Review Article

Harnessing the abscopal effect for gastrointestinal malignancies in the era of immunotherapy

Christopher Hino[1]^, Edward W. Lee[2], Gary Y. Yang[2]

[1]Department of Internal Medicine, Department of Medicine, Loma Linda University, Loma Linda, CA, USA; [2]Department of Radiation Medicine, Loma Linda University, Loma Linda, CA, USA

Contributions: (I) Conception and design: C Hino, GY Yang; (II) Administrative support: GY Yang; (III) Provision of study of materials or patients: GY Yang; (IV) Collection and assembly of data: C Hino, EW Lee; (V) Data analysis and interpretation: C Hino, EW Lee; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Gary Y. Yang, MD. Department of Radiation Medicine, Loma Linda University Medical Center, 11234 Anderson Street, Loma Linda, CA 92354, USA. Email: gyang@llu.edu.

Abstract: Gastrointestinal (GI) cancers are among the leading causes of cancer-related mortality and have traditionally been treated using a combination of surgical resection and chemoradiotherapy (CRT). While the introduction of immunotherapies over the last decade have dramatically changed the treatment landscape for some GI malignancies, including esophageal, gastric, and colorectal cancer, treatment resistance remains a major unaddressed obstacle for many patients. There has thus been emerging interest in determining the optimal treatment strategy for the delivery of immunotherapy in combination with traditional therapies. In this regard, a growing number of preclinical and clinical studies have suggested that combining radiation therapy (RT) with immunotherapy may work synergistically to improve treatment response through amplification of the abscopal effect. In this review, we discuss the rationale for RT in combination with immunotherapy. We further discuss how this knowledge may lead to a paradigm shift in the application of RT and highlight remaining issues pertaining to the delivery of combination therapy.

Keywords: Immunotherapy; radiotherapy; radiation therapy; immune checkpoint inhibitor; gastrointestinal cancer; gastric cancer; abscopal effect

Submitted Feb 09, 2023. Accepted for publication May 23, 2023. Published online Jun 02, 2023.
doi: 10.21037/jgo-23-105
View this article at: https://dx.doi.org/10.21037/jgo-23-105

Introduction

Gastrointestinal (GI) cancers such as esophageal, gastric, pancreatic, hepatobiliary and colorectal cancers (CRCs) account for approximately 20% of newly diagnosed cancers and a substantial proportion of all cancer-related deaths in the United States each year (1). Radiation therapy (RT) has become an important treatment modality in the management of GI malignancies for definitive local therapy, adjuvant treatment or palliative care. With technological advances in the treatment planning and delivery, including incorporation of functional imaging, CT/MRI-based 3-dimensional treatment planning, and image-guided radiotherapy, RT has become a safer, more precise and effective approach to achieving local control of tumor progression (2).

Over the past decade the rapid emergence and availability of targeted immunotherapies, especially immune checkpoint blockade (ICB) therapies have dramatically transformed the treatment landscape for solid tumor oncology (3). Unlike traditional chemotherapy or RT, which directly kill cancer cells, immunotherapy harnesses the host's preexisting immune system to eradicate tumor

^ ORCID: 0000-0003-4637-4481.

cells by activating immune cell anti-tumor activity. For GI malignancies, immunotherapies have likewise gained increasing attention over the past several years. ICB, vaccine therapies, and adoptive cell transfer therapies have particularly demonstrated promising clinical activity for a subset of patients with metastatic GI disease. However further investigation is still required to maximize its efficacy in the clinical setting.

In this regard, there is growing evidence to suggest the immunomodulatory function of RT, and its potential to work synergistically with immunotherapy through a phenomenon known as the abscopal effect. In this review we provide an overview of current evidence, recent advances, and future directions for the potential combinatory role of immunotherapy with low-dose radiation therapy in GI malignancies.

Rationale for combining radiotherapy and immunotherapy in GI malignancies

Radiation therapy has systemic immunomodulatory effects that impact tumor growth

The focus of RT has traditionally been on the direct cytotoxic effects of ionizing radiation on cancer cells through its ability to irreparably damage DNA and generate reactive oxygen species (ROS) (4). Its clinical role has therefore been primarily to achieve local tumor control. However, there is growing evidence to suggest that RT can also induce a series of systemic immunomodulatory effects both within and outside of the irradiated field (5,6). The best known clinical example of this was first reported in 1953 by Mole when he made the observation that local radiation could induce spontaneous tumor regression at distant non-irradiated sites, a phenomenon he termed the "abscopal effect" (7,8). At the same time, a number of early studies have also demonstrated that the efficacy of radiotherapy and abscopal effect is at least partly dependent on the immunocompetence of its recipient (9-13).

Since then, an abundance of preclinical studies have uncovered the biological basis for how radiotherapy may enhance antitumor immunity (*Figure 1*). Radiation induced tumor cell death results in an increased release of tumor antigens and damage associated molecular patterns (DAMPs). In essence, radiotherapy can function as a personalized *in situ* tumor vaccine by enhancing tumor antigen cross- presentation on dendritic cells (DCs) and subsequently promoting the priming and activation of cytotoxic $CD8^+$ T cells (14,15). This is process is additionally mediated by the increased translocation of calreticulin and other ligands that help promote DC phagocytosis, as well as upregulated expression of MHC Class I (16,17). There is further evidence to suggest that radiation therapy may help to expand and diversify the tumor-directed TCR repertoire, thereby increasing the likelihood of tumor-antigen recognition (18,19).

Low to moderate doses of radiation have also been shown to modulate the inflammatory milieu through the release of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interferon-α (IFN-α), IFN-β, and IFN-γ, from irradiated cancer cells (20-22). The accumulation of cytosolic DNA by RT and subsequent activation of cytosolic nucleic acid sensor pathways such as cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) has notably been cited as an important mechanism driving type I IFN expression (23-25). A multitude of other alterations to the tumor microenvironment (TME) also occur with radiation exposure and may influence anti-tumor immunity (6,26,27). The release of pro-inflammatory cytokines as previously discussed, as well as the chemokines CCL5, CXCL16 and CXCL10 have been shown to promote infiltration of effector T cells and antigen presenting cells to the TME (21,25,28,29).

