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Radiation therapy for patients with locally advanced pancreatic cancer: Evolving techniques and treatment strategies

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ABSTRACT

Despite ongoing efforts, patients with locally advanced pancreatic cancer (LAPC) continue to have a dismal prognosis. Such tumors are unresectable, and optimal treatment with chemotherapy and/or radiation therapy is still not established. While chemotherapy is conventionally aimed at preventing metastatic spread of disease, radiation therapy acts locally, improving local control which can potentially improve overall survival and most importantly quality of life. Here, we aim to review the primary literature assessing the role of diverse radiation therapy strategies for patients with LAPC.

Many radiation regimens can be considered, and no standard treatment has demonstrated a clear improvement in clinical outcomes. We advise that the modality of choice be dependent on the availability of equipment, the dose and fractionation of treatment, as well as the dose received by normal tissue. Moreover, a candid discussion with the patient concerning treatment goals is equally as essential. Three notable strategies for LAPC are intensity-modulated radiation therapy, volumetric modulated arc therapy, and proton. These radiation modalities tend to have improved dose distribution to the target volumes, while minimizing the radiation dose to surrounding normal tissues. Stereotactic body radiation therapy can also be considered in LAPC patients in cases where the tumor does not invade the duodenum or other neighboring structures. Because of the high doses delivered by stereotactic body radiation therapy, proper respiratory and tumor motion management should be implemented to reduce collateral radiation dosing. Despite im-

Abbreviations: LAPC, locally advanced pancreatic cancer; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; SBRT, stereotactic body radiation therapy; MR-Linac, magnetic resonance Linac.

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proved clinical outcomes with modern radiation modalities, evolving techniques, and more accurate planning, future studies remain essential to elucidate the optimal role for radiation therapy among patients with LAPC.

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Introduction

Pancreatic cancer is known to be one of the most aggressive forms of cancers, with an estimated 5-year overall survival of around 9%.[1] Recent statistics from the American Cancer Society show that the incidences of pancreatic cancer, along with pancreatic cancer mortality are increasing.[1] Moreover, around one third of patients with pancreatic cancer are diagnosed with locally advanced disease at presentation.[2] Locally advanced pancreatic cancer (LAPC) is defined as any pancreatic cancer that is neither surgically resectable nor metastatic. LAPC carries a strikingly poor prognosis, with a median overall survival of 9-11 months[3,4]. In addition to poor survival, patients with LAPC often suffer from severe disease- and treatment-related morbidity that further impairs quality of life. Ongoing debate regarding treatment strategy, sequencing of chemotherapy and radiation therapy, and even choice of radiation therapy modality, dosage, and fractionation has resulted gap in standard of care for LAPC patients. The main goals of treatment are to improve local and distant progression of disease, in the hopes of improving overall survival while preserving quality of life. Since surgical resection is not an option, the prognosis of these patients remains poor, and depends highly on optimal chemotherapy and radiotherapy combinations. In that regard, while chemotherapy addresses the issue of distant spread, radiation therapy focuses mainly on controlling local or locoregional disease. Local control is particularly important in LAPC as around 30% of patients with pancreatic cancer die from local disease without developing distant metastases.[5] In this article, we aim to review the literature for the main studies addressing different radiation therapy options in patients with LAPC. In particular, we expand on the potential effectiveness of chemoradiotherapy before expounding upon 4 different treatment strategies: chemoradiation, intensity-modulated radiation therapy, stereotactic body radiation therapy, magnetic resonance linear accelerators (MR Linac), and particle therapy.

