ADAM10 Evens Out the Double-Edged Sword of Radiotherapy in Pancreatic Cancer

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Radiotherapy plays an important role in the management of pancreatic ductal adenocarcinoma (PDAC), especially when patients are not surgical candidates. Radiation-induced tumor death provokes an acute inflammation followed by a late-fibrotic response that parallels the fibroinflammatory tumor microenvironment of PDAC, inciting the question of whether radiation-induced fibrosis contributes to PDAC progression. The study published in this issue by Mueller and colleagues presents a potential mechanism linking radiation-induced fibrosis with expression of a disintegrin and metalloprotease 10 (ADAM10) and ephrinB2, which may also contribute to tumor progression. The authors show that ablation of ADAM10 decreases radiation-induced fibrosis and improves survival in preclinical models. These data suggest that targeting ADAM10 may help to improve clinical outcomes with radiotherapy, particularly if definitive radiation is not possible. A better understanding of the biology of radiotherapy in pancreatic cancer remains crucial, and Mueller and colleagues offer important insight in this regard.

See related article by Mueller et al., p. 3255

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer that spreads rapidly and is resistant to nearly all forms of modern therapy. Patients who have their pancreatic tumors surgically removed have the best outcomes, but the vast majority of patients have disease too advanced for a curative operation. Radiotherapy targets therapeutic X-rays at tumors anywhere in the body and in some cases, it can serve as a noninvasive substitute for surgery, especially if an operation is not possible (1). PDAC, however, is challenging to target with radiotherapy because this tumor is resistant to radiation damage and it grows next to organs that are sensitive to radiation injury, such as the stomach and duodenum. Because of these concerns, patients with pancreatic cancer often receive a radiation dose that is close to 50 Gy when given in 2 Gy fractions. This dosing scheme is safe, but unlikely to improve survival without surgery (2).

PDAC has a dense fibroinflammatory stroma that plays a complex role in its pathobiology (3). This desmoplastic stroma increases intratumoral pressure, which leads to hypoxia and limits the delivery of chemotherapy. Moreover, proinflammatory stromal responses in PDAC have been linked to tumor invasion, metastasis, and treatment resistance (3). Unfortunately, approaches to disrupt PDAC desmoplasia have produced equivocal or sometimes worse outcomes compared with controls, further highlighting the complex biology of the tumor microenvironment of pancreatic cancer (3).

Radiation-induced tumor death almost always provokes an acute inflammation, followed by a late-fibrotic response in irradiated areas (4). The inflammation that stems from radiation eventually leads to increased collagen deposition, fibrosis, scarring, and poor vascularity. This common biology between the radiation response and pancreatic cancer raises a fair question on whether postradiation inflammation may inadvertently promote cancer progression, especially if the radiation dose does not eliminate every cancer clonogen. Thus, there is a knowledge gap in the biology of the interactions between radiotherapy and the PDAC tumor microenvironment.

The study published in this issue by Mueller and colleagues provides an advance in our understanding of the mechanisms that might link radiation-induced fibrosis to tumor progression and radioresistance. The authors identified a disintegrin and metalloprotease 10 (ADAM10) and ephrinB2 as drivers of radiation-induced tumor fibrosis, invasiveness, and treatment resistance (5). ADAM10 is a protease that cleaves fibroblast membrane–bound ephrinB2, leading to myofibroblast activation and excessive extracellular matrix deposition (6). The roles of these genes in PDAC are supported by The Cancer Genome Atlas data that suggested better outcomes in patients with low expression of both *ADAM10* and *EFNB2* (5). However, individual expression of either *ADAM10* or *EFNB2* alone was not independently prognostic. The authors confirmed that the ADAM10–ephrinB2 axis is stimulated by radiotherapy (5). They detected soluble ephrinB2 in the plasma of patients with PDAC treated with neoadjuvant chemoradiotherapy and found that ephrinB2 levels increased 6 weeks postradiation in patients that received higher doses of radiotherapy (10–11 Gy × 3), but not in those that received a low dose (9 Gy × 3; ref. 5).