Finally, there is some evidence to suggest that RT may also lead to the upregulated expression of PD-L1 in tumor cells and that this may portend a worse prognosis in certain solid malignancies (30). Nevertheless, the expression of PD-L1 on tumor cells has been shown to be a useful biomarker for predicting response to ICB therapy (31). This provides additional rationale for combining PD-1/PD-L1 inhibitors with radiotherapy.

Immunotherapy may enhance the abscopal effect

While the occurrence of the abscopal effect observed in clinical practice is relatively rare, an increasing number of anecdotal cases have been reported in a variety of metastatic solid tumors (32). In 2012, Postow and colleagues were notably the first to describe this phenomenon in a melanoma patient who developed a systemic response after stereotactic body radiation therapy (SBRT) combined with ipilimumab, an anti-CTLA-5 antibody (33). These findings have since garnered growing interest in combining RT with immunotherapies to boost the occurrence of the abscopal effect for the purpose of enhancing anti-tumor immunity.

Prospective trials investigating the efficacy of combining

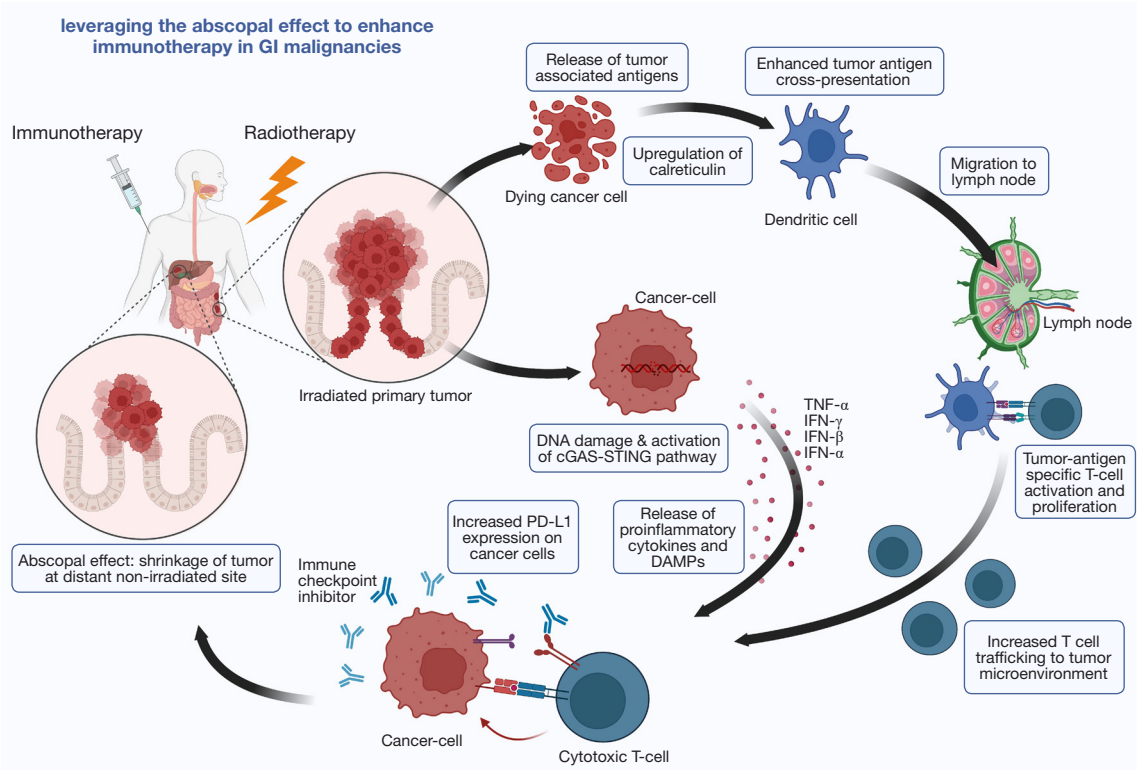

Figure 1 Schematic overview illustrating the mechanisms of synergy between radiotherapy and immunotherapy. Radiation therapy induces immunomodulatory effects that can boost anti-tumor immunity in several ways. Damage and death of cancer cells by radiation causes the release of tumor associated antigens, increased calreticulin, DAMPS which activate dendritic cells which prime $CD8^+$ cytotoxic T cells. The activation of the cGAS-STING Pathway further leads to increase in pro-inflammatory cytokines, especially type I interferons which help to recruit active immune cells to the tumor microenvironment. The addition of immune checkpoint inhibitors such as anti-CTLA4 and anti-PD1/PD-L1 based therapies work synergistically with radiation therapy to promote an effective anti-tumor response. An anti-tumor immune response seen at a distant non-irradiated site through the abscopal effect may be one such benefit of combining immunotherapy with radiation (Elements of diagram created with Biorender.com). GI, gastrointestinal; DAMPs, damage associated molecular patterns; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; CTLA4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

immunotherapy and RT have recently gained momentum over the last decade. An initial proof-of-principle clinical trial (NCT02474186) first showed that RT (35 Gy in 10 daily fractions) combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) could boost the incidence of the abscopal effect in patients with metastatic solid tumors (34). Results from the KEYNOTE-001 trial further demonstrated that patients with advanced non-small lung cancer (NSCLC) who previously received RT had longer progression-free survival (PFS) and overall survival (OS) with pembrolizumab, an anti-PD1 inhibitor, than those who did not receive previous radiotherapy (35,36). Similar findings have also been observed when ipilimumab, an anti CTLA-4 inhibitor, was combined with RT in metastatic NSCLC (18). Since then, the combination of radiotherapy and immunotherapy has demonstrated success in several solid malignancies including NSCLC, gliomas, and melanoma (37-43). Recent data in NSCLC, notably showed that stereotactic body radiotherapy (SBRT) on a single tumor site preceding pembrolizumab could double out-of-field anti-tumor responses when compared to treatment with pembrolizumab alone (44). While these early clinical results have been promising, the application of RT with immunotherapy for treatment of gastroesophageal malignancies remains ongoing.

