Review Article

Radiation induced antitumor autoimmunity: immunotherapies and pancreatic adenocarcinoma

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Abstract: Radiation therapy plays a critical role for the local control of cancer by direct cytotoxicity. In addition to the direct target effect, radiation therapy can modify the immunosuppressive tumor microenvironment. Preclinical data have demonstrated that radiation can enhance the anticancer activity of cancer immunotherapy. In addition, several clinical studies have revealed that local radiation treatment could induce systemic tumor responses by radiation induced antitumor immunity. Here, we review preclinical and clinical evidence of the immunomodulatory effects of radiation and the preclinical rationale of combination of radiation and immunotherapy as a potential treatment strategy in pancreatic cancer.

Keywords: Anti-programmed cell death protein-1; anti-cytotoxic T lymphocyte antigen-4; immunotherapy; radiation therapy; stereotactic body radiation therapy (SBRT)

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Introduction

With a 5-year survival of 8% overall and 52% of patients with distant disease at presentation, pancreatic adenocarcinoma (ACA) is the fourth leading cause of cancer death for both men and women in the United States (1). Current standard of care chemotherapy regimens for patients with metastatic disease center around a combination of 5-FU, leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) and gemcitabine combined with nab-paclitaxel (2,3) but are only associated with a response rate of up to 30%. Even those patients deemed resectable at initial presentation who undergo surgery and adjuvant therapy have 5-year overall survival rates in the range of 20% with the most favorable subsets of patients undergoing node negative, margin negative (R0) resections at high volume centers still no higher than 39% (4).

Recently, rapid advances in tumor immunology have improved the understanding of key regulators of T cell response and have led to the development of a new immunotherapeutic approach targeting immune checkpoint signaling pathways such as cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed death-1 (PD-1). CTLA-4 and PD-1 are negative immune regulators which play an essential role in the immunosuppression of antitumor immunity in the local tumor environment. CTLA-4, expressed on activated T cells, competes with CD28 for binding to B7 on antigen presenting cells to interrupt the costimulatory signal and blunt the T cell response (5). PD-1 is also expressed on the surface of activated T cells. The ligation of PD-1 and PD-L1 (a ligand of PD-1) inhibits T cell proliferation and activation, inducing apoptosis of antigen-specific T cells to prevent collateral tissue damage and autoimmune disease (6). The PD-1/PD-L1 pathway is hijacked by tumor cells to inhibit antitumor immunity, and various cancer cells have been reported to upregulate PD-L1 to escape immune

surveillance (7). Several different antibodies blocking these immune checkpoints such as ipilimumab (anti-CTLA-4 antibody), pembrolizumab (anti-PD-1 antibody), nivolumab (anti-PD-1 antibody), atezolizumab (anti-PD-L1 antibody), and durvalumab (anti-PD-L1 antibody) have been extensively studied in a wide spectrum of malignancies. These efforts are rapidly translating into remarkable success of PD-1 blockade agents in melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial cancer, gastric cancer, hepatocellular carcinoma, mismatch repair deficient colorectal cancer and head and neck cancer (8), and immunotherapy has led to a paradigm shift in cancer therapy. However, remarkable success has not been replicated with pancreatic cancer. Several clinical trials of single agent CTLA-4 or PD-L1 antibodies failed to show antitumor activity in patients with locally advanced or metastatic pancreatic cancer (9,10). These data reinforce the concept that pancreatic cancer has a different tumor microenvironment which has direct implications for the integration of immunotherapy agents.

