of Sublobar Resection (SR) Versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients With Stage I Non-Small Cell Lung Cancer (NSCLC), The STABLE-MATES Trial*. clinicaltrials.gov; 2023. Accessed December 31, 2022. https://clinicaltrials.gov/study/NCT02468024

12. Subramanian MP, Meyers BF. Surgical Resection Versus Stereotactic Body Radiation Therapy for Stage I NSCLC: Can Randomized Trials Provide the Solution? *Cancers*. 2018;10(9):310. doi:10.3390/cancers10090310

13. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2005;76(1):48-53. doi:10.1016/j.radonc.2004.12.022

14. Courtney PT, Paravati AJ, Atwood TF, et al. Phase I Trial of Stereotactic Body Radiation Therapy Dose Escalation in Pancreatic Cancer. *Int J Radiat Oncol Biol Phys*. 2021;110(4):1003-1012. doi:10.1016/j.ijrobp.2021.02.008

15. Mahadevan A, Moningi S, Grimm J, et al. Maximizing Tumor Control and Limiting Complications With Stereotactic Body Radiation Therapy for Pancreatic Cancer. *Int J Radiat Oncol Biol Phys*. 2021;110(1):206-216. doi:10.1016/j.ijrobp.2020.11.017

16. Hassanzadeh C, Rudra S, Bommireddy A, et al. Ablative Five-Fraction Stereotactic Body Radiation Therapy for Inoperable Pancreatic Cancer Using Online MR-Guided Adaptation. *Adv Radiat Oncol*. Published online June 25, 2020. doi:10.1016/j.adro.2020.06.010

17. Chuong MD, Bryant J, Mittauer KE, et al. Ablative 5-Fraction Stereotactic Magnetic Resonance–Guided Radiation Therapy With On-Table Adaptive Replanning and Elective Nodal Irradiation for Inoperable Pancreas Cancer. *Pract Radiat Oncol*. Published online September 16, 2020. doi:10.1016/j.prro.2020.09.005

18. Viewray Inc. *Locally Advanced Pancreatic Cancer Treated With ABLAtivE Stereotactic MRI-Guided Adaptive Radiation Therapy (LAP-ABLATE)*. clinicaltrials.gov; 2022. Accessed December 31, 2022. https://clinicaltrials.gov/study/NCT05585554

19. Reyngold M, O'Reilly EM, Varghese AM, et al. Association of Ablative Radiation Therapy With Survival Among Patients With Inoperable Pancreatic Cancer. *JAMA Oncol*. 2021;7(5):735-738. doi:10.1001/jamaoncol.2021.0057

20. Varian, a Siemens Healthineers Company. *A Prospective Trial of Stereotactic Adaptive Radiation Therapy for Borderline Resectable/Locally Advanced Pancreatic Cancer: An Individualized Approach to Minimizing Gastrointestinal Toxicity (ARTIA-Pancreas)*. clinicaltrials.gov; 2023. Accessed December 31, 2022. https://clinicaltrials.gov/study/NCT05764720