Review Article

Ablative radiation therapy advances in pancreatic cancer

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Abstract: The addition of combined conventional radiation to systemic therapy for both borderline and locally advanced pancreatic cancer (LAPC) has questionable benefits, with no clear survival advantage beyond chemotherapy alone. Advancements within the field of radiation oncology has enabled safe delivery of dose escalated and ablative radiation therapy for pancreatic adenocarcinomas. Delivery of radiation therapy in pancreatic cancers is complicated by the anatomic location of the pancreas. Historically, gastrointestinal toxicity has been a major limiting factor in the delivery of escalating doses of radiation for pancreatic cancer. However, with the advent of improved radiation delivery techniques and image guidance, administering escalated doses of radiation for pancreatic cancer has become more feasible. Improvements in image guidance, integrated boosting, nonhomogeneous dosing schema, and adaptive replans have allowed for escalated doses safely to the pancreas. Current, nonrandomized data, suggest improvements in local regional control as well as overall survival compared to historical controls. While the technology has been made more readily available to implement this escalated technique, the benefit of this approach in reference to key variables such as regional control and overall survival remain to be further evaluated and tested in reference to the current standard dosing approach. Herein, a review on current data for escalated and ablative regimens will be reviewed. Additional prospective studies are needed to further improve the use of ablative radiation in pancreatic cancer.

Keywords: Pancreatic cancer; stereotactic body radiation therapy (SBRT); ablative

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Introduction

The incidence of pancreatic cancer is increasing throughout the world due to the aging population as well as increase in the prevalence of modifiable risk factors such as obesity and diabetes (1). According to the American Cancer Society, the number of estimated new cases of pancreatic cancer in 2022 is 62,210 and the number of estimated deaths is 49,830, making it the third leading cause of death from cancer in men and women combined. Furthermore, pancreatic cancer ranks last in prognostic outcomes out of all cancer sites with a 5-year survival rate of 11% (2). Survival rates for pancreatic cancer are low due to the advanced stage at diagnosis. Only about 20% of patients present with early stage, surgically resectable cancer, and for the patients that undergo resection, the five-year survival rate is still less than 25% (1).

Surgery, if possible, is often considered the most effective treatment for pancreatic cancer. However, many patients present with locally advanced pancreatic cancer (LAPC), borderline resectable pancreatic cancer (BRPC) which are unresectable. Thus, both chemotherapy and radiation therapy (RT) are ways to downstage tumors until they become resectable. For treatment of borderline resectable

cancer, the American Society for Radiation Oncology (ASTRO) conditionally recommends either a neoadjuvant therapy regimen of systemic chemotherapy followed by conventionally fractionated RT with chemotherapy or a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction stereotactic body radiation therapy (SBRT). For treatment of unresectable pancreatic cancer, ASTRO conditionally recommends a definitive therapy regimen of systemic chemotherapy followed by either conventionally fractionated RT with chemotherapy, dose-escalated chemoradiation, or multifraction SBRT without chemotherapy (3). Historically, mostly conventional or palliative RT regimens (e.g., 30 Gy in 10 fractions or 50–54 Gy in 25–28 fractions) have been used for pancreatic cancer since escalation in dose would have been limited by toxicity. These regimens have not shown a difference in survival when compared to chemotherapy alone and usually provide a local control benefit only, which was demonstrated in the phase 3 LAP-07 trial (4,5). Since improvements in systemic chemotherapy regimens have been shown to increase overall survival as well as metastases free survival and approximately 30% of patients are estimated to die of locally destructive disease, there has been renewed interest in utilizing modern technological advances to investigate the benefit of dose escalated, or ablative, radiation (6,7). The evidence for this is slowly emerging, and primarily retrospective in nature. The doses utilized, volumes treated, and heterogeneity have considerable variance at this time. Prospective, randomized studies will be needed to further ascertain the clinical benefits that high dose radiation can yield and the role it plays in the paradigm of pancreatic cancer management.

Definitions

The use of the terms "ablative radiation" and "stereotactic body radiation therapy (SBRT)" is inconsistent within the radiation oncology community. Oftentimes, SBRT is equated with the delivery of ablative radiation, which some argue is not always the case (8). For example, the American Association of Physics in Medicine (AAPM) Task Group 101 defines SBRT fairly generally as delivery of a high doses of radiation in a few fractions which result in a high biologically effective dose (BED). Task Group 101 most importantly emphasizes that the stereotactic component is utilizing proper image guided radiation therapy (IGRT) to help localize the internal targets, making a traditional external body frame obsolete (9).

While a precise definition of SBRT will vary slightly depending on national society guidelines, generally some define ablative SBRT as 5 or less fractions of radiation or 100 Gy in BED plus 5 or less fractions (10). While in disease sites such as lung cancer, ablating the tumor to at least a minimum dose of 100 BED is easily achievable, certain challenges exist with pancreatic cancer due to its proximity to luminal GI organs. Using longer fractionation schemes such as 15 or 25 can also be called, "ablative" albeit not SBRT if it achieves 100 Gy of BED. With pancreatic cancer, ablative doses can be delivered to a portion of the tumor, but the minimum dose to the tumor (dose that covers 100% volumetrically) can be quite low in comparison due to compromises required. Therefore, there is often heterogeneity in the treatment plan.

Rationale for dose escalation

Pancreatic cancers are known to have areas of significant tumor hypoxia, which yields cells that are more resistant to radiation than aerobic cells. Pancreatic cancers express median oxygen levels of less than 0.7% compared to the adjacent normal pancreatic tissue of 1.2–12.3%. Hypoxic cells are less sensitive to chemotherapy and radiation therapy. However, the relationship between oxygen response and radiation sensitivity of a tumor generally is inversely hyperbolic after about 0.5% oxygen, suggesting that considerably higher doses of radiation would be necessary to balance out the hypoxic environment of pancreatic cancer. In fact the oxygen enhancement ratio would suggest that approximately double the doses of radiation would be necessary for this value (11). Furthermore, the more hypoxic environment induces an immunosuppressive stroma (12-14). This stroma is filled with inflammatory factors that are hypothesized to increase tumor resistance to both chemotherapies and immunotherapies. Cancer associated fibroblasts (CAFs) are the main producers of the stroma in pancreatic adenocarcinoma. In mouse models, increased numbers of CAF are found in areas of hypoxia versus areas of normoxia in pancreatic adenocarcinoma. The same study showed that hypoxia can also drive CAF formation *in vitro* (13). Other factors that play a role in CAF formation are the hypoxia-inducible factors (HIFs). These factors also exist in the stroma to mediate the cellular response to hypoxia and contribute to the resultant therapeutic resistance of pancreatic adenocarcinoma (14). While more research is being done on potential immunotherapies to overcome this treatment resistance, dose-escalation

radiotherapy should be considered as another possible method of overcoming the hypoxic and immunosuppressive environment of pancreatic cancers. This suggests that conventional doses, such as those used in the LAP-07 trial, are likely not sufficient to cause adequate radiation induced cytotoxicity. Escalating the dose of radiation in an ablative fashion could potentially induce a more effective dose response.