Radiation therapy, one of the main pillars of cancer therapy, plays an essential role in the treatment of a wide variety of cancers. Approximately 60% of patients with solid tumors receive radiation therapy for local disease control (11). Radiation exerts tumoricidal activity through direct DNA damage leading to mitotic catastrophe, apoptosis, necrosis, autophagy and senescence (12). In addition to the direct target effect, radiation can modify the tumor microenvironment, which can lead to systemic antitumor activity at non-irradiated distant sites, a phenomenon known as the abscopal (ab, off; scopus, target) effect which was first described in 1953 (13). It has been believed that the abscopal effect is mediated by radiation induced antitumor immunity (14). In practice, clinical confirmation of the abscopal effect has been rare, with a systematic review evaluating studies reported between 1960 and 2014 reporting only 51 patients as having such responses (14). Barriers to higher rates of the abscopal effect are thought to be secondary to the tumor microenvironment causing local immune suppression characterized by local T-cell inhibition and inadequate priming by dendritic cells (15). Emerging preclinical and clinical data have demonstrated immune-stimulatory effects of radiation which may enhance antitumor immunity of cancer immunotherapy in pancreatic cancer. In this review, the immunomodulatory effects of radiation and the preclinical rationale of the combination of radiation and immunotherapy as a potential treatment strategy in pancreatic cancer will be discussed.

Immunosuppressive tumor microenvironment of pancreatic cancer

The immune system plays a critical role in surveillance against the development and progression of tumors. Pancreatic cancer cells develop several strategies to induce an immunosuppressive tumor microenvironment and evade antitumor immunity in primary and distant metastatic sites, which may contribute to resistance mechanisms of checkpoint immunotherapy in pancreatic cancer.

Primary and metastatic pancreatic cancer cells downregulate major histocompatibility complex (MHC) class I to inhibit tumor antigen cross presentation to cytotoxic T cells (16), which is one of the mechanisms incorporated to escape antitumor immunity. Indoleamine 2,3-dioxygenase (IDO) exhibits an immunosuppressive effect and induces immune tolerance by catabolizing tryptophan which is essential for T cell proliferation (17). High expression of IDO and correlation between IDO expression and poor prognosis were reported in pancreatic cancer (18). In addition, interferon-γ secreted by activated effector T cells for innate and adaptive immune activation upregulated IDO expression, and upregulation of IDO was associated with an increased number of regulatory T cells (Tregs) in metastatic pancreatic cancer (19). Interestingly, it has been suggested that IDO may be a critical resistance mechanism of cancer immunotherapy agents such as ipilimumab, and inhibition of IDO can augment the effectiveness of immunotherapy strategies such as CTLA-4 blockade and PD-1/PD-L1 blockade in a preclinical study (20).

TGF-β is a well-known immunosuppressive cytokine and has direct and indirect immune suppressive effect by inhibiting NK cell mediated cytolysis (21), suppressing CD8 cytotoxic T cell function (22), expanding Tregs and enhancing the function of Tregs (23). Pancreatic cancer cells secrete TGF-β (24) which induce type 2 T helper cell (TH2) immune response associated with tumor growth and reduced survival in patients with pancreatic cancer (25).

To prevent autoimmune disease and minimize collateral damage, activated T cells express Fas, and its ligation with FasL induces apoptosis of activated T cells for immune homeostasis, a process known as activation-induced cell death (26). Pancreatic cancer cells take advantage of activation-induced cell death to escape immune surveillance

Table 1 Immunosuppressive and tumorigenic activities of Treg, MDSC, TAM

Immune cell activity	Immunosuppressive and/or tumorigenic activity
Treg suppression of antitumor immunity	• Direct cytotoxicity against effector cells via granzyme and perforin release; • Conversion of ATP, an inflammatory molecule and a danger signal, to inhibitory adenosine by CD39 and CD73 expression; • Inhibition of maturation of antigen presenting cells and induction of IDO in antigen presenting cells by expression of CTLA-4; • Consumption of IL-2 via CD25 expression which are essential for T cell proliferation and differentiation; • Release of immunosuppressive cytokines such as IL-10 and TGF-β.
MDSC Immunosuppressive and tumorigenic activities	• Deprivation of amino acids arginine and cysteine, which are essential for T cell proliferation; • Production of nitric oxide and reactive oxygen species that causes the nitration of T cell receptors and chemokines for preventing T cell migration and inducing apoptosis of T cells and NK cells; • Production of immunosuppressive cytokines such as IL-10 and TGF-β skewing immune reactions toward Th2 type with activation of Tregs; • Upregulation of PD-L1 expression which induces T cell exhaustion and deletion; • Downregulation of TCR ζ-chain expression which are essential for TCR signaling after antigen recognition.
TAM suppression of cytotoxic T Cell response in tumor microenvironment	• Secretion of immunosuppressive IL-10 and TGF-β; • Expression of arginase-1 which suppresses T cell activity by depletion of L-arginine, essential amino acid for T cell function; • Upregulation of PD-L1; • Overexpression of IDO.