Current status and ongoing efforts for immunotherapy in gastrointestinal cancers

Esophagogastric cancers

Esophageal cancers make up one of the most aggressive GI malignancies and contribute significantly to cancer-related deaths worldwide (45). While early stage or locally advanced esophageal cancers can often be cured with endoscopic resection or esophagectomy, more advanced stage disease requires additional systemic chemotherapy with or without RT for suppression of local tumor growth and alleviation of dysphagia (46,47). More recently, immune checkpoint inhibitors have been incorporated into the management of patients with upper GI cancers (48).

In regards to the treatment of early-stage disease, the phase III CheckMate 577 was the first trial to demonstrate that nivolumab, an anti-PD1 inhibitor, significantly improves disease-free survival for resected (R0) stage II/III esophageal or gastroesophageal junction (GEJ) cancer who received neoadjuvant chemoradiation and had residual pathologic disease. The median disease-free survival had doubled with adjuvant nivolumab compared with placebo (22.4 *vs.* 11 months; HR 0.69; 96.4% CI: 0.56–0.86; P=0.0003) (49). Based on these results, the FDA approved the use nivolumab for stage II/III esophageal or GEJ cancer with residual pathologic disease after complete resection and neoadjuvant chemoradiotherapy. There are now multiple ongoing trials to investigate the use of combining immune checkpoint inhibitors with RT for early stage disease (*Table 1*).

For advanced esophageal cancer, a series of landmark trials have also demonstrated the efficacy of utilizing immunotherapy for first-line treatment. The results from the phase III CheckMate 649 trial showed that for untreated, advanced, HER2 negative gastric, GEJ, or esophageal adenocarcinoma with a PD-L1 combined positive score (CPS) ≥5%, use of Nivolumab plus chemotherapy prolonged OS [hazard ratio (HR) 0.71 (98.4% CI: 0.59–0.86); P<0.0001] and progression-free survival (HR 0.68; 98% CI 0.56–0.81; P<0.0001) *vs.* chemotherapy alone (50). This led to FDA approval of nivolumab plus chemotherapy as first-line setting for all patients with esophageal cancer, however, NCCN has recommended that nivolumab should be reserved for patients with PD-L1 CPS ≥5%. The results from the phase III KEYNOTE 590 trial, similarly demonstrated significant improvement in OS and PFS in patients treated with pembrolizumab plus chemotherapy *vs.* chemotherapy alone (51). The CheckMate 648 trial also showed improved overall survival with the addition of nivolumab *vs.* standard-of-care chemotherapy alone for advanced esophageal squamous-cell carcinoma (52). While a majority of studies combining chemotherapy and radiation therapy remain ongoing (*Table 1*), the results of a phase 2 trial combining pembrolizumab with palliative radiation therapy for metastatic gastroesophageal cancer demonstrated promising durable responses, however, the study was unable to distinguish abscopal biologic changes (53).

Colorectal and anal cancer

The introduction of immune checkpoint inhibitor therapies have transformed the treatment landscape for patients with mismatch repair deficient (MMR-D)/microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC) (54,55). Based on the results of several seminal studies, the FDA first approved the use of the PD-1 inhibitor, pembrolizumab, in 2017 for any unresectable or metastatic MSI-H/dMMR solid tumors that had failed prior treatment and without alternative treatment options (56). This was the first time the agency had approved a cancer treatment based on a tumor biomarker rather than the site of origin.

Since then, several trials have been underway to expand the use of ICB therapy in MSI-H/dMMR CRC. Notably, results from the open label, phase III KEYNOTE-177 trial demonstrated that treatment with pembrolizumab resulted in longer PFS (16.5 *vs.* 8.2 months) compared to standard of care chemotherapy in untreated MSI-H/dMMR mCRC (57). The initial trial results led to the approval of pembrolizumab as single-agent, first-line therapy in MSI-H/dMMR mCRC. However, final post-hoc analysis showed that while pembrolizumab continued to show durable activity with fewer treatment-related adverse events compared to chemotherapy, pembrolizumab failed to demonstrate statistically significant improvement in overall survival compared to chemotherapy (58). An open label, non-randomized phase II trial (NCT04165772), similarly showed promising treatment response in dMMR locally advanced rectal cancer using dostarlimab, an anti-PD1 inhibitor (59). Findings from the phase II CheckMate 142 trial, further demonstrated durable clinical benefit of combined nivolumab and low-dose ipilimumab for first-line treatment of MSI-H/dMMR mCRC (60). These findings justify the necessity to validate the efficacy of dual ICB therapy in future randomized clinical trials.

Despite these advances, both single or dual ICB therapy

Table 1 Ongoing clinical trials involving immunotherapy combined with radiotherapy for GI malignancies