Background on radiation in locally advanced and borderline resectable disease

Radiation has a role in both LAPC and BRPC. Within National Comprehensive Cancer Network (NCCN) guidelines, there are a multitude of options for the treatment of LAPC, including omission of radiation for LAPC (4). Currently per NCCN guidelines, LAPC can be treated with chemotherapy alone, or adding sequential chemoradiation. Due to the LAP-07 trial, the benefit of sequential chemoradiation has been questionable. Patients were given induction gemcitabine or gemcitabine/erlotinib and if there was no progression, then patients were randomized to chemoradiation to 54 Gy with concurrent capecitabine. Median survival was 16 months in the systemic therapy arm and 15.2 months in the chemoradiation arm (P=0.83). There was a significant difference, however, between local progression which was 32% *vs.* 46% (P=0.03) in the chemotherapy arm *vs.* the chemoradiation arm (4).

Recently, the Alliance for Clinical Trials in Oncology Trial A021501 also raised into question the benefit of radiation for borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC). This trial examined the difference between preoperative extended chemotherapy *vs.* chemotherapy plus hypofractionated radiation therapy in BR-PDAC patients (15). In 2016, a predecessor single arm trial A021101 treated patients to 50.4 Gy in 28 fractions (BED10 =59.47 Gy). The overall survival rate of all patients at 18 months was 50%, and 68% of patients underwent pancreatectomy with an R0 rate of approximately 93% (16). In the second trial, A021501, 126 patients received induction chemotherapy. They were then randomized into two treatment arms. Arm A (n=70) received chemotherapy alone while arm B (n=56) received chemotherapy followed by SBRT to (33–40 Gy in 5 fractions, BED10 =49.5–72 Gy, n=35) or hypofractionated image guided radiation therapy (25 Gy in 5 fractions, BED10 =37.5 Gy, n=5). It is worth noting, the SBRT delivered was not ablative, as the BED were considered low. Afterwards, those with a performance status (PS) of 0 or 1 underwent pancreatectomy. The median overall survival (OS) was 31 and 17.1 months in Arm A and B, respectively. The study concluded that when compared to historical data, chemotherapy alone was associated with favorable OS while chemotherapy plus RT was not (15,17). However, there are multiple issues with this study. It is important to firstly recall that these arms, while randomized, were not powered to be compared to one another. There also was considerable imbalance in the arms. The radiation arm had a higher baseline level of carbohydrate antigen 19-9 (CA19-9), of nearly 100 ng/mL higher. Patients were also randomized upfront and not after completing induction chemotherapy to ensure there was no progression in each arm. Not surprisingly, many patients were unable to proceed to surgery or were unable to complete surgery following RT due to progression either locally or distantly. The interim analysis was based on an R0 endpoint leading to early closure and an R0 rate not consistent with other literature (18). This trial should not be utilized as a definitive answer yet for the role of radiation in borderline disease, let alone ablative radiation. Further trials investigating SBRT in this setting will be important to qualify the role.

Delivery of ablative radiation

Delivery of radiotherapy in pancreatic cancers is complicated by the anatomic location of the pancreas. There are no set guidelines, however the ones below will detail how it has practically been used in both retrospective series as well as prospective studies. Ablative radiation can be delivered between 5–25 fractions, can utilize CT or MRI guidance, and can include adaptation. Attention must be utilized during simulation, contouring, planning, and most importantly, onboard imaging to ensure safe delivery. Due to the close proximity of the pancreas to the gastrointestinal tract where radiation induced toxicity can cause multiple adverse events, a careful approach is required. The majority of current SBRT for pancreatic cancer is given in BED10 doses of (54 to 72) to avoid GI toxicity. Ablative radiotherapy would require giving approximately 100 Gy in BED, although some users aim for more modest levels to avoid toxicity. In order to safely deliver these ablative doses of radiation, Crane *et al.* outlines a treatment strategy that uses fractionation, CT image guidance, intentional dose heterogeneity, respiratory gating, and simultaneous integrated dosing with sensible volumes (19). Dosing depends on user comfort and available technology. Possible

approaches include utilizing 75 Gy in 25 fractions (if within 1 cm of luminal GI structures) or 67.5 Gy in 15 fractions to the high dose volume (if greater than 1 cm away).

Patients can first be simulated using diagnostic CT pancreatic protocol. Fiducial markers or a metal biliary stent can be placed first to best align to the tumor during image guidance, although this may not be necessary if using MRI guidance (20). However, aligning to biliary stents should be done with caution (19,21). With alignment and shifting on the machine, utilizing fiducials and soft tissue anatomy may allow for better targeting of the tumor. Caution should be performed before aligning strictly to bony anatomy as this may irradiate more luminal GI structures (22). The protocol involves giving 150 mL iodinated contrast at 5 mL/s with imaging at 45s and between 1.5 and 2 minutes after the start of contrast administration (23). Patients can also be given loperamide to slow bowel movements and a half-cup of water to differentiate between duodenum and gross tumor volume (GTV) (24). A common method to protect the GI tract and better target the tumor volume is respiratory motion control, which can be achieved via 4D-CT images, gating, abdominal compression, or end expiratory breath hold techniques (25). Breath hold involves a feedback-guided inspiratory breath hold or if the patient is unable to hold their breath for treatment, end expiratory gating during free breathing can be used. This helps to minimize intrafraction motion. While there are a few treatment strategies, one strategy uses intensity-modulated radiation therapy (IMRT) with a simultaneous integrated boost (SIB) and simultaneous integrated protection (SIP). In this method there are usually 3–4 separate volumes. There is an elective volume which covers the regional lymph nodes, one which encompasses the tumor and tumor vessel interface (high dose PTV aiming for BED of 100), and an intra GTV boost, shaped by safety expansions on the GI luminal structures and a contracted dose to the hypoxic core.