MSDC, myeloid derived stem cell; TAM, tumor associated macrophage; Treg, regulatory T cell; IDO, dioxygenase; CTLA-4, cytotoxic T lymphocyte associated protein 4.

by expression of FasL on pancreatic cancer cells and induction of apoptosis of cytotoxic T cells (27).

PD-L1, which induces T cell exhaustion and deletion by binding to PD-1 on activated T cells, is expressed on various cancer cells to suppress antitumor immunity in the local tumor microenvironment. A majority of pancreatic cancers also express PD-L1 for immune evasion (28). Immunosuppressive cells such as Tregs, myeloid derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs) play an essential role in inhibition of antitumor immunity (*Table 1*) (29). Infiltrated immune cells in the tumor and tumor environment of pancreatic cancer are predominantly Tregs, MDSCs and TAMs, and the immunosuppressive cell population is associated with progression of pancreatic cancer (30-32).

Immunomodulatory effects of radiation

Radiation at conventional doses was considered to be immunosuppressive due to the inherent radiosensitivity of immune cells and the attendant normal tissue damage to lymphatic tissue and/or bone marrow secondary to non-conformal older treatment techniques. However, emerging preclinical and clinical data suggest that there are immune-stimulatory effects of radiation. Exposure to radiation can elicit changes in tumor cells and the tumor microenvironment which can enhance the vulnerability of cancer cells to immune attack as shown in *Figure 1*.

Upregulation of MHC class I molecules and tumor antigens

Radiation enhances tumor antigen presentation to cytotoxic T cells by upregulation of MHC class I molecules. Cell surface expression of MHC class I molecules is increased in a radiation dose dependent manner as a consequence of (I) degradation of existing proteins by radiation, resulting in an increased intracellular peptide pool, (II) enhanced protein synthesis by radiation, resulting also in an increased intracellular peptide pool and (III) increased diversity of the intracellular peptide pool by the radiation induced novel proteins (33). In addition, radiation enhances immunological recognition of cancer cells by tumor specific