Trial ID	Phase	Tumor type and histology	Immunotherapy	Radiation	Study design
Esophagogastric cancers					
NCT02735239	I/II	Metastatic/locally advanced esophageal cancer (N=73)	Durvalumab ± tremelimumab	Unspecified EBRT	Non-randomized, open label trial evaluating the safety of Durvalumab ± tremelimumab in combination with oxaliplatin/capecitabine chemotherapy and standard RT
NCT02642809	I	Metastatic esophageal cancer	Pembrolizumab	Brachytherapy (16 Gy in 2 fractions of 8 Gy per fraction, separated by 7–10 days between fractions	Open label trial evaluating tolerability of localized brachytherapy combined with pembrolizumab as measured by treatment related adverse events
NCT03377400	II	Inoperable ESCC	Durvalumab and tremelimumab	Unspecified	Open label, single-arm study evaluating progression-free survival with combination of chemotherapy (5FU/CDDP) and Durvalumab + Tremelimumab with concurrent RT
NCT03437200	II	Inoperable, early stage and locally advanced ESCC or EAC	Nivolumab ± ipilimumab	50 Gy in 25 fractions	Randomized, open label study evaluating safety of nivolumab ± Ipilimumab in combination with standard RT and FOLFOX
NCT03792347	I	Stage II/III ESCC	Pembrolizumab	41.4 Gy in 23 fractions	Open label, single arm study evaluating the safety of preoperative pembrolizumab with standard carboplatin, paclitaxel, and RT
NCT02844075	II	Stage II/III ESCC	Pembrolizumab	41.4 Gy in 23 fractions	Open-label, single arm study evaluating pathologic response rate of patients receiving preoperative chemoradiotherapy with paclitaxel, carboplatin and pembrolizumab
NCT02520453	II	ESCC (N=86)	Durvalumab	Unspecified	Randomized, double blind study evaluating treatment response of adjuvant Durvalumab or placebo for completely resected esophageal squamous cell carcinoma previously treated with neoadjuvant concurrent chemoradiotherapy
NCT02830594	II	ESCC, EAC, GEJ, GAC (N=14)	Pembrolizumab	Unspecified EBRT	Open-label, single arm study evaluating pathologic response rate of pembrolizumab and palliative EBRT
NCT03087864	II	Stage II EAC or GEJ (N=40)	Atezolizumab	23 x1.8 Gy	Open-label, single arm study evaluating the feasibility of preoperative treatment with atezolizumab combined with preoperative carboplatin, paclitaxel and radiation
NCT03278626	I/II	Locally advanced ESCC (N=12)	Nivolumab	50.4 Gy (1.8 Gy/fraction x28 fractions)	Open-label single arm study evaluating the safety and efficacy treatment with Nivolumab in combination with paclitaxel, carboplatin, RT
NCT03544736	I/II	ESCC or EAC or GEJ (N=30)	Nivolumab	20-50 Gy in 25 fractions *vs.* 50.4 Gy in 28 fractions *vs.* 41.4 Gy in 23 fractions	Open-label, multi-arm, non-randomized study evaluating the safety and feasibility of treatment of advanced/inoperable *vs.* operable EC with Nivolumab in combination with paclitaxel, carboplatin, RT
NCT03257163	II	Stage II/III dMMR or EBV+ GAC (N=40)	Pembrolizumab	Conventional Fractionation	Open-label, single arm study evaluating RFS with treatment with pembrolizumab in combination with capecitabine and RT
NCT03064490	II	Stage II/III GAC or EAC (N=38)	Pembrolizumab	41.4 Gy in 23 fractions	Open-label, non-randomized, single arm study evaluating pathologic complete response of neoadjuvant pembrolizumab in combination with carboplatin and paclitaxel and RT
NCT02730546	I/II	Stage II/III GC or GEJC (N=31)	Pembrolizumab	41.4 Gy in 23 fractions	Open-label, single arm study evaluating the safety and efficacy of pembrolizumab in combination with concurrent chemoradiotherapy, carboplatin, and paclitaxel
NCT03044613	I	Stage II/III EAC, OSCC or GEJC (N=32)	Nivolumab or Relatlimab	41.4 Gy in 23 fractions	Open-label, non-randomized study evaluating treatment with nivolumab or Relatlimab in combination with carboplatin and paclitaxel in the pre-operative setting
NCT03776487	I/II	Stage II/III GC or GEJC (N=30)	Nivolumab and ipilimumab	50 Gy in 25 fractions	Open label study evaluating the safety and toxicity profile of nivolumab in combination with ipilimumab after standard chemotherapy and followed by nivolumab in combination with fluoropyrimidine and RT
NCT02962063	II	Stage II/III GEJC and GC (N=78)	Durvalumab and tremelimumab	50 Gy in 28 fractions	Open label study evaluating the safety of treatment with durvalumab and tremelimumab in combination with carboplatin, paclitaxel and RT