During the planning process it is imperative to not exceed constraints to the OARs. The minimum dose to the GTV (the highest isodose line covering 100% of the GTV volume) will be variable depending on proximity to the relevant organs at risk. Allowing for escalation of the hotspot (usually the doses to 0.035 cc) within the tumor itself to the hypoxic core can allow for more conformality of higher dose volumes that encompass the GTV itself.

The luminal GI structures (or iBowel if using 4D-CT) can be visualized with cone-beam CT image guidance, CT-on-Rails, or with MRI linear accelerators (MRL). Daily adaptive planning using novel MRL can be used to account for the day-to-day differences in organ position. Daily imaging can be used with this technique in order to align the clinical target volume (CTV) based on stimulation for each fraction. Depending on the changes in positioning, the OARs might need to be re-contoured or a new plan must be generated (23). Furthermore, high dose isodose lines from the planning process should be visualized on the cone beam to ensure that there is not excessive dose being delivered to the luminal structures.

Of note, early studies on the use of online adaptive radiotherapy either alone or in conjunction with cone beam CT-guided stereotactic adaptive radiotherapy (CT-STAR) show promise in the treatment of pancreatic cancer. Milder *et al.* published a report in early 2022 demonstrating the feasibility of online adaptive SBRT on a robotic radiosurgery system (26). Four patients with LAPC and four patients with lymph node oligometastases received repeat CTs. For both tumor sites, a dummy run was completed, which demonstrated an in-room treatment time that was similar to other online adaptive SBRT techniques but 2.5 times longer than standard treatment delivery. Then, in late 2022, Kim *et al.* published the first case report on the use of CT-STAR on a patient with pancreatic cancer. The patient received 35 Gy in 5 fractions (BED10 =59.5 Gy) without complications (27). This method of delivering radiation decreased the number of critical OAR hard constraint violations. However, the patient eventually passed away several months after treatment due to local progression. Schiff *et al.* also published a study on the use of CT-STAR for LAPC in late 2022 (28). In this study, eight patients received five additional cone-beam CTs using the ETHOS system either before or after their original radiation treatment. The use of CT-STAR in this study decreased the number of OAR constraint violations from 94 (using non-adaptive SBRT) to one. Thus, the study concluded that CT-STAR was dosimetrically superior to non-adaptive SBRT.

Novel MRI linear accelerators can make image guidance, and adaptation considerably easier. There are several vendors and several work flows that can be performed. In brief, patients can have a combined MRI simulation and CT simulation for contouring prior to plan delivery. Utilizing the 1.5 T unity, after creating a step and shoot IMRT plan, patients receive a pretreatment MRI prior to delivery which can be fused to the CT simulation with a rigid technique. An adapt to shape adjustment and new plan can be then delivered prior to delivery (29). Furthermore, using a 0.35 T unit, patients can receive on board adaptations where in addition to superior visualization of luminal GI organs

for image guidance, a new plan can be generated for the patient's daily anatomy, especially as bowel fill can alter. This can safely readjust and ensure the luminal organs are not in the high dose regions (30).

Radiation dose escalation

Koong *et al.* explored ablative radiation ranging from 15 Gy (n=3), 20 (n=5), and 25 Gy (n=7) in one fraction (31). Seven patients were treated with 25 Gy in 1 fraction (BED10 =87.5 Gy). Median OS was 8 months, and all achieved local control until death or at last follow-up at 7 months. No Grade 3+ toxicity was observed. However, the dose escalation portion of this trial was stopped before reaching any dose limiting toxicity as the study reached its primary objective of local control. In a study from 2005, 22 patients were treated with 45 Gy in 3 fractions (BED10 =112.5 Gy) (32). Median survival from the time of first treatment was 5.7 months with 1-year survival of 5%. Acute grade 2+ toxicity was 79% and late grade 2+ toxicity was 94%. The authors concluded that they could not recommend ablative therapy due to the unacceptable toxicity and poor outcomes observed in this study. Since then, a Phase II study at Stanford University published in 2008 treated 16 patients with SBRT (25 Gy in 1 fraction, BED10 =87.5 Gy) by Cyberknife (33). The PTV with central maximal doses ranged from 32 to 40 Gy (BED10 134.4–200 Gy). Median survival from start of SBRT was 11.4 months with 1-year survival at 50%, and one-year freedom from local progression (FFLP) was 100%. Acute grade 2 GI toxicity was 13% and grade 3 was 6%. Late grade 2 GI toxicity was 33% and grade 3+ was 13%. The authors concluded that although SBRT showed comparable survival to conventional RT, the toxicities (especially duodenal ulcer development) were significant. In 2009, Stanford conducted a study where 77 patients were treated with a single fraction of SBRT of 25 Gy (BED10 =87.5 Gy) (34). The median OS from SBRT was 6.4 months and the FFLP at 1-year was 84%. Grade 2+ acute toxicity was seen in 5% of patients. Grade 2 and grade 3+ late toxicity was seen in 4% and 9% of patients, respectively.

In 2010, Mahadevan *et al.* published a study where 36 patients with nonmetastatic, unresectable pancreatic cancer were treated with 24–36 Gy of SBRT in three fractions of 8, 10, or 12 Gy (total BED10 =43.2–79.2 Gy), depending on the relationship between the tumor location and the duodenum (35). Patients then underwent 6 months of gemcitabine chemotherapy. For all patients, the median OS from start of SBRT was 14.3 months, and the local control rate was 78% at 24 months. No difference in outcomes was observed among the different dose groups, but the statistical power to detect this was limited by the number of patients. Grade 2 toxicity was 25%. Acute and late grade 3+ toxicity was 8% and 6%, respectively. Polistina *et al.* also published a prospective study of 23 patients treated with SBRT (30 Gy/3 fractions, BED10 =60 Gy) (36). Median OS from diagnosis was 10.6 months, and at 6 months, 9 of the remaining 11 patients (82%) demonstrated local control. No grade 2+ or late toxicities were observed. However, the radiation dose used in this study was not ablative. In a study published in 2011, Stanford conducted another phase II trial where 20 patients were treated with a single fraction of SBRT of 25 Gy (BED10 =87.5 Gy) (37). This time, SBRT was delivered using a linear accelerator and a nine-field intensity-modulated radiotherapy technique. Median survival was 11.8 months with 1-year survival of 50%. FFLP was 94% at 1 year. Three patients (15%) developed grade 2 toxicity (ulcers), but there was no acute grade 3+ toxicities and only one (5%) late grade 3+ toxicity. Overall, this study demonstrated excellent local control but similar to the one in 2008, had comparable rates of duodenal toxicity.