Radiation therapy treatment strategies

Chemoradiation

Patients with LAPC are commonly treated with a combination of chemotherapy and radiation therapy. However, clinical outcomes remain suboptimal, and improved combinations are still required. The 2 most common chemotherapy regimens adopted are FOLFIRINOX or gemcitabine and/or nab-paclitaxel. There is no consensus on which regimen is superior, but FOLFIRINOX is typically the first choice for patients with good performance status and no contraindications. After sufficient stabilization of the tumor size and CA19-9 with chemotherapy, definitive concurrent chemoradiation is often considered. A commonly used approach is the use of concurrent chemotherapy and hypofractionated intensity-modulated radiation therapy (IMRT).[6] One of the early studies on chemoradiation was published by Shinchi et al in 2002. The study conducted was a prospective randomized trial that showed better overall survival and quality of life in patients who received chemoradiotherapy when compared to best supportive care alone.[7] Some evidence also shows that the use of concurrent chemoradiotherapy might be superior to the use

of radiotherapy alone. A study by the Gastrointestinal Tumor Study Group in the 1980s evaluated patients with LAPC who received concurrent chemoradiotherapy with 5-FU at either low (4000 rads) or high (6000 rads) dose radiation therapy and patients that received only high dose radiation therapy (6000 rads).[8] Radiation therapy was delivered using supervoltage equipment with anterior-posterior, and posterior-anterior fields. The study showed improved overall survival in the group that received concurrent chemoradiotherapy (60 Gy + 5-FU 1-year overall survival: 46%) vs those who received high dose radiotherapy alone (60 Gy 1-year overall survival: 10%).[8] Similarly, a more recent phase III trial conducted by the Eastern Cooperative Oncology Group in 2005 compared patients receiving high dose external beam radiotherapy (59.4 Gy over 33 fractions) alone to patients receiving radiation therapy with additional 5-FU and mitomycin chemotherapy. Surprisingly, they observed an astonishingly different result. Their patients exhibited increased toxicity in the chemoradiation arm and did not show any improvement in overall and disease-free survival.[9]

Furthermore, comparing concurrent chemoradiotherapy to chemotherapy alone still presents mixed results. While data from the Gastrointestinal Tumor Study Group offers some survival benefit with the addition of radiation therapy to 5-FU chemotherapy, other studies report no significant changes in outcome between these groups.[10-12] The 2000-01 FFCC and/or SFRO (FFCC, Federation Francophone de Cancerologie Digestive; SFRO, Societe Francophone de Radiotherapie Oncologique) study randomized patients to either receive initial chemoradiotherapy in conjunction with 5-FU and cisplatin or the induction of gemcitabine alone.[13] Radiation therapy was given with conformational radiotherapy (60 Gy over 30 fractions). Both treatment arms were subsequently treated with gemcitabine maintenance chemotherapy until disease progression or severe toxicity. Results from this study actually showed better outcomes in the gemcitabine alone arm with improved survival rates and reduced toxicities.[13] On the other hand, the Eastern Cooperative Oncology Group compared the use of gemcitabine alone or in combination with 3D-conformal radiotherapy to a dose of 50.4 Gy over 28 fractions. The study showed that the use of chemoradiotherapy was associated with better survival rates (Chemoradiotherapy: median survival of 11.1 months vs Chemotherapy: median survival of 9.2 months).[14] The LAP 07 trial, another recent study, compared chemoradiotherapy (3D-conformal radiotherapy, 54Gy/30 fractions + Capecitabine) vs chemotherapy alone (gemcitabine or gemcitabine and erlotinib) in patients that already received prior chemotherapy (either gemcitabine or gemcitabine and erlotinib).[15] The results show improved local control in the chemoradiotherapy arm, but no survival benefit after addition of radiation therapy. Nevertheless, this study used gemcitabine-based chemotherapy, rather than FOLFIRINOX which might limit the applicability of the results to the current FOLFIRINOX-based regimens.[15]

The conflicting findings of these clinical trials has made it difficult to establish an ideal chemoradiation protocol for patients with LAPC. It is important to note that the results of these trials should be interpreted with caution as the limited sample sizes and recent advances in radiation delivery and chemotherapeutics do not recapitulate the critical role of radiotherapy in LAPC.

Intensity-modulated radiation therapy

IMRT is an advanced radiation therapy modality that utilizes photon energy, and allows for radiation delivery using multiple radiation beams at varying intensities and varying angles.[16] IMRT is particularly useful when treating targets with complex concave shapes, which makes it well suited for pancreatic tumors.[17] Table 1 presents the major studies addressing the role of IMRT in LAPC. A retrospective analysis by Wang et al in 2015 included 63 patients with pancreatic cancer, of which 31 had LAPC.[18] All patients were treated with IMRT to a median dose of 46 Gy. The subgroup of patients with LAPC had a median overall survival (OS) of 15.7 months, and 1-year OS rate of 62.4%. Treatment was well tolerated, with around 14.0% of grade 3 hematological toxicities, and no severe non-hematological toxicities.[18] Furthermore, a prospective study by Nakamura et al in 2018 showed excellent clinical outcomes with IMRT.[19] The study showed a

Table 1
Summary of the literature on the use of IMRT in LAPC.