NCT04159974	II	Stage II/III EAC or GEJC (n=56)	Durvalumab and tremelimumab	41.4 Gy in 23 fractions	Open label, randomized study evaluating the safety and efficacy of adding Durvalumab to standard neoadjuvant radichemotherapy and of Durvalumab +/- Tremelimumab
NCT02639065	II	Stage II/III EAC or GEJC with residual disease (N=39)	Durvalumab	41.4 Gy in 23 fractions	Open label, single arm study evaluating the safety and efficacy of durvalumab following multi-modality therapy
NCT03490292	I/II	Stage II/III ESCC or EAC (N=22)	Avelumab	41.4 Gy in 23 fractions	Open label, Non-randomized study evaluating the safety tolerability and efficacy of avelumab in combination with carboplatin, paclitaxel, and RT
NCT03604991	II/III	Stage II-IV EAC, GEJC (N=514)	Ipilimumab and nivolumab	Unspecified	Open label, randomized trial evaluating the peri-operative use of Nivolumab and Ipilimumab in addition to standard of care chemotherapy and RT
Colorectal and anal cancers					
NCT03104439	II	MSI-high colorectal and pancreatic cancer (N=80)	Nivolumab and ipilimumab	24 Gy in 3 fractions	Open label study evaluating the safety and efficacy of Nivolumab and ipilimumab in combination with RT
NCT04663763	II	Locally advanced rectal cancer (N=40)	Sintilimab	25 Gy over 5 fractions	Open label, single arm study evaluating Sintilimab in combination with Capecitabine, Oxaliplatin, and RT
NCT04518280	II	Locally advanced rectal cancer (N=130)	Toripalimab (Anti-PD-1)	25 Gy over 5 fractions	Open label, randomized trial evaluating combination of Toripalimab and neoadjuvant short-course RT
NCT04558684	I/II	Non-metastatic rectal cancer (N=30)	Camrelizumab	25 Gy over 5 fractions	Open label trial evaluating preoperative treatment with camrelizumab, neoadjuvant chemotherapy, and RT
NCT04621370	II	Locally advanced rectal adenocarcinoma (N=48)	Durvalumab	25 Gy over 5 fractions or 50 Gy over 25 fractions	Open label, randomized trial evaluating Durvalumab in combination with FOLFOX and RT
NCT04109755	II	Untreated, localized rectal adenocarcinoma (N=25)	Pembrolizumab	25 Gy over 5 fractions	Open label study evaluating the safety and efficacy of neoadjuvant Pembrolizumab and RT
NCT03503630	II	Locally-advanced rectal adenocarcinoma (N=44)	COMPOUND 2055269 (Anti-PD-L1)	25 Gy in 5 fractions	Open Label study evaluating the pCR rate following short course RT then mFOLFOX-6 in combination with COMPOUND 2055269
NCT04503694	II	Stage II-III rectal adenocarcinoma (N=60)	Nivolumab	25 Gy in 5 fractions	Multicenter, single-arm, open label trial evaluating the efficacy of Nivolumab in combination with Regorafenib when administered before and after standard, pre-operative short course RT
NCT04636008	I/II	MSI-H/dMMR non-metastatic rectal cancer (N=20)	Sintilimab (anti PD-1)	25 Gy in 5 fractions	Open label, single arm study evaluating the safety and efficacy of Sintilimab combined with hypofractionated RT
NCT04411537	II	MSS locally advanced rectal adenocarcinoma (N=50)	PD-1 antibody (unspecified)	50 Gy in 25 fractions	Open label, single arm study evaluating pathologic complete response rate for treatment of Anti-PD1 therapy in combination with neoadjuvant capecitabine, irinotecan, and RT
NCT04411524	II	MSI-H locally advanced rectal adenocarcinoma (N=50)	PD-1 antibody (unspecified)	50 Gy in 25 fractions	Open label, single arm study evaluating pathologic complete response rate for treatment of Anti-PD1 therapy in combination with neoadjuvant capecitabine, irinotecan, and RT
NCT03854799	II	Locally advanced, resectable rectal adenocarcinoma (N=101)	Avelumab	50.4 Gy in 28 fractions	Open label, single arm study evaluating pCR of preoperative Avelumab in combination with Capecitabine and RT
NCT04357587	I	MSI-H/dMMR stage II-III rectal adenocarcinoma, or oligometastatic locally advanced stage IV that are candidates for curative surgery (N=10)	Pembrolizumab	Daily fractions of 200 cGy, 5 days a week for 5 weeks	Open label, single arm study evaluating the safety, tolerability, and feasibility of Pembrolizumab in combination with Capecitabine and RT
NCT03921684	II	Locally advanced rectal adenocarcinoma (N=29)	Nivolumab	50.4 Gy in 28 fractions	Open label, single arm study evaluating safety and pCR of Nivolumab in combination with neoadjuvant mFOLFOX6, Capecitabine, and RT
NCT02921256	II	Locally advanced rectal adenocarcinoma (N=362)	Pembrolizumab	Unspecified	Open label, randomized trial evaluating the efficacy of Veliparib or pembrolizumab in combination with mFOLFOX6, capecitabine, and RT