Using several elegant mouse models, the authors then directly linked ADAM10 to radiation-induced tumor fibrosis and tumor progression by providing evidence that ADAM10 expression is necessary for the development of radiation-induced PDAC fibrosis (5). The authors also demonstrated that genetic ablation of ADAM10 reduces radiation-induced tumor fibrosis and improves survival in syngeneic pancreatic cancer mouse models. Moreover, they showed that the addition of an ADAM10 inhibitor to radiotherapy modestly reduces tumor growth (5). Together, these data suggest that altering the ADAM10–ephrinB2 axis may help radiotherapy achieve its full potential in reducing disease burden, without inducing pathogenic fibrosis.

The results of this study, however, do not necessarily apply to every radiation approach used in PDAC, because the doses used in these mouse models were fairly modest. Although the Gray (Gy) is the international unit of radiation dose, it does not directly reflect the biological effects in tissues and tumors. To compare the relative effects

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among radiation dosing schemes, it can be helpful to convert the dose of radiation to an equivalent dose in 2 Gy fractions, or EQD2 (7). Previous studies have indicated that an EQD2 exceeding 80 Gy would be required to ablate pancreatic cancer (8). To put this into context, the most common radiotherapy dose for pancreatic cancer in the clinic is close to EQD2 of 50 Gy, which is safe, but not as effective as might be needed in selected patients. The high-dose radiation schemes in this study were 16 Gy × 1 (EQD2 = 34.7 Gy) for the preclinical studies and 11 Gy × 3 (EQD2 = 57.8 Gy) for the patients who received the high-dose arm of stereotactic body radiotherapy (SBRT). Thus, this study is useful in understanding how insufficient radiotherapy might inadvertently promote tumor progression and underscores the need to deliver ablative radiation doses.

The study by Mueller and colleagues highlights that radiation is indeed a double-edged sword in pancreatic cancer. For patients with PDAC who cannot get surgery, radiotherapy may be the only way to cytoreduce their primary tumor and reduce morbidity, but it may come at the cost of unacceptable toxicity and worsened quality of life. On the other hand, if radiation is not delivered at an ablative dose, tumor recurrence becomes quite likely due to the inflammation that results from the body's response to dying tumor clonogens, and which may unfortunately promote the survival of any remaining cancer cells (4). Thus, although there are some very promising data to support radiotherapy in PDAC, there are also several mixed results that temper enthusiasm (9).

The advent of SBRT has enabled the delivery of high doses with great accuracy to the tumor bed itself while sparing normal surrounding tissues. These approaches have been further improved by using MRI or other advanced imaging to guide radiotherapy in real-time. In addition, combining SBRT with radiation sensitizers enables the radiation treatment to reach ablative dosing. A multicenter phase I/II trial used high-dose SBRT (10–11 Gy × 5, EQD2 = 83.3–96.3 Gy) with a radiosensitizing superoxide dismutase mimetic, GC4419, and recently presented preliminary results showing that adding GC4419 to SBRT significantly improved clinical outcomes, presenting hope for patients with pancreatic cancer (10). Unfortunately, such technologies are not yet available to all patients.

In spite of mixed data regarding SBRT clinical outcomes, what multiple trials seem to indicate is that neoadjuvant SBRT delivery may not benefit every patient (9). As important as locoregional treatment is, it unfortunately cannot be considered standard of care for all patients with PDAC. Nevertheless, given radiotherapy's success as a cytoreductive agent in the management of pancreatic cancer (10), we need a wider adoption of ablative radiation techniques and the development of biomarkers to select patients who would benefit from aggressive locoregional control, either through surgery or ablative radiation. Until that time, the current study provides a deeper understanding of the molecular links between radiation-induced fibrosis and pancreatic cancer biology, and may thus, be useful in designing adjuvant treatments to improve current approaches with radiotherapy.

Authors' Disclosures

C.M. Taniguchi was on the clinical advisory board of Accuray during the conduct of the study, has a patent for oral amifostine as a radioprotectant of the upper GI tract issued, licensed, and with royalties paid from Xerient Pharmaceuticals and PHD inhibitors as a radioprotectant of the GI tract pending, and was the lead principal investigator of a multicenter trial testing the effects of high-dose SBRT with the radiomodulator, GC4419. No disclosures were reported by the other authors.

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