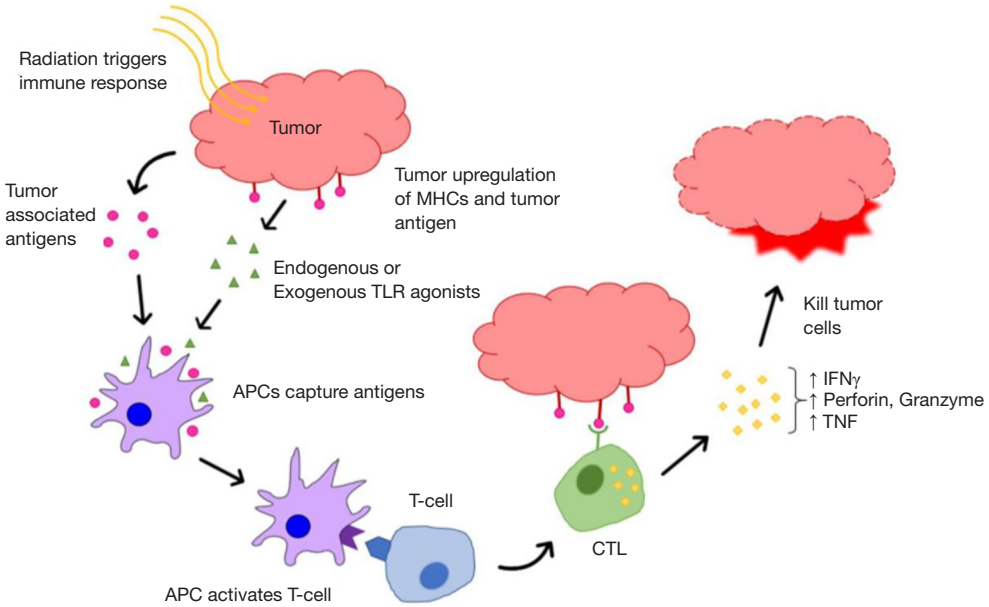

Figure 1 Schematic diagram outlining radiation-induced immune response and subsequent antitumor activity. APC, antigen presenting cell; MHC, major histocompatibility complex; CTL, cytotoxic T lymphocyte.

CD8 T cells through increased expression of tumor specific antigens in tumor cells (34).

Secretion of damage-associated molecular patterns (DAMPs) from tumor cells

Irradiated tumor cells can release DAMPs including calreticulin, adenosine triphosphate (ATP), high mobility group box 1 (HMGB1) and nucleic acids which elicit an antitumor immune response by activation of innate immune systems. Radiation exposure induces translocation of calreticulin from the endoplasmic reticulum to the plasma membrane in cancer cells (35). Calreticulin plays an essential role in the enrichment of endogenous peptides in the endoplasmic reticulum and assembly of MHC class I peptide complex for efficient antigen presentation export (36). Furthermore, the translocation of calreticulin acts as a phagocytic signal (eat-me signal) for antigen presenting cells such as dendritic cells (DC)s (37).

During phagocytosis of irradiated tumor cells in antigen presenting cells, DNA fragments in irradiated tumor cells are released from phagosomes to cytoplasm (cytosolic DNA) (38). Cytosolic DNA induces type I interferons production by activation of stimulator of interferon genes (STING) (39). Type I interferons, bridging the innate immune response to the adaptive response, promotes the cross-priming of cytotoxic T cells and leads to effective tumor growth control.

ATP also stimulates innate immune system by activation of the purinergic receptor P2RX7 which is expressed in immune cells such as macrophages, DCs, monocytes, natural killer cells, B cells and T cells. The activation of P2RX7 by extracellular ATP following tissue damage mediates activation of the innate immune system through the release of pro-inflammatory cytokines such as IL-18 and IL-1β and stimulation of inflammasome and T lymphocyte survival and differentiation (40).

HMGB1 is a soluble protein which is released from dying tumor cells after radiation. HMGB1, which binds to Toll-like receptor 4 (TLR4) on DCs and macrophages, promotes efficient antigen processing and cross presentation of tumor antigen presentations to T cells and induces a potent Th1 cell response by secretion of proinflammatory cytokines such as type I interferons, IL-12, MCP-1, MIP-1α and IP-10 (41).

Effects on regulatory immune cells

Tregs, MDSCs and TAMs are main regulatory immune cells to promote tumor growth and antitumor immune evasion in the tumor microenvironment. The effects of radiation on these regulatory immune cells have not yet been fully

elucidated. Previous data demonstrated that Tregs were resistant to radiation induced death, and radiation increased the frequency of Tregs (42,43). However, the effects of radiation on Tregs may be dose dependent. Low dose irradiation (0.94 Gray) induces significant apoptosis of Tregs compared with effector T cells and activates naïve T cells ($CD4^+CD25^-$) to express CD25 (44).

Several studies have demonstrated recruitment of MDSCs and TAMs into the tumor microenvironment after radiation treatment (45). Irradiation with a daily dose of 3 Gy for 5 days induces a systemic and local increase of MDSCs and TAMs with elevation of serum CSF1 level (46). Blocking of the CSF1 receptor inhibited migration of MDSCs and TAMs into the tumor microenvironment leading to more effective and durable tumor growth control after local irradiation (46). In addition, a single 15 or 20 Gy fraction of radiation also recruits MDSCs and TAMs to the tumor by overexpression of hypoxia inducible factor-1 (HIF-1) and secretion of stromal derived factor-1 (SDF-1) which recruits MDSCs by binding CXCR4 (47,48). Inhibition of HIF-1 or SDF-1/CXCR4 interaction prevents the influx of MDSCs and TAMs and delayed tumor regrowth (47,48). Interestingly, recent data showed that a single fraction of 12 Gy combined with anti-PD-L1 reduced the local accumulation of MDSCs by cytotoxic actions of TNF against MDSCs from activated CD8 T cells (49).