In 2013, Tozzi *et al.* published a study where 30 patients with pancreatic adenocarcinoma were treated with gemcitabine and then SBRT (38). Twenty-five patients received 45 Gy in 6 fractions (BED10 =78.75) while 5 patients only received 36 Gy in 6 fractions (BED10 =57.6) due to dose constraints of organs at risk. The median OS was 11 months from SBRT. The difference in FFLP between the 45 Gy and the 36 Gy groups at 2 years (96% *vs.* 75%, respectively) demonstrates the difference made by dose reduction. Three patients (10%) received additional antiemetic drugs (grade 2 toxicity), and three patients (10%) presented with pain (grade 2 toxicity). There were no grade 3+ toxicities.

Chuong *et al.* conducted a study that was also published in 2013 where 73 patients with LAPC or BRPC were treated with 5 fractions of SBRT with a median dose of 35 Gy to the region of vessel involvement and 25 Gy to the remainder of the tumor (mean BED10 =63 Gy) (39). The median OS from the first day of any treatment for BRPC *vs.* LAPC patients was 16.4 *vs.* 15 months. Of the BRPC patients, 56.1% of patients underwent surgery. Of the remaining nonsurgical patients, the 1-year LC was 81%. The acute grade 3+ toxicity was 0%, and the late grade 3+ toxicity was 5.3%.

Published in 2015, a phase II study by Herman *et al.*

was conducted on 49 patients with unresectable LAPC. Patients received 3 doses of gemcitabine followed by a 1-week break and then SBRT (33 Gy in 5 fractions, BED10 =54.78 Gy) (40). After completing this, patients continued to receive gemcitabine until disease progression or toxicity. Median overall survival from diagnosis was 13.9 months and FFLP at 1 year was 78%. Acute grade 2+ GI toxicity was only 2%. Furthermore, the rate of late grade 2+ GI toxicities after this multifractionated SBRT (11%) was much less than that previously observed in the single-fraction SBRT regimen (47%) conducted by (Schellenberg *et al.*, 2008) (33).

Krishnan *et al.* published a retrospective study, which allowed for a variety of dose and fractionation to aid in determining if higher BED levels (at least 70) can yield better clinical outcomes (22). In this study, 47 out of 200 patients with unresectable tumors >1 cm from the luminal organs received dose-escalated IMRT at a BED >70 Gy (range: 70.4–100.0). The remaining patients received IMRT (n=13) or 3D-CRT (conformal radiation therapy) (n=140) at a BED ≤70 Gy. Importantly, the dose escalated volume was administered to the tumor with an additional 2 mm added on. When compared to the patients receiving BED ≤70, the patients in the dose-escalated cohort had increased median overall survival (17.8 *vs.* 15.0 months, P=0.03), 2-year survival (36% *vs.* 19%), and local-regional recurrence-free survival (10.2 *vs.* 6.2 months). All outcomes were measured from the time of chemoradiation start date. Of the patients in the high-dose cohort, Grade 2 toxicity was seen in 13 patients (28%) while grade 3 toxicity was seen in 1 patient (2%). No additional toxicity was noted in the high-dose cohort. Notably, in many cases the GTV did not receive prescription escalated (BED >70) dose to the entire tumor to protect the GI organs. Even in these instances, there was no difference seen in control within the escalated group. The study notes that the higher BED was a strong independent predictor of improved OS, and that the improved OS does not seem to be due to shorter follow-up, decreased size of tumors, increased frequency of surgical resection, or variations in therapeutic approach. While this study assessed a population with favorable anatomy, it speaks to the importance of modern technology and IMRT to help spare luminal GI structures

A phase II clinical trial published in 2017 by Quan *et al.* explored utilizing induction chemotherapy followed by stereotactic ablative radiation therapy (SABR) (36 Gy in 3 fractions, BED10 =79.2 Gy) on 35 patients with borderline resectable or locally advanced PDAC (41). Only 32 patients ended up qualifying for SABR. Median OS from the time of enrollment was 18.8 months, and the 2-year LPFS was 44.9%. There was no significant change in quality of life for patients before or after any of the treatments. There was also no grade 3+ acute or late toxicities observed with SABR treatment. However, there were two patients with grade 3 and two patients with grade 4 postoperative toxicities. Sutera *et al.* also published a retrospective study in 2017 comparing outcomes of one- *vs.* three-fraction SBRT for PDAC in 289 patients (42). The median dose for the single fraction was 24 Gy (range, 18–25, median BED10 =81.6 Gy). The median dose for the three-fraction therapy was 36 Gy (range, 24–36, median BED10 =79.2 Gy). Univariate analysis but not multivariate analysis showed higher 2-year OS in the multifraction therapy at 37.5% compared to 30.5% in the single fraction therapy. LC at 2 years in the single fraction versus the multi-fraction regimens was 56.8% and 69.7%, respectively. All outcomes were calculated from the start of SBRT. Late grade 3+ toxicity was 2.5% at 2 years based on Kalpan-Meier estimates with no significant difference between the single or multi-fraction therapies. Thus, the study demonstrated the benefit of multi-fractionation regimens of SBRT over single fractionation regimens.

In 2018, Bernard *et al.* published the initial results of a study on 49 patients with pathologically proven T1–4N0–1M0 PDAC with close or positive margins after resection (43). The patients were treated with SBRT (36 Gy in 3 fractions, BED10 =79.2 Gy). The median OS from enrollment was 23.7 months. Local, regional, and distant progression free survival at 2 years from completion of SBRT was 77%, 73%, and 49%, respectively. Grade 3+ toxicity was 4.1%. Goldsmith *et al.* also published a paper in 2018 on 42 patients with inoperable non-metastatic pancreatic cancer that were treated with CyberKnife SABR [18–36 Gy in 3 fractions, median BED10 =50.3 (47.7–53.0) Gy] (44). OS from start of SBRT was 8.4 months and median FFLP was 9.8 months. Grade 3 acute toxicities occurred in 8.1% of patients. Late toxicity was observed in 5 patients (15.6%), of which 4 (12.5%) patients showed grade 4 duodenal toxicities. Most importantly, the study noted that there was no association between toxicity and either maximum dose to PTV or prescription dose. Thus, they concluded that there is space to escalate SABR doses to a more effective BED >70 Gy without inducing toxicity.