Study ID	Study design	Number of patients	Overall survival	Progression free survival
Wang, 2015[18]	Retrospective	LAPC = 31 Metastatic = 32	Median OS LAPC = 15.7 months 1-year OS LAPC = 62.4% 2-year OS LAPC = 32.2%	N/A
Huguet, 2017[55]	Retrospective	134	OS = 23 months after 20-month follow-up 1-year OS: 85% 2-year OS: 47%	N/A
Goto, 2018[56]	Prospective	11	Median follow-up of 22.9 months OS = 100% at 23.6 months	1-year LRPFSl = 90.9% DMFS = 70.7%
Goto, 2018[57]	Retrospective	107	Overall OS = 17.5 months, 1-year OS = 74.3% 3DCRT: 1-year OS = 68.2% IMRT: 1-year OS = 92.3%	3DCRT: 1-year LRPFS = 63.2%, 1-year DMFS = 48.4% IMRT: 1-year LRPFS = 73.1%, 1-year DMFS = 49.3%
Nakamura, 2018[19]	Prospective	10	1-year OS: 100% 2-year OS: 50% Median OS: 25.9 months	2-year: 30% Median: 14.6 months
Oh, 2018[58]	Prospective	47	OS = 14.2 months	LRPFS = 18.1 months DMFS = 10.3 months
Felice, 2019[20]	Prospective	10	1-year OS = 83.3%	DMFS = 68.6%

3DCRT, 3D conformal radiation therapy; DMFS, distant metastasis free survival; IMRT, intensity-modulated radiation therapy; LAPC, locally advanced pancreatic cancer; LRPFS, locoregional progression free survival; OS, overall survival; PFS, progression free survival.

1-year OS of 100%, a 2-year OS of 50%, and a median OS of 25.9 months. Those outcomes were probably the result of an excellent local disease control in this study, as the 2-year local-disease free survival was around 74.0%. While the results of this study seem promising, the study is mainly limited by its small sample size of 10 patients, which might speculate the validity of the results.[19] A recent prospective pilot study by Felice et al enrolled 10 patients with unresectable LAPC that were subsequently treated with IMRT.[20] The study shows a 1-year OS of 83.3%, and a 1-year DFS of 68.3%. No severe toxicity was noted in this cohort.[20] In light of decreased toxicities from IMRT treatment, the concept of dose escalation evolves. Despite some success from previous studies, pancreatic cancer still led to modest local control and survival rates, and thus increased radiation doses might offer improved local control. Escalated dose radiation - defined as a biological equivalent dose of 70 Gy or higher - with IMRT planning shows improved locoregional control and overall survival when compared to standard dose radiation with concurrent chemotherapy.[21,22] Moreover, hypofractionated IMRT allows for the delivery of similar radiation doses over a shorter number of fractions. Minimizing radiation treatment duration is particularly important in patients with LAPC, where prolonged radiation treatments might negatively impact quality of life furthermore.[20] Hypofractionated IMRT is well tolerated by patients, with minimal gastrointestinal and overall toxicities.[21] Another promising regimen is the use of IMRT to a total dose of 75 Gy in 25 fractions, along with concurrent capecitabine, in cases where surgery cannot be guaranteed.[23] The use of higher radiation doses might be able to achieve local control rates that are comparable to those achieved with resection. Additionally, volumetric modulated arc therapy (VMAT), has also shown good clinical outcomes in patients with LAPC. VMAT radiotherapy also utilizes photon energy, and focuses on the delivery of a high number of radiation beams in a relatively short period. A dosimetric study comparing VMAT, IMRT and 3D conformal radiation therapy, showed that VMAT planning could be achieved with less radiation dose to organs at risk, mainly the duodenum when compared to the 2 other modalities.[24] Furthermore, VMAT treatment was associated with less severe gastrointestinal toxicities when compared to IMRT or 3D conformal radiation therapy[24] As such, limited data on VMAT shows promising clinical results, and future studies should be encouraged to focus more on the role of VMAT in patients with LAPC.