Radiation can polarize myeloid cells and TAMs to a M2 phenotype which promotes tumor progression and suppresses an antitumor immune response. Irradiation with 15 fractions of 4Gy, 3 fractions of 20 Gy or a single fraction of 25 Gy polarized infiltrated macrophages towards immune suppression which was mediated by transcriptional regulation by NF-κB (50,51). However, it may be a radiation dose dependent manner. A recent study showed that low doses of radiation (≤ 2 Gy) polarized TAMs towards a M1 phenotype with induction of inducible nitric oxide synthase (iNOS), which led to normalization of aberrant vasculature, efficient recruitment of tumor specific T cells and T cell mediated tumor rejection (52).

Clinical role of radiation therapy in pancreatic cancer

Over the last 30 years, radiation treatment techniques have significantly improved with the integration of advanced computer planning and delivery. Treatment has thus become highly conformal, such that the dose can be precisely mapped to the tumor region with a sharp fall off to the normal tissue beyond. Such precision has now evolved to the focal delivery of high dose per fraction treatment in a course of 1 week or less termed stereotactic body radiation therapy (SBRT) (53). As pancreatic cancer moves with breathing (54), escalation of dose is complicated by the proximity of the adjacent normal stomach and duodenum which can change position with organ filling and peristalsis (55). Indeed, when extracranial SBRT techniques were first reported for pancreatic cancer they were typically delivered in a single fraction of 25 Gy (56,57), but maturation of these trials showed an increase in late toxicity with reports of duodenal perforation and stricture; delivery in 5 fractions instead of one fraction reported significantly less late toxicity and no worse local control with current clinical practice favoring multi-fraction treatment (58). With continued advances, the ability to change the treatment plan during a course of treatment (adaptive RT, ART) is now possible, with results showing less duodenum in the high dose range with ART and controlling for the breathing motion with respiratory gating (19%) vs no image guidance nor gating (72%) with a concordant reduction in grade 2 or greater duodenal toxicity from 23% to 7% (59).

The optimal role of radiation therapy (RT) in the pancreatic cancer treatment paradigm is currently not well defined (60). In the adjuvant setting, although early trials showed a survival benefit to regimens containing RT (61,62), these results were not replicated in subsequent European studies (63-65). With the introduction of gemcitabine, an appropriate standard of care became adjuvant gemcitabine with/without capecitabine (66,67) or with appropriately quality assured RT to 50.4 Gy in 28 fractions, biologically effective dose (BED) of 59.47 Gy in patients with a postoperative CA 19 9<90 (68,69). In the neoadjuvant setting, there is data to support RT as part of the regimen to facilitate a margin negative resection, ranging from long course chemoradiation (70,71) to short course SBRT (72,73). In the setting of locally advanced pancreatic cancer, data from a recently published randomized trial did not show a survival advantage to the integration of conventionally fractionated chemoradiation to 54 Gy after systemic therapy (74). This phase III trial data of conventional dosing differed from retrospective data of patients with tumors at least 1 cm away from a luminal GI organ which suggested improved survival and local control if the BED was escalated to 70 Gy (75). In the context of SBRT for locally advanced disease, prospective data in a multi-institutional trial of 6.6 Gy × 5 fractions

has shown that RT integration is safe, well tolerated, and associated with a 10% rate of surgical resection (76). With MRI onboard imaging, recent data presented by Rudra et al showed that with ART and dose with a maximum BED >90 Gy, there was a near doubling of local control and overall survival for patients with locally advanced disease (77).