Table 1 (*continued*)

Table 1 (*continued*)

Trial ID	Phase	Tumor type and histology	Immunotherapy	Radiation	Study design
NCT03127007	I/II	Untreated, locally advanced rectal adenocarcinoma (N=54)	Atezolizumab	45–50 Gy in 25 fractions	Open Label, Randomized trial evaluating the safety and efficacy of preoperative Atezolizumab in combination with 5-FU and RT
NCT04443543	II	Locally advanced rectal adenocarcinoma (N=222)	Tislelizumab	50 Gy in 25 fractions	Multicenter, open label, non-randomized trial evaluating CCR rate in patients treated with long course chemoradiation based on their MSI-H/dMMR status. After completion of consolidation chemotherapy, patients who reach CCR will receive organ preservation (watch and wait) strategy in place of radical surgery
NCT04017455	II	Locally advanced rectal adenocarcinoma (N=38)	Atezolizumab and bevacizumab	unspecified	Open label, single arm trial evaluating the efficacy of neoadjuvant RT followed by Atezolizumab and Bevacizumab
NCT04124601	II	Locally advanced rectal adenocarcinoma (N=80)	Nivolumab and ipilimumab	50 Gy in 2 Gy fractions	Open label, randomized trial to evaluate the safety and tolerability of sequential Nivolumab and Ipilimumab in combination with chemoradiotherapy
NCT04293419	II	Untreated locally advanced rectal adenocarcinoma (N=58)	Durvalumab	50.4 Gy in 28 fractions	Open label, non-randomized, single arm study evaluating the pCR rate of Durvalumab in combination with mFOLFOX6, capecitabine, and RT
NCT03102047	II	MSS stage II-IV rectal adenocarcinoma (N=45)	Durvalumab	Unspecified	Open label, single arm study evaluating the efficacy of Durvalumab after chemo-radiotherapy
NCT02948348	I/II	Locally advanced, resectable rectal adenocarcinoma (N=90)	Nivolumab or ipilimumab	45 Gy in 25 fractions	Open-label, single-arm, multicenter study evaluating the safety and efficacy of Nivolumab or ipilimumab as sequential therapy following capecitabine and RT and subsequent surgical therapy
NCT03299660	II	Locally advanced, resectable rectal adenocarcinoma (N= 37)	Avelumab	50.4 Gy in 28 fractions	Open label, single-arm study evaluating the pathological response rate of Avelumab following neoadjuvant long course RT with Capecitabine, 5-FU. This will be followed by surgical resection
NCT04083365	II	Locally advanced rectal adenocarcinoma (N=60)	Durvalumab	5040 cGy radiotherapy for 5 days per week for 5 weeks	Open-label, single arm study evaluating pCR of Durvalumab in combination with Capecitabine and RT
NCT03300544	I	Rectal adenocarcinoma of any stage, excluding patients with CNS metastasis (N=3)	Talimogene laherparepvec (oncolytic herpes virus)	50.4 Gy in 28 fractions	Open label, single-arm study evaluating the safety and feasibility of talimogene laherparepvec in combination with standard neoadjuvant chemotherapy and RT
NCT04130854	II	Untreated, locally advanced rectal adenocarcinoma (N=58)	APX005M (Anti-CD40)	25 Gy in 5 fractions	Open-label, Randomized study evaluating pCR of APX005M in combination with mFOLFOX and RT
NCT03916510	I	Locally advanced rectal adenocarcinoma (N=30)	Enadenotucirev (Oncolytic virus)	50 Gy in 25 fractions	Open-label, single arm study evaluating the safety and efficacy of Enadenotucirev in combination with Capecitabine and RT
NCT04304209	II	Stage II or III CRC (N=195)	Sintilimab	50 Gy in 25 fractions	Open label, randomized study evaluating the efficacy of Sintilimab in combination with standard chemoradiation therapy according to their MMR/MSI status
NCT03233711	III	High risk stage II-IIIB anal squamous cell carcinoma (N=344)	Nivolumab	Must have received at least 54 Gy of radiation to the primary and 45 Gy to elective nodal region prior to start of trial	Randomized, open label study evaluating whether Nivolumab *vs.* observation alone improves disease-free survival in patients who have previously received combined modality therapy (including RT)
Hepatobiliary cancers					
NCT03203304	I	Unresectable HCC (N=14)	Nivolumab or ipiliomumab	40 Gy in 5 fractions	Open label, randomized study evaluating the safety and efficacy of SBRT followed by Nivolumab or Ipilimumab with Nivolumab
NCT03812562	I	Resectable HCC (N=2)	Nivolumab	Yttrium-90 radioembolization	Open label, non-randomized study evaluating the safety and recurrence rate of standard of care yttrium Y glass microspheres followed by Nivolumab
NCT05063565	II	Unresectable HCC (N=150)	Durvalumab, tremelimumab	ThereaSphere Y-90 glass microsphere therapy	Multi-center, open label, randomized study evaluating the efficacy of TheraSphere Y-90 microsphere therapy in combination with Durvalumab and Tremelimumab
NCT03817736	II	Unresectable HCC (N=33)	Immune checkpoint inhibitor (unspecified)	SBRT (unspecified)	Open label, single arm study evaluating the efficacy and safety of sequential administration of TACE and SBRT with an immune checkpoint inhibitor
NCT04988945	II	Unresectable HCC (N=33)	Durvalumab, tremelimumab	SBRT (unspecified)	Open label, single arm study evaluating efficacy of downstaging HCC for hepatectomy with sequential TACE, SBRT and Durvalumab + Tremelimumab
NCT04167293	II/III	HCC with portal vein invasion after TACE or hepatic arterial infusion chemotherapy (n=116)	Sintilimab	30–54 Gy in 3–6 fractions	Open label, randomized study evaluating the efficacy of SBRT followed by Sintilimab
NCT03753659	II	HCC (N=30)	Pembrolizumab	RFA/MWA/Brachytheraopy	Multicenter, single arm, open-label study evaluating the clinical activity of pembrolizumab in combination with RFA/MWA/brachytherapy
NCT05286320	I/II	Unresectable HCC (N=27)	Pembrolizumab	SBRT (Unspecified)	Open label, single arm study evaluating the safety and efficacy of Pembrolizumab+ lenvatinib with SBRT combinations
NCT03898895	II	Unresectable biliary tract cancer (N=36)	Camrelizumab	45 Gy total	Open label, single-arm study evaluating the efficacy and safety of Camrelizumab combined with RT
Pancreatic cancer					
NCT02305186	I/II	Borderline resectable PDAC (N=68)	Pembrolizumab	50.4 Gy in 28 Fractions	Open label, randomized study evaluating the safety and efficacy of Pembrolizumab in combination with neoadjuvant chemoradiation
NCT03161379	II	Borderline resectable PDAC (N=30)	Nivolumab, GVAX pancreas vaccine	6.6 Gy in 5 fractions	Open label, randomized study evaluating the safety and clinical activity of FOLFIRINOX along with a whole cell vaccine with immune modulating doses of cyclophsophamide and nivolumab combined with SBRT
NCT01595321	N/A	Surgically resected PDAC (N=19)	GVAX	6.6 Gy in 5 fractions	Open label, non-randomized study evaluating the safety of pancreatic tumor cell vaccine (GVAX) with immune modulating doses of cycophosphamide followed by SBRT and FOLFIRINOX after surgery
NCT03104439	II	MSS and MSI high CRC and pancreatic cancer (N=80)	Nivolumab, ipilimumab	Unspecified	Open label, single arm study evaluating efficacy of combination Nivolumab, Ipilimumab, and RT
NCT02648282	II	Locally advanced PDAC (N=58)	GVAX, pembrolizumab	6.6 Gy in 5 fractions	Open label, single arm study evaluating distant metastasis free survival of GVAX combined with cyclophosphamide, pembrolizumab and RT
NCT03563248	II	Localized pancreatic cancer (N=168)	Nivolumab	Unspecified	Open label, randomized study evaluating the safety and efficacy of Losartand and nivolumab in combination with FOLFIRINOX and SBRT
NCT02311361	I/II	Unresectable PDAC (N=65)	Tremelimumab and/or durvalumab	8 Gy in 1 fraction or 5 Gy in 5 fractions	Open label, multi-arm, non-randomized study evaluating the safety and efficacy of Durvalumab and/or tremelimumab with SBRT
NCT03104439	II	MSI-High colorectal and pancreatic cancer (N=80)	Nivolumab and ipilimumab	24 Gy in 3 fractions	Open label study evaluating the safety and efficacy of Nivolumab and ipilimumab in combination with RT

GI, gastrointestinal; EBRT, external beam radiation therapy; ESCC, esophageal squamous cell carcinoma; GAC, gastric cancer; dMMR, DNA mismatch repair deficiency; EBV, Epstein-Barr Virus; EAC, Esophageal adenocarcinoma; GEJC, gastroesophageal junction adenocarcinoma; FOLFOX, oxaliplatin, leucovorin, fluorouracil; RT, radiation therapy; RFS, recurrence free survival; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy; MSS, microsatellite stable; MSI, microsatellite instability; CNS, central nervous system; RT, radiation therapy; pCR, pathologic complete response; TACE, trans-arterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation.

have been largely ineffective for patients with microsatellite stable (MSS) mCRC (61). The dramatic difference in ICB treatment response has been hypothesized to be due to lower tumor mutational burden and neoantigen generation (54). More recently, comprehensive single-cell and spatial analysis of both MMRd and MSS colorectal tumors have identified differences in spatially organized immune networks within the intestinal microenvironment that may contribute to ICB responsiveness (62). While tumor-infiltrating lymphocytes (TILs) are generally highly enriched in MSI-H CRC, they are relatively uncommon in MSS CRC (63).