Toesca *et al.* conducted a study published in 2020 on 149 patients who received multi-fraction SABR for unresectable PC (45). The median SABR dose was 33 Gy

(range: 20–45). 143 patients received 5 fractions (median BED =49.5 Gy) and 6 patients received 3 or 6 fractions. 72% of patients received gemcitabine-based chemotherapy while 21% received modified FOLFIRINOX. The median OS from diagnosis for all patients was 16 months. For patients treated with SABR dose ≥40 Gy (BED10 ≥72 Gy) *vs.* SABR dose <40 Gy (BED10 <72 Gy), median OS was 23 *vs.* 14 months, and median PFS was 13 *vs.* 10 months, respectively. For SABR dose ≥40 *vs.* <40 Gy, grade 2+ toxicity was 10% *vs.* 15%, and Grade 3+ toxicity was 6% *vs.* 7%, respectively. For SABR dose <40 Gy, there was one grade 4 and one grade 5 toxicity. The paper concluded that the combination of SABR dose ≥40 Gy and mFFX may be superior to SABR doses <40 Gy and gemcitabine-based chemotherapy because they showed superior median OS and PFS.

Jolissaint *et al.* at Memorial Sloan Kettering Cancer Center published a study in 2021 that compares overall survival and disease control in 104 patients treated with ablative dose radiotherapy (A-RT) (49.8%) *vs.* resection (50.2%) after induction chemotherapy (46). A-RT was delivered as 75 Gy in 25 fractions (BED10 =97.5 Gy) or 67.5 Gy in 15 fractions (BED10 =97.88 Gy). There was no difference in local control at 18-month between A-RT and resection (16% *vs.* 21%). However, the 18-month cumulative incidence of distant recurrence/progression for A-RT and resection was 58% and 30%, respectively. The median OS from completion of chemotherapy for A-RT *vs.* resection was 20.1 and 32.9 months, respectively. After A-RT, 25% patients had a toxicity/complication (complication with biliary stent =10.6%, upper GI bleeding =5.8%, new biliary obstruction =3.8%, vertebral body fracture =2.9%). After resection, 56.2% of patients had any complication, and 28.6% of those patients had a grade 3+ complication. The study concluded that although there was a 12.8-month survival difference in favor of resected patients, A-RT still had an encouraging median OS in addition to similar local control rates and toxicities to resection, showing its promise as a new treatment option.

Reyngold *et al.* published a trial in 2021 where 119 patients with localized, unresectable, or medically inoperable pancreatic cancer were treated with ablative radiation therapy (BED =98 Gy) using standard equipment (47). For tumors less than 1 cm from the stomach or intestines, 75 Gy in 25 fractions (BED =97.5 Gy) was delivered. For tumors greater than 1 cm from the stomach or intestines, 67.5 Gy in 15 fractions (BED =97.88 Gy) was delivered. Most patients (97.5%) also received induction chemotherapy. Median overall survival from diagnosis and A-RT was 26.6 and 18.4 months with 12- and 24-month OS at 74% and 38%, respectively. The 12- and 24-month local tumor progression rates were 17.6% and 32.8%, respectively. Ten patients (8%) developed grade 3 GI bleeding with no grade 4 or 5 events. This study emphasizes the importance of the fractionation scheme dependent on the location to luminal GI anatomy. The thought is that with increased fractionation, any interfraction setup variability on a particular treatment will have less of an OAR impact. While this requires further study, the rates of local failure in this study seem to approach the 30% failure rates seen in surgery, perhaps suggesting ablative radiation may be an appropriate alternative.

A phase II trial at Memorial Sloan Kettering Cancer Center (NCT03523312) is investigating the ability of ablative radiation plus chemotherapy to improve the possibility of surgery in patients with potentially resectable LAPC from historic controls of 15% to 30% (48). Patients will receive hypofractionated ablative IMRT (HFA-IMRT) (67.5 Gy in 15 fractions, BED10 =97.88 Gy or 75 Gy in 25 fractions, BED10 =97.5 Gy) to areas of gross tumor with concurrent capecitabine. Cross-sectional imaging will be repeated 4–6 weeks after the end of CRT to assess for resectability. R0 resection was 58%, and 2-year OS was 38.9%. The study met the prespecified endpoints.

MRI guided radiation therapy

While data is emerging regarding MRI guided radiation therapy, there needs to be continued prospective and randomized studies to best clarify its role regarding key clinical and toxicity endpoints. Hassanzadeh *et al.* published an experience on 44 patients receiving 50 Gy in 5 fractions (BED =100) (49). In this series, the goal was to prescribe at least 95% of the dose to 95% of the volume and to limit coverage when there were adjacent OARs. Readaptation occurred on 93% of all fractions. In this series, median overall survival was 15.7 months with low rates of Grade 3 bleeding (6.8%). This demonstrated the feasibility and safety of ablative radiation utilizing image guidance and replanning.

In a study published in 2019, Rudra *et al.* also showed that dose-escalation RT improves OS in patients with inoperable pancreatic cancer (50). This study used adaptive magnetic resonance imaging-guided radiation therapy (MRgRT) to compare outcomes in patients treated with high-dose RT (BED >70 Gy) and standard-dose RT (BED

≤70 Gy). The high-dose cohort consisted of 16 patients treated with high dose SBRT [40–52 Gy in 5 fractions, median BED =77.6 (72.0–106.1)] Gy and 9 patients treated with hypofractionated RT [50–67 Gy in 10–15 fractions, median BED =82.7 (67.8–97.9) Gy]. The standard-dose cohort consisted of 13 patients treated with conventionally fractionated RT [40–55 Gy in 25–28 fractions, median BED =55.5 (38.2–67.1) Gy] and 6 patients treated with conventional SBRT [30–35 Gy in 5 fractions, median BED =55.8 (48.0–59.5) Gy]. High-dose patients (n=24, 55%) had statistically significant improvement in 2-year OS from start of RT (49% *vs.* 30%, P=0.03) when compared to standard-dose patients (n=20, 45%). However, freedom from local failure at 2-year was not statistically significant when comparing high-dose to standard-dose (77% *vs.* 57%, P=0.15) and neither was freedom from distant failure at 18 months (24% *vs.* 48%, P=0.92). Grade 3+ GI toxicity occurred in 3 patients (7%) from the standard-dose cohort and in no patients from the high-dose cohort.