Safe dose escalation in pancreatic cancer is thus of considerable clinical interest. Despite these advances, we are still not able to prospectively personalize the dose of RT for each patient although a number of strategies to integrate radiosensitivity have been described (78). One such model is called the Radiation Sensitivity Index (RSI) which is a 10-gene expression model based on a systems biology approach (79,80). Similarly, a 12-gene model has been developed based on 12 chemokine genes that are immune related and inflammation related called the 12-CK (81,82). Recent data now suggests that RSI and 12-CK are associated and, if combined, may serve as a future pretreatment biomarker to identify individual tumors that would have an increased response to immunotherapy and RT treatment (83). Future prospective trials will need to validate the findings that radiosensitive tumors are more frequently present in tumors with a phenotype of immune activation since these signatures could significantly impact patient selection for treatment modality.

Combination of radiation and immunotherapy

Despite the remarkable success of PD-1 blockade immunotherapy in diverse cancers, a single agent immune checkpoint inhibitor therapy failed to improve the outcome of metastatic pancreatic cancer (84). Several resistance mechanisms of pancreatic ACA to immunotherapy have been suggested. As discussed above, pancreatic cancer has an immunosuppressive tumor microenvironment with downregulation of MHC class I, high expression of IDO, low level of TIL, abundant immune suppressive molecules such as TGF-β and predominant immune suppressive cell population such as Tregs, MDSCs and TAMs. In addition, pancreatic cancer has a low tumor mutation load and low immunogenicity compared with other cancers (85). Tumor mutation burden is associated with neoantigen burden and response to immune checkpoint inhibitor therapy (86,87) since neoantigens can be recognized as non-self by immune cells and elicit cytotoxic T cell immune response. Interestingly, a subset of pancreatic cancers with mismatch repair protein (MMR) deficiency, which is approximately 2% of all pancreatic cancers, (88) harbors greater than 100-fold frameshift and missense mutations compared with MMR proficient tumor (89), and pembrolizumab showed significant anticancer activity in the subset of pancreatic cancer with MMR deficiency (88). Finally, the tumor microenvironment of pancreatic cancer consists of complex and heterogeneous stroma with extracellular matrix protein, cancer associated fibroblasts and endothelial cells, and this dense, fibrotic stroma works as a barrier to effector T cell infiltration (90). To overcome the resistance and improve clinical outcomes, immune checkpoint inhibitors are combined with targeting other immunosuppressive molecules such as LAG-3, TIL-3 and IDO or with chemotherapy, cancer vaccine, T cell therapy or radiation therapy. Here we focus on the combination of immune checkpoint inhibitors and radiation therapy.

Preclinical rationale in solid cancer

The question, then, is how to consider the best way to explore combined RT strategies incorporating immunotherapy to enhance T cell activation and modulate the tumor microenvironment to decrease immunosuppression. Conventionally fractionated radiation relies on the induction of DNA damage to directly kill tumor cells with DNA double-strand breaks leading to mitosis associated cell death or to TP53-mediated apoptosis (91). Doses delivered with stereotactic technique in the 8–10 Gy or higher range have shown higher biological effectiveness, the mechanism of which is still not entirely known, but thought to be related to increased damage to the acid sphingomyelinase apoptotic system of microvascular endothelial cells (92,93). Further, such ablative doses are thought to induce more significant effects on the tumor vasculature, stroma and antitumor immune responses within the local microenvironment, thus causing more cell death (94,95). The question of optimization of dose to achieve this effect is under active investigation since data has shown that a single high dose RT fraction can enhance presentation and T-cell recognition of tumor associated antigens (96). Preclinical data from a murine colorectal tumor model showed that a single dose of 30 Gy, and not fractions of 3 Gy delivered in 10 fractions, was associated with significantly more T cell infiltration in the tumor bed and improved systemic antitumor responses compared with single doses of 15 and 20 Gy (95).