Table 2
Summary of the literature on the use of SBRT in LAPC.

Study ID	Study design	Number of patients	Overall survival	Progression free survival
Koong, 2004[25]	Prospective	15 15 Gy = 3 20 Gy = 5 25 Gy = 7	Median OS = 11 months	Median PFS = 2 months
Hoyer, 2005[59]	Prospective	22	Median OS = 5.4 months 1-year OS = 5%	Median PFS = 4.8 months 1-year PFS = 9%
Mahdevan, 2011[27]	Retrospective	47	Median OS = 20 months	Median PFS = 15 months
Shellenberg, 2011[26]	Prospective	20	Median OS = 11.8 months 1-year OS = 50% 2-year OS = 20%	Median PFS = 9.2 months
Chuong, 2013[60]	Retrospective	73	OS = 22.5 months	Median PFS = 14.9 months
Herman, 2014[29]	Prospective	49	Median OS = 13.9 months 1-year OS = 59% 2-year OS = 18%	Median PFS = 7.8 months 1-year PFS = 32% 2-year PFS = 10%
Lin, 2015[61]	Retrospective	41 SBRT = 20 IMRT = 21	OS = 22.5 months SBRT = 20 months IMRT= 13.5 months	N/A
Pollom, 2014[28]	Retrospective	167	Median OS = 13.6 months	N/A
Mellon, 2015[62]	Retrospective	159	Median OS = 18.1 months	Median PFS = 12.7 months
Comito, 2016[30]	Prospective	45	Median OS = 13 months 1-year OS = 59% 2-year OS = 18%	Median PFS = 8 months 1-year PFS = 39% 2-year PFS = 15%
Gurka, 2017[63]	Retrospective	15 15 Gy = 31 25 Gy = 13 30 Gy = 24	Median OS = 14.3 months	Median PFS = 9.2 months

IMRT, intensity-modulated radiation therapy; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression free survival; SBRT, stereotactic body radiation therapy.

Stereotactic body radiation therapy (SBRT)

SBRT is an advanced modality in radiation therapy that delivers highly conformal radiation. SBRT treatment allows for the delivery of higher doses per fraction, and thus is typically delivered in fewer fractions when compared to conventional radiotherapy (typically 1-5 fractions). This is crucial for limiting exposure of organs at risk that are found in close proximity to the radiation site in pancreatic cancer.

Table 2 presents the major studies addressing the role of SBRT in LAPC. SBRT was initially studied in a phase I dose escalation trial by Koong et al using CyberKnife technology.[25] The trial included 15 patients with LAPC who were treated with a single fraction of 15 Gy, 20 Gy, or 25 Gy. Single fraction SBRT treatment was well tolerated, and no patients developed severe gastrointestinal toxicities.[25] A subsequent Phase II study from the same group at Stanford included patients treated with single 25Gy-fraction SBRT and gemcitabine.[26] Results showed an overall mean survival of 11.8 months, a 1-year overall survival of 50%, a 2-year overall survival of 20% and a 94% local progression-free disease at 1 year. Similar to the original phase I trial by Koong et al, no patients developed acute grade 3 or more toxicity, and only 1 patient developed long term grade 4 duodenal perforation.[25, 26] These results were replicated by Mahadevan et al, who reported on 39 patients with LAPC who received 3 fractions of SBRT. These patients exhibited excellent local control at 21 months (85%), with a median OS of 20 months, and a median

disease-free survival of 15 months.[27] Late grade 3 toxicities were observed in less than 10% of patients.[27] Moreover, Pollom et al performed a single-center retrospective analysis comparing the clinical outcomes of patients with unresectable pancreatic adenocarcinoma receiving either single or 5 fractions SBRT.[28] Results showed that multi-fraction SBRT was associated with less toxicity, and did not compromise local control and survival rates.[28]