Preliminary results from Schaff *et al.* comparing stereotactic MR guided adaptive radiation therapy (SMART) to external beam RT with chemotherapy were published in 2020 (51). The study reviewed 29 patients that received standard RT (50.4 Gy in 28 fractions, BED10 =59.47 Gy) and 28 patients that received SMART (50 Gy in 5 fractions, BED10 =100 Gy). They analyzed outcomes using the Kaplan-Meier and log-rank tests, which demonstrated overall survival benefit in the SMART group (P=0.07). They also found statistically significant 180-day survival improvement in SMART patients when compared to chemoRT (94% *vs.* 70%, P=0.046). Outcomes were calculated from the start of RT. The grade 3+ GI toxicity at 90 days in SMART vs chemo RT patients was 11% and 28%, respectively, with the types of toxicity being comparable. Results from this study were used to support the ongoing clinical trial NCT03621644 with the primary objective being the demonstration of <15.8% acute grade 3+ GI toxicity to assess whether novel image guidance can improve this essential endpoint (52). Preliminary endpoint results for the single arm phase 2 SMART trial (NCT03621644 trial) were released in 2022 by Parikh *et al.* (53). The trial studied 136 patients who received induction chemotherapy and SMART (50 Gy in 5 fractions, BED10 =100 Gy). One year OS from diagnosis and from SMART was 93.9% and 65.0%, respectively. One-year LC from SMART was 82.9%. The incidence of acute grade 3+ toxicity definitely related and probably related to SMART were 0% and 2.2% (n=3), respectively, thus meeting the trial's primary objective.

Chuong *et al.* studied the use of ablative stereotactic magnetic resonance image-guided adaptive radiation therapy (A-SMART) (54). In this study, 62 patients with inoperable non-metastatic PDAC were treated first with induction chemotherapy and then with 5-fraction A-SMART. The median dose was 50 Gy (range, 40–50) in 5 fractions (median BED10 =100 Gy). The study results showed 2-year LC from diagnosis was 87.7%, but median LC after diagnosis was not reached. The 2-year PFS was 40% and median PFS was 20 months. The 2-year OS was 45.5% and the median OS from diagnosis was 23 months. The acute grade 3+ toxicity rate was 4.8%. Toxicities included duodenal stenosis that required stents (two patients) and abdominal pain for several hours after the first fraction, which resolved with medication and did not return (one patient). The late grade 3+ toxicity rate was also 4.8%. Toxicities included a grade 3 GI bleed, which resolved after transfusion (two patients), and a death that was 6 weeks after a Whipple procedure and 7 weeks after A-SMART. The death was due to a bleed in the gastroduodenal artery that was not definitively related to A-SMART (possible grade 5 toxicity). Overall, the study concluded that for patients with inoperable pancreatic adenocarcinoma, the combination of induction chemotherapy and dose escalation using A-SMART shows promise in achieving long-term LC and OS without causing severe toxicities.

In the Tringale *et al.* study published in 2022, 30 patients with pancreatic cancer were treated with 50 Gy in 5 fractions (BED10 =100 Gy) using a 1.5 T magnetic resonance-linac system (24). Most (73%) received FOLFIRINOX before radiation. Median OS from diagnosis and A-RT was not reached. One year OS from diagnosis and A-RT was 96.4% and 80.0%, respectively. Median PFS from A-RT was 10.1 months. Acute grade 2 toxicities were observed in 4 patients (13.3%). No acute grade 3+ or late toxicities were observed. This is the first study reporting clinical outcomes on the use of a 1.5 T Unity MR linac to deliver A-RT for LAPC. Overall, the results are promising as they show excellent local control with low toxicities.

Given all of the advancements with delivering ablative SBRT with adaptive MRI guidance, there is currently a new phase III trial called LAP-ABLATE enrolling patients, NCT05585554 (55). This study is a randomized controlled phase III trial designed to test superiority of novel image guided radiation. These findings will add significantly more context to the results of the LAP-07 trial and using modern dose escalation, will assess the clinical benefits and safety of

treating pancreatic cancer to ablative doses.

Role in metastatic disease

Published in 2022, Elamir *et al.* conducted a retrospective review of 41 patients with oligometastatic pancreatic ductal adenocarcinoma (Opanc) (56). Of those patients, 20 received SABR to all active metastatic sites and 21 only received chemotherapy. SABR was defined as a 1 to 5 fractions with a minimum dose of 7.65 Gy per fraction, or a total of 67.5 Gy in 15 fractions. The median dose of SABR to the primary tumor was 40 Gy in 5 fractions (24–67.5 Gy in 3–15 fractions) and the median BED10 was 100 Gy. For the SABR and chemotherapy-only cohorts, median poly progression-free survival was 40 and 14 months and OS from the date of Opanc diagnosis was 42 and 18 months, respectively. In the SABR cohort, 85% of patients had more than a 6-month break from chemotherapy when compared to 33.3% of patients in the chemotherapy-only cohort. Toxicities were not reported. The authors also note that the study was limited by selection bias as the SABR cohort had favorable baseline characteristics. A summary of key trial data is in *Table 1*.

Volumes and heterogeneity

While earlier studies were primarily covering the tumor for SBRT or dose escalated radiation, there is increasing evidence to treat the nodal basins. Since pancreatic adenocarcinomas are neurotropic, covering the regional nodal basins is also essential. When Kharofa *et al.* evaluated the use of 33 Gy in 5 fraction SBRT in 18 patients that were planning to receive surgery for borderline or resectable PDAC, the majority of patients had local failure outside of the 33 Gy volume (57). When an elective volume of 25 Gy in 5 fractions was included, the local failures were less frequent. In a study by Miller *et al.*, a comparison was done on treating the pancreatic tumor with SBRT alone (n=100) or adding in elective nodal irradiation to SBRT (n=50) (58). The ENI volume followed contouring recommendations per the RTOG 0848 trial (59). At 24 months locoregional failure was nearly double in the SBRT arm (44.6%) *vs.* the SBRT + ENI arm (22.6%). There were, however, no differences noted in survival and SBRT+ENI came on with increases in grade 1 and 2 nausea.