With the enthusiasm for the potential synergy of SBRT and immunotherapy comes a need to further understand the possible mechanisms of interaction. In addition to the

Table 2 Clinical trials of radiation and anti-PD-1/PD-L1 therapy*

Malignancy	Immunotherapeutic agent	Radiation fraction	Treatment intent	Phase	Primary endpoint	Clinical trial identifier
Locally advanced pancreatic adenocarcinoma	Pembrolizumab and GVAX	SBRT (6.6 Gy × 5)	Definitive	II	DMFS	NCT02648282
Metastatic melanoma, NSCLC, breast and pancreatic carcinoma	Pembrolizumab	SBRT	Metastatic	I	Number of AEs	NCT02303990
Borderline resectable pancreatic adenocarcinoma	Nivolumab and GVAX pancreas vaccine	SBRT	Neoadjuvant	II	pCR at surgical resection	NCT03161379
Resectable/borderline resectable pancreatic cancer	Pembrolizumab	RT (50.4 × 28)	Neoadjuvant	I/II	Number of TIL, incidence of DLTs	NCT02305186
Borderline resectable and locally advanced pancreatic adenocarcinoma	Durvalumab	SABR (6.6 Gy × 5)	Neoadjuvant/ definitive	I/II	Number of DLTs, PFS, Proportion of participants who have resectable disease	NCT03245541

*, anti-PD-1/PD-L1 therapeutics included in the table are limited to (A) nivolumab, (B) pembrolizumab or (C) durvalumab. DMFS, distant metastasis free survival; AE, adverse event; pCR, pathologic complete response rate; TIL, tumor infiltrating lymphocytes; DLT, dose-limiting toxicities; PFS, progression free survival; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiation therapy; GVAX, granulocyte-macrophage colony-stimulating factor (GM-CSF) gene transfected tumor cell vaccine.

immunomodulatory effects of RT discussed above, recent preclinical models have demonstrated the upregulation of PD-L1 by tumors as a response to both fractionated and single high dose RT regimens (49,97), suggesting PD-L1 upregulation may be one of the resistant mechanisms to RT. In the studies, the combination of PD-1/PD-L1 blockade with RT induced higher treatment response and generation of tumor antigen-specific memory immune responses (49,97). Another preclinical study suggests upregulation of PD-L1 expression may be one of the resistance mechanisms of anti-CTLA-4 with RT and dual checkpoint blockade with anti-CTLA-4 and anti-PD-L1 plus RT can reverse the resistance and increase antitumor activity (98). The combination of RT with anti PD-1 therapy has also shown improved local tumor control by upregulation of tumor associated antigen-MHC complexes, enhancement of antigen cross presentation and increased T cell infiltration into tumors in murine melanoma and breast cancer models (96).

Preclinical rationale in pancreatic cancer

Applying this data to pancreatic cancer poses specific challenges due to the highly immunosuppressive tumor microenvironment of pancreatic cancer as discussed above. Furthermore, pancreatic tumors have a lower cumulative mutational load (85) which is associated with poor responses to immunotherapy (86,87). This resulting milieu creates a non-immunogenic tumor microenvironment.

Recent preclinical data suggest the combination of RT, vaccination and checkpoint inhibition may be a new strategy for shifting non-T-cell inflamed pancreatic cancers to T-cell inflamed cancers which respond to immunotherapy (99). In the study, sequential combination of RT, vaccination and PD-L1 blockade enhanced the effector function of tumor infiltrating T cells, leading to significantly improved tumor regression in engineered murine pancreatic cancer expressing SIY antigen to mimic non-inflamed cancer. The findings are provocative, suggesting a new model for converting non-T-cell inflamed cancers to T-cell inflamed cancers with a combination of RT, vaccination and checkpoint blockade. Further preclinical data supports RT's potential to convert a "cold" pancreatic tumor microenvironment to a "hot" state with data in a mouse pancreatic cancer model showing any combination of an immune checkpoint inhibitor with RT significantly improved overall survival when compared to activity without RT; the best outcome was radiation plus dual checkpoint blockade (anti-CTLA-4 and anti-PD-L1 antibodies) (98).