More recently, Herman et al performed a multi-center phase II trial investigating fractionated SBRT (33 Gy/5 fractions) with gemcitabine. The study showed a 1-year OS of 59% and a 1-year local progression-free survival of 78%.[29] SBRT was again well tolerated by patients (acute grade 2 or more GI toxicities: 2%; Late grade 2 or more GI toxicities: 11%).[29] Another phase II trial published by Comito et al in 2017 showed that SBRT with 45Gy in 6 fractions achieved excellent local control in patients with LAPC (90% local-progression free at 2 years) and had a median OS of approximately 19 months.[30] No patient developed any severe toxicity.[30] In light of improved clinical outcomes with SBRT treatment, current trials are investigating the incorporation of concurrent intestinal radioprotection. Radioprotective agents could potentially allow for further dose escalation, with the hope of better local control, overall survival, and toxicity rates (NCT03340974).[31]

Magnetic resonance linac-based treatment

Proper tumor visualization and respiratory motion monitoring is essential while delivering radiation therapy in order to ensure proper tumor targeting, and decrease collateral radiation doses. Some of the most commonly used techniques are fiducial markers, or CT-on-rails, which both allow proper tumor visualization during treatment, and help guide radiation therapy. MR LINAC use MR imaging to properly visualize and target the tumor during treatment.[32] The MR-LINAC is a hybrid linear accelerator combined with a magnetic resonance imaging scanner.[33] This set-up enables real-time tumor visualization, and better tumor targeting despite the multiple organ shifts due to respiratory motions. As such, comparing four-dimensional computed tomography (4DCT) and MR-guided radiation therapy shows favorable outcomes with MR real-time monitoring, especially when dealing with tumors susceptible to respiratory motion.[34]

The pancreas has a particularly complex anatomical environment, with many surrounding critical organs at risk, and an extensive tumor motion with respiration. Furthermore, pancreatic radiation therapy treatment typically utilizes high doses of radiation to ensure proper response. For the following reasons, pancreatic cancer is considered an ideal candidate for MR-LINAC treatment.[35] Retrospective data from 44 patients with inoperable pancreatic cancer treated with MR-guided radiation therapy showed a 2-year OS of 49%.[36] Despite high radiation dosing (biological effect dose $>$ 70 Gy), no grade 3+ GI toxicity was noted.[36] Currently, more trials are evaluating the role of MR-guided radiation therapy in LAPC (NCT03621644).[37]

Particle therapy: Proton and carbon ion therapy

Proton therapy is based on the use of proton beam radiation to deliver high doses of radiation to the tumor. Protons are charged particles that deliver higher relative biological effectiveness when compared to proton therapy, even under the same dosage and fractionation.[38] Hence, proton therapy allows for the delivery of the radiation dose in the beam path with minimal or no exit dose.[39] This feature of proton therapy enables proper therapeutic dosing to the tumors, while minimizing radiation side effects to normal tissue beyond the target. By minimizing toxicity to normal tissues, proton therapy allows dose escalation to the target tumor, which may provide stronger local control.

Terashima et al performed a phase I/II trial to assess the efficacy and safety of proton therapy in LAPC.[40] Patients were treated with 50 Gy in 25 fractions, 67.5 Gy in 25 fractions, or 70.2 Gy in 26 fractions. All patients received concurrent gemcitabine. The results of this trial show

comparable 1-year local-progression, progression-free and overall survival rates to historical data (81.7%, 64.3%, and 76.8%, respectively). Additionally, proton therapy treatment was well tolerated by the patients, with less than 10% grade 3 toxicities.[40] Patients were subsequently assessed by endoscopy, and around half of the patients had radiation-induced gastric or duodenal ulcers, but only 3% exhibited grade 3 or higher ulceration, and no patients developed GI hemorrhage or perforations.[41] Another prospective study of 11 patients was published by Sachsman et al in 2014, and showed that proton therapy with concomitant capecitabine was well tolerated by patients, with no grade 2 or higher gastrointestinal toxicities.[42] The results also showed a median overall survival of 18.4 months, with a 69% local-progression free rate at 2 years.[42]