Besides this, there currently is no clear consensus on minimum doses that the tumor should receive (dose that covers 100% of the volume, known as D min). For example in Reyngold *et al.*, the median prescription covering the whole gross disease was 60% of the ablative prescription (47). Depending on user technology, comfort, and dosimetric comfort, this value is likely to vary and should be noted. Furthermore, there is no clear dosimetric constraints on OARs to luminal GI organs, albeit most practitioners utilize similar ranges for values such as the duodenum, which is usually limited between 30–35 Gy in 5 fractions maximum.

Discussion

While studies for many years were limited by GI toxicity, advances in technology have allowed more precise delivery of ablative doses to the tumor, resulting in improved local control and decreased GI toxicity. Multiple clinical trials on ablative RT are in progress at the time of publication. The first trial (NCT03621644) is a phase II trial studying the use of stereotactic MRI-guided On-table Adaptive Radiation Therapy (50 Gy in 5 fractions, BED10 =100 Gy) on patients with borderline or inoperable LAPC (52). The primary outcome measure will be Grade 3+ GI toxicity. No preliminary trial results have yet been presented. LAP-ABLATE is activating which will be assessing whether there is an overall survival benefit to dose escalated radiation, NCT05585554 (55).

Furthermore, a study at Sidney Kimmel Comprehensive Cancer Center (NCT05141513) is investigating the efficacy of intraoperative radiation therapy (IORT) after SBRT and chemotherapy to treat PDAC (60,61). Patients will undergo chemotherapy, then SBRT (40 Gy in 5 fractions, BED10 =72 Gy), and lastly, IORT (15 Gy in 1 fraction, BED10 =37.5 Gy) to the tumor volume during the Whipple procedure. The primary objective of this study is to measure acute toxicity after IORT. No preliminary trial results have yet been presented. Lastly, a trial at MD Anderson Cancer Center (NCT04484909) is investigating the use of NBTXR3, a radio enhancer composed of hafnium oxide nanoparticles that can be injected into a tumor before radiotherapy (62). The particles are activated upon exposure to radiation and work to enhance the radiation dose to the tumor, thereby causing tumor cell death without increasing toxicity to the surrounding tissue. In the current phase 1 trial, patients with LAPC or BRPC receive NBTXR3 IT on day 1. Between days 15–43, patients will then undergo 15 fractions of radiation in the absence of disease progression or unacceptable toxicity. No preliminary trial results have yet been presented.

Table 1 A comprehensive list of the data in review

Study	Radiation dose	Chemotherapy	Overall survival	LC/FFLP/PFS	Toxicities
Koong *et al.*, 2004 (31)	25 Gy/1 fx (BED10 =87.5 Gy)	Various	Median OS: 8 months	LC: 100%	Grade 3+ toxicity: none
Hoyer *et al.*, 2005 (32)	45 Gy/3 fx (BED10 =112.5 Gy)	None	Median OS from start of first treatment: 5.7 months	PFS 1 year: 9%	Acute grade 2+ toxicity: 79%
					Late grade 2+ toxicity: 94%
Schellenberg *et al.*, 2008 (33)	25 Gy/1 fx (BED10 =87.5 Gy)	Gemcitabine	Median OS: 11.4 months	FFLP 1 year: 100%	Acute grade 2: 13%
					Acute grade 3: 6%
					Late grade 2: 33%
					Late grade 3: 13%
Chang *et al.*, 2009 (34)	25 Gy/1 fx (BED10 =87.5 Gy)	Various gemcitabine-based	Median OS from start of SBRT: 6.4 months	FFLP 1-year: 84%	Acute grade 2+: 5%
					Late grade 2: 4%
					Late grade 3+: 9%
Mahadevan *et al.*, 2010 (35)	25–36 Gy/8, 10, or 12 Gy (BED100 =43.2–79.2 Gy)	Gemcitabine after SBRT	Median OS from start of SBRT: 14.3 months (no difference in outcome between dose groups)	LC 2 years: 78%	Grade 2: 25%
					Acute grade 3+: 8%
					Late grade 3+: 6%
Polistina *et al.*, 2010 (36)	30 Gy/3 fx (BED10 =60 Gy)	Gemcitabine	Median OS from diagnosis: 10.6 months	LC 6 months: 9 of remaining 11 patients (82%, originally 36 patients)	Grade 2+ toxicity: none
Schellenberg *et al.*, 2011 (37)	25 Gy/1 fx (BED10 =87.5 Gy)	Gemcitabine	Median OS: 11.8 months	FFLP 1 year: 94%	Acute grade 2: 15%
					Acute grade 3+: none
					Late grade 3+: 5%
Tozzi *et al.*, 2013 (38)	45 Gy/6 fx (BED10 =78.75 Gy); 36 Gy/6 fx (BED10 =57.6 Gy)	Gemcitabine	Median OS from start of SBRT: 11 months	FFLP 2 years:	Grade 2: 10% (nausea); 10% (pain)
				For 45 Gy: 96%	Grade 3+ toxicity: none
				For 36 Gy: 75%	
Chuong *et al.*, 2013 (39)	25–35 Gy/5 fx (mean BED10 =63 Gy)	Gemcitabine	Median OS from start of treatment:	LC 1 year: 81%	Acute grade 3+: none
			BRPC: 16.4 months		Late grade 3+: 5.3%
			LAPC: 15 months		
Herman *et al.*, 2015 (40)	33 Gy/5 fx (BED10 =49.5 Gy)	Gemcitabine	Median OS from diagnosis: 13.9 months	FFLP 1 year: 78%	Acute grade 2+: 2%
					Late grade 2+: 11%

Table 1 (*continued*)

Table 1 (*continued*)