Table 3 Clinical trials of radiation and combination anti-PD-1/PD-L1 and anti-CTLA-4 therapy*

Malignancy	Immunotherapeutic agent	Radiation fraction	Treatment intent	Phase	Primary endpoint	Clinical trial identifier
Metastatic pancreatic carcinoma	Nivolumab or nivolumab + ipilimumab	SBRT (15 Gy × 1)	Metastatic	II	CBR	NCT02866383
MSS and MSI high colorectal cancer, pancreatic cancer	Nivolumab + ipilimumab	Not specified	Metastatic	II	DCR	NCT03104439
Unresectable pancreatic carcinoma	Durvalumab, tremelimumab or durvalumab + tremelimumab	SBRT (8 Gy × 1; 5 Gy × 5)	Definitive	I	AE frequency	NCT02311361
Unresectable and non-metastatic pancreatic cancer	Durvalumab, tremelimumab or durvalumab + tremelimumab	SBRT (6 Gy × 5)	Definitive	I	OS	NCT02868632
Metastatic melanoma, NSCLC, breast cancer, pancreatic adenocarcinoma	Durvalumab + tremelimumab	SBRT (8 Gy × 3 or 17 Gy × 1)	Metastatic	I	Number of AEs	NCT02639026

*, anti-PD-1/PD-L1 therapeutics included in the table are limited to (A) nivolumab, (B) pembrolizumab or (C) durvalumab; anti-CTLA-4 therapeutics included in the table are limited to (A) ipilimumab and (B) tremelimumab. CBR, clinical benefit rate; DCR, disease control rate; OS, overall survival; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy; AE, adverse event; CTLA-4, cytotoxic T lymphocyte associated protein 4.

Ongoing clinical trials of combination of radiation and immunotherapy in resectable, locally advanced or metastatic pancreatic cancer

To date, multiple clinical studies are underway that combine RT with anti-PD-1/PD-L1 (*Table 2*), RT with anti-PD-1/anti-PD-L1 plus cancer vaccine (*Table 2*) or with dual checkpoint blockade (anti-CTLA-4 and anti-PD-1/PD-L1) (*Table 3*) in borderline resectable, locally advanced or metastatic pancreatic cancer. The most common form of radiation therapy in these studies involves high dose SBRT delivery alone, most commonly delivered in multiple fractions. A majority of the studies are the combination of SBRT and immune checkpoint blockade using PD-1/PD-L1 inhibitors to evaluate safety and clinical outcome of the combination in the locally advanced or metastatic disease setting (NCT02648282, NCT02303990, NCT02866383, NCT02311361, and NCT02868632). This combination is also investigated in the neoadjuvant setting with borderline resectable disease (NCT03161379, NCT02305186 and NCT03245541). Although most of the clinical trials are currently in early stages, the results will help characterize the proper fractionation of radiotherapy, dosing and sequencing of treatment for future clinical application.

Conclusions

Despite the remarkable success of immune checkpoint blockade immunotherapy in diverse cancers, the immunotherapeutic approach has very limited clinical activity to date in pancreatic cancer. Accumulating evidence demonstrates that radiation is a potent immune stimulator which induces antitumor immune response locally and systemically in addition to direct cytotoxic activity. Ablative radiation may have a significant role as part of the therapeutic strategy in combination with immune therapy to convert non-T cell inflamed ("cold") tumors into highly immunogenic (hot) tumors by upregulation of MHC class I molecules and tumor antigen, secretion of DAMPs, regulation of immunosuppressive cells, and potentially damaging the tumor stroma and microenvironment. However, it is still unclear how to optimally combine radiation and immunotherapy in pancreatic cancer, including optimal sequencing, radiation dose and fractionation to effectively overcome the

immunosuppressive pancreatic tumor microenvironment. Completion of ongoing preclinical and clinical studies with the combination of radiation and checkpoint inhibitors is eagerly awaited to answer these questions and may one day improve clinical outcomes in this resilient cancer.

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