Carbon ion therapy is based on a novel radiotherapy technique that utilizes heavy and charged particles.[43] The use of carbon ions has a few advantages over protons.[44] First, carbon ions tend to have a higher relative biological effectiveness, with less lateral scattering, and hence may provide a better radiation delivery. Furthermore, carbon ion therapy has a lower oxygen enhancement ratio than proton beam therapy.[45] The decreased oxygen enhancement ratio, which suggests that the tumor-killing effect of carbon ions is increasingly independent of tumor oxygenation, is particularly desirable for the eradication of hypoxic radioresistant tumor environments (such as those in LAPC).[46] As such, carbon therapy brings a new treatment potential for cancers that have been historically resistant to conventional X-Ray-based radiation[43]. The 1 major limitation to the introduction of carbon therapy its limited availability in cancer centers around the world, with no operational carbon ion therapy centers in the Americas.

Despite the limited availability of carbon ion therapy, we do have some clinical data evaluating its effectiveness. A large study by a group in Japan presents novel information on the use of carbon therapy.[47] The study included 353 patients with pancreatic cancer treated with carbon therapy. Patients with LAPC were treated in 2 phases. The first phase consisted of radiation therapy with 43.2 Gy in 12 fractions and concurrent gemcitabine. Then, the gemcitabine and radiation doses were increased by constant increments. This regimen resulted in a 2-year local control rate of 58% and a 2-year overall survival of 54%.[47] Additionally, retrospective data from the Japan Carbon-Ion Radiation Oncology Study Group analyzed 72 patients with LAPC treated with carbon ion therapy.[48] The study showed a 1-year overall survival of 73%, along with a median overall survival of 21.5 months. Moreover, the study showed excellent local control rates at 1 and 2 years (84% and 76%, respectively). These remarkable clinical outcomes should be taken with some caution, as most patients included in the Japan Carbon-Ion Radiation Oncology Study Group series had tumors in either the body or tail of the pancreas (58%). The heterogeneity in tumor location could result in a selection bias as those tumors might have a different innate biology.[49,50] Lastly, despite these promising clinical outcomes, around a quarter of the patients experienced severe grade 3 or 4 hematological toxicities, which might potentially lead to further increased morbidity in those patients.[48] With the potential promising outcomes of carbon therapy, the CIPHER phase III trial is currently comparing the use of IMRT to carbon ion therapy in patients with LAPC (NCT03536182).[51]

Recommendations and conclusions

In light of these studies and other data regarding systemic therapy for pancreatic cancer, our approach relies on a multimodality treatment for most LAPC patients. We first treat patients with LAPC with neoadjuvant chemotherapy for around 2 to 6 months. Chemotherapy is continued as long as the patient is responding by CA19-9 decrement or radiologic evidence. In cases where the tumor stops responding to treatment, the chemotherapy regimen is often switched.[52] Although pancreatic tumors do not commonly downstage with chemotherapy alone, there are a few cases reported in the literature of excellent responders, whose tumor became resectable after chemotherapy alone.[53,54]

This approach would address the high risk of micrometastatic disease and subsequent development of distant metastases. The following would also reduce over-treatment of patients who will eventually develop distant progression, as those patients would only derive minimal clini-

cal benefits from chemoradiation. Nevertheless, no gold standard for radiation therapy in LAPC has been established despite overwhelming recent evidence that points to its beneficial role in control local disease. It is imperative that future studies be done to not only compare different treatment modalities but to also institute treatment plans that address quality of care in unresectable pancreatic cancer patients.

In conclusion, different radiation regimens can be considered for patients with LAPC. IMRT, VMAT, and proton therapy can be used in LAPC, and tend to have improved dose distribution to the target volumes while minimizing radiation dosing to collateral normal tissues. Carbon ion therapy might also provide improved clinical outcomes, but is still not widely available in cancer centers around the world. Furthermore, carbon therapy prospective trials are required to better assess its role in the management of LAPC. Lastly, SBRT can be considered in patients with LAPC that does not invade the duodenum. Because of the high doses delivered by SBRT, proper respiratory and tumor motion management should be implemented to reduce collateral radiation dosing.

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