Study	Radiation dose	Chemotherapy	Overall survival	LC/FFLP/PFS	Toxicities
Krishnan *et al.*, 2016 (22)	Dose-escalated IMRT: BED 70.4–100.0 Gy	Gemcitabine or FOLFIRINOX	Dose-escalated: median OS from start of chemoradiation: 17.8 months	Local-regional recurrence-free survival:	Dose-escalated:
	Standard: BED ≤70 Gy		2-year OS: 36%	Dose-escalated: 10.2 months	Grade 2: 38%
			Standard: median OS: 15.0 months	Standard: 6.2 months	Grade 3: 2%
			2-year OS: 19%		No data for standard
Quan *et al.*, 2017 (41)	36 Gy/3 fx (BED10 =79.2 Gy)	Gemcitabine and capecitabine	Median OS from enrollment: 18.8 months	Local PFS 2 years: 44.9%	Grade 3+: none
Sutera *et al.*, 2017 (42)	Median dose 24 Gy/1 fx (BED10 =81.6 Gy)	Various	2-year OS from start of SBRT:	LC 2 year:	Grade 3+ at 2 years: 2.5% (no difference between single or multi fx)
	Median dose 36 Gy/3 fx (BED10 =79.2 Gy)		In single fx: 30.5%	In single fx: 56.8%	
			In multi fx: 37.5%	In multi fx: 69.7%	
Bernard *et al.*, 2018 (43)	36 Gy in 3 fractions, BED10 =79.2 Gy	Various	Median OS from enrollment: 23.7 months	Local PFS 2 years: 77%	Grade 3+: 4.1%
Goldsmith *et al.*, 2018 (44)	18–36 Gy in 3 fractions, median BED10 =50.3 (47.7–53.0) Gy	Various	Median OS from start of SBRT: 8.4 months	Median FFLP: 9.8 months	Acute grade 3: 8.1%
					Late grade 4: 12.5%
Rudra *et al.*, 2019 (50)	High-dose cohort (BED >70): SBRT 40–52 Gy/5 fx [median BED =77.6 (72.0–106.1) Gy] or hypofractionated RT 50–67 Gy/10–15 fx [median BED =82.7 (67.8–97.9) Gy]	Various	High-dose cohort:	High-dose cohort: FFLP	Grade 3+:
	Standard-dose cohort (BED ≤70 Gy): conventionally fractionated RT [40–55 Gy in 25–28 fractions, median BED =55.5 (38.2–67.1) Gy] or conventional SBRT [30–35 Gy in 5 fractions, median BED =55.8 (48.0–59.5) Gy]		2-year OS from start of RT: 49%	2-year: 77%	High-dose cohort: none
			Standard-dose cohort:	Standard-dose cohort: FFLP	Standard-dose cohort: 7%
			2-year OS from start of RT: 30%	2-year: 57%	
Hassanzadeh *et al.*, 2020 (49)	50 Gy/5 fx (BED10 =100 Gy)	Various	Median OS from diagnosis: 15.7 months	Median PFS: 12.4 months	Acute grade 3: none
					Late grade 2: 6.8%
					Late grade 3: 4.6%

Table 1 (*continued*)

Table 1 (*continued*)

Study	Radiation dose	Chemotherapy	Overall survival	LC/FFLP/PFS	Toxicities
Schaff *et al.*, 2020 (51)	SMART 50 Gy/5 fx (BED10 =100 Gy) Standard RT 50.4 Gy/28 fx (BED10 =59.47 Gy)	Not reported	180-day survival from start of RT: SMART: 94% Chemo RT: 70%	Not reported	Grade 3+: SMART: 11% Chemo RT: 28%
Toesca *et al.*, 2020 (45)	SABR dose ≥40 Gy (BED10 ≥72 Gy) SABR dose <40 Gy (BED10 <72 Gy)	Gemcitabine or mFFX	OS from diagnosis: SABR dose ≥40 Gy: 23 months SABR dose <40 Gy: 14 months	PFS for SABR dose ≥40 Gy: 13 months SABR dose <40 Gy: 10 months	For SABR dose ≥40 Gy Grade 2+: 10% Grade 3+: 6% SABR dose <40 Gy Grade 2+: 15% Grade 3+: 7% (including one grade 4 and one grade 5)
Jolissaint *et al.*, 2021 (46)	75 Gy/25 fx (BED10 =97.5 Gy) or 67.5 Gy/15 fx (BED10 =97.88 Gy)	FFX/mFFX or gemcitabine plus paclitaxel	Median OS from completion of RT: 20.1 months	LC 18-month: 16%	Any toxicity/ complication: 25% (complication with biliary stent =10.6%, upper GI bleeding =5.8%, new biliary obstruction =3.8%, vertebral body fracture =2.9%)
Reyngold *et al.*, 2021 (47)	75 Gy/25 fx or 67.5 Gy/15 fx (median BED =98 Gy)	Various induction (97.5%)	Median OS from diagnosis: 26.6 months; 2-year OS: 38%	2-year local tumor progression rate: 32.8%	Grade 3: 8%
Elamir *et al.*, 2022 (56)	Median SABR dose 40 Gy/5 fx (median BED10 =100 Gy)	Various	Median OS from date of OPanc diagnosis: 42 months	Median PFS: 40 months	Not reported
Chuong *et al.*, 2022 (54)	40–50 Gy/5 fx (median BED =100 Gy)	Various	Median OS from diagnosis: 23 months 2-year: 45.5%	2-year LC from diagnosis: 87.7% 2-year LC from A-SMART: 68.8%	Acute grade 3+: 4.8% Late grade 3+: 4.8%
Tringale *et al.*, 2022 (24)	50 Gy/5 fx (BED10 =100 Gy)	FFX (73%)	Median OS from diagnosis: not reached 1 year OS: 96.4%	Median PFS from A-RT: 10.1 months	Acute grade 2: 13.3% Acute grade 3+: none Late toxicities: none
Parikh *et al.*, 2022 (53)	50 Gy/5 fx (BED10 =100 Gy)	FFX (65.4%) or gemcitabine doublet (16.9%)	1-year OS from diagnosis: 93.9% 1-year OS from SMART: 65.0%	1-year LC from SMART: 82.9%	Acute grade 3+ toxicity: definitely related to SMART: 0%; probably related to SMART: 2.2% (n=3)

BED, biologically effective dose; FFLP, freedom from local progression; FFX, FOLFIRINOX; LC, local control; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SABR, stereotactic ablative radiation therapy; SBRT, stereotactic body radiation therapy; SMART, stereotactic MR guided adaptive radiation therapy.

Conclusions

With the current improvements in technology, comfort with dose escalation (to BED >70 or ablative RT) is increasingly being performed with considerable improvement in the therapeutic ratio of limited GI toxicity and acceptable local regional control particularly for LAPC. The objective clinical benefits that can be provided by dose escalated or ablative RT (with or without the additions of improved image guidance and plan adaptation), compared to standard fractionated chemoRT, is still pending clarity as there has yet to be a head-to-head trial, and these are the subjects of ongoing trials.

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Footnote

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