The development of strategies, including use of combined RT, to overcome the intrinsic resistance to ICB in MSS CRC are currently underway. Results from a phase II, single-arm trial (NCT04231552; N=30) evaluating the efficacy of preoperative short course RT (5×5 Gy) with subsequent CAPOX (capecitabine and oxaliplatin) and camrelizumab in locally advanced rectal cancer demonstrated a pathologic complete response (pCR) rate of 48.1% (43). By comparison, previous studies utilizing preoperative chemoradiation therapy without immunotherapy showed a pCR rate of 15-30% in rectal cancer (64-68). More importantly, the trial had demonstrated a pCR rate of 46.2% in patients with proficient mismatch repair (pMMR)/MSS (43).

Comparatively, a recent single-arm, non-randomized, phase 2 trial (NCT03104439) evaluated the efficacy and safety of combined PD-1 (nivolumab) and CTLA4 (ipilimumab) inhibitors with RT in an effort to improve ICB therapy response in MSS CRC and pancreatic adenocarcinoma (PDAC) (69). In patients with MSS CRC, the disease control rate (DCR) by intention to treat was 25% (n=10/40 pts, 95% CI: 13–41%) and in those who received RT per protocol, the DCR was 37% (N=10/27 pts, 95% CI: 10–56%). While modest, these preliminary results demonstrate that the addition of RT may help to improve therapeutic response in MSS CRC and PDAC tumors that have historically had limited response to immunotherapy.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC), which accounts for greater than 90% of pancreatic malignancies, is associated with a dismal prognosis with an estimated 5-year survival rate of 11% (1). Given the lack of specific early presenting symptoms or screening tools, a majority of patients with PDAC have locally advanced or metastatic disease at the time diagnosis. To date, surgical resection remains the only potentially curative treatment option for locally advanced disease. Traditional FOLFIRINOX or gemcitabine-based chemotherapies with or without radiation remain standard of care in unresectable disease (70).

Compared to other solid malignancies, PDAC have proven largely refractory to immunotherapy (71). Clinical trials utilizing either mono or dual ICB therapy have not demonstrated significant improvement in PFS or OS (72-76). Most recently, results from a phase 2 clinical trial (NCT02558894) investigating the efficacy of combining durvalumab (anti-PD-1) with tremelimumab (anti-CTLA-4) for patients with refractory metastatic PDAC demonstrated an overall-response rate (ORR) of 3.1% (95% CI: 0.08–16.22), while patients receiving durvalumab monotherapy had an ORR of 0% (95% CI: 0.00–10.58) (72). Furthermore, while pembrolizumab is approved for use in all metastatic solid tumors with MSI, the prevalence of MSI/dMMR in pancreatic cancer is very low (around 1–2%) (54,77). Although the intrinsic mechanisms of resistance to immunotherapy in PDAC are not fully understood, the immunosuppressive tumor microenvironment in PDAC is believed to be an important contributor in shielding tumors from effective cytotoxic immune responses (78). Nevertheless, other immunotherapeutic strategies, such as cancer vaccines, adoptive cell therapies, and novel checkpoint blockade targets are also presently under investigation (71).

There is some evidence to suggest that radiation therapy may help to boost the immune responsiveness of pancreatic cancer to immunotherapy. Preclinical PDAC murine models have demonstrated that cGAS-STING agonism can promote cytotoxic T-cell responses and Treg populations in the TME (79). More recently, a preclinical study using a syngeneic pancreatic orthotopic tumor demonstrated that combination of RT with anti-PD-1 treatment could induce systemic IFN-γ responses in the host (80). The potential efficacy of combined RT and immunotherapy in pancreatic cancer has also been demonstrated in at least one case report. A patient with refractory metastatic pancreatic cancer who received palliative radiotherapy (45 Gy in 15 fractions) combined with GM-CSF achieved rapid reduction in both primary and metastatic tumors (81). As previously discussed, the combination of nivolumab and ipilimumab with radiation therapy has demonstrated promising efficacy in MSS CRC and PDAC (69). For

PDAC, the DCR in the per protocol analysis was 29% (N=5/17 pts, 95% CI: 10–56%), while the ORR was 18% (N=3/17; 95% CI: 4–43%).

Hepatobiliary cancer

Cancers of the hepatobiliary system, which include hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA) and gallbladder carcinoma (GBC), are aggressive malignancies often with poor long-term survival. Surgical resection has traditionally been mainstay for treatment during early stage disease, however given the high incidence of advanced stage disease at the time of diagnosis and high rate of recurrence, many patients require systemic therapy.

In the last several years, immune checkpoint inhibitors have demonstrated superior efficacy compared to traditional systemic therapies in patients with advanced-stage HCC. Results from the phase III IMbrave 150 trial demonstrated that atezolizumab (anti-PD-L1) combined with bevacizuamab (anti-VEGF-A) resulted in significantly improved overall and progression-free survival compared to sorafenib in patients with untreated advanced unresectable HCC (82). Based on these results, combination atezolizumab and bevacizumab was approved as first-line therapy for advanced HCC. Furthermore, based on early results from KEYNOTE-244 and CHECKMATE 040 trials, the FDA granted accelerated approval of pembrolizumab monotherapy and nivolumab + ipilimumab combination therapy for the treatment of patients with HCC who had progressed on sorafenib therapy.

The addition of RT to systemic therapy has likewise demonstrated promising efficacy for advanced HCC. Recently published results from the randomized phase III NRG/RTOG 1112 trial demonstrated improved OS, PFS, and time to progression (TTP) for SBRT in combination with sorafenib than sorafenib alone for unresectable liver cancer (83). Additional clinical trials will be needed to see if the addition of radiation therapy continues to show improved efficacy in the era of atezolizumab/bevacizumab. A single arm phase II clinical study (NCT04193696) combining SBRT with camrelizumab demonstrated manageable toxicity and promising antitumor activity in patients with unresectable HCC (84), providing proof of concept. After a median follow-up of 19.7 months, the median progression-free and overall survival was 5.8 and 14.2 months respectively.

Biliary tract cancers are a heterogenous group and patients often present with advanced disease and have poor prognosis. The global phase 3 TOPAZ-1 trial for advanced biliary tract cancer showed an overall and progression-free survival benefit with the addition of durvalumab to chemotherapy which had been standard-of-care for over a decade (85). An ongoing single-arm, phase II trial (NCT03898895) seeks to investigate both the efficacy and safety of radiotherapy followed by camrelizumab in unresectable biliary tract cancer patients.

Important considerations for combining and optimizing radiotherapy and immunotherapy

Despite the growing body of evidence supporting the combination of radiation and immunotherapy, the optimal treatment parameters remain an open question. Post-hoc analysis of the PACIFIC trial showed that patients who received radiation therapy at the same time or within 2 weeks after immunotherapy had better outcomes than patients who received radiation therapy more than 2 weeks after immunotherapy, supporting a time-dependent component to combined therapy efficacy (86). Preliminary studies have also suggested that moderately higher doses per fraction may offer better synergy with immunotherapy compared to conventional fractionated radiation, but additional studies will be required to clarify optimal dose fractionation with regards to efficacy (87).

The efficacy and toxicity to combined therapy in relation to patient-related factors and disease-related factors is also an area of active investigation. Multiple biomarkers, such as PD-L1 expression status, microsatellite instability (MSI), and tumor mutational burden (TMB) have been utilized to help predict response to immunotherapy (88). However, due to rarity of the abscopal effect, no markers have been identified to predict which patients have an abscopal response. As we have previously discussed, there is accumulating evidence that radiation therapy can elicit anti-tumor responses, but also increase the expression of PD-L1 on cancer cells, which may be one promising predictor for abscopal response. Future studies will be necessary to clarify predictive biomarkers, which would help to inform patient selection, and allow us to optimize future treatment strategies.

Concluding remarks

The development of immunotherapies, especially immune checkpoint inhibitors, have ushered in a new era for the

treatment of GI malignancies. However, predicting response to immunotherapy and its integration with other treatment modalities remains an area of active exploration. As we have reviewed, there is promising preclinical and clinical evidence to suggest that the efficacy of immunotherapy may be enhanced when combined with RT through its ability to elicit the abscopal effect. Before these combined therapies can be successfully implemented, further research will be necessary to determine its long-term benefits, toxicity profile, as well as optimal timing, dosage, and coordination of treatment.

Acknowledgments

Funding: This research was supported by the Del E Webb Endowed Chair in Proton Research.

Footnote

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-105/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-105/coif). GYY serves as the Editor-in-Chief of *Journal of Gastrointestinal Oncology*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Kumar R, Rosati LM, Herman JM. Advances in Radiation Therapy for Gastrointestinal Cancers. In: Yalcin S, Philip PA, editors. Textbook of Gastrointestinal Oncology. Cham: Springer International Publishing; 2019 [cited 2022 Nov 7]. p. 421-43.
3. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350-5.
4. Sia J, Szmyd R, Hau E, et al. Molecular Mechanisms of Radiation-Induced Cancer Cell Death: A Primer. Front Cell Dev Biol 2020;8:41.
5. Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009;10:718-26.
6. Jiang W, Chan CK, Weissman IL, et al. Immune Priming of the Tumor Microenvironment by Radiation. Trends Cancer 2016;2:638-45.
7. Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, et al. Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect. Trends Immunol 2018;39:644-55.
8. MOLE RH. Whole body irradiation; radiobiology or medicine? Br J Radiol 1953;26:234-41.
9. Stone HB, Peters LJ, Milas L. Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma. J Natl Cancer Inst 1979;63:1229-35.
10. Cameron RB, Spiess PJ, Rosenberg SA. Synergistic antitumor activity of tumor-infiltrating lymphocytes, interleukin 2, and local tumor irradiation. Studies on the mechanism of action. J Exp Med 1990;171:249-63.
11. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
12. Takeshima T, Chamoto K, Wakita D, et al. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy. Cancer Res 2010;70:2697-706.
13. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys 2004;58:862-70.
14. Lin W, Xu Y, Chen X, et al. Radiation-induced small extracellular vesicles as "carriages" promote tumor antigen release and trigger antitumor immunity. Theranostics 2020;10:4871-84.
15. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-

Presentation of Tumor Antigen. Cancer Immunol Res 2015;3:345-55.
16. Obeid M, Panaretakis T, Joza N, et al. Calreticulin exposure is required for the immunogenicity of gamma-irradiation and UVC light-induced apoptosis. Cell Death Differ 2007;14:1848-50.
17. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med 2006;203:1259-71.
18. Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med 2018;24:1845-51.
19. Rudqvist NP, Pilones KA, Lhuillier C, et al. Radiotherapy and CTLA-4 Blockade Shape the TCR Repertoire of Tumor-Infiltrating T Cells. Cancer Immunol Res 2018;6:139-50.
20. Hallahan DE, Spriggs DR, Beckett MA, et al. Increased tumor necrosis factor alpha mRNA after cellular exposure to ionizing radiation. Proc Natl Acad Sci U S A 1989;86:10104-7.
21. Burnette BC, Liang H, Lee Y, et al. The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity. Cancer Res 2011;71:2488-96.
22. Lugade AA, Sorensen EW, Gerber SA, et al. Radiation-induced IFN-gamma production within the tumor microenvironment influences antitumor immunity. J Immunol 2008;180:3132-9.
23. Deng L, Liang H, Xu M, et al. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity 2014;41:843-52.
24. Harding SM, Benci JL, Irianto J, et al. Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature 2017;548:466-70.
25. Vanpouille-Box C, Alard A, Aryankalayil MJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun 2017;8:15618.
26. Barker HE, Paget JT, Khan AA, et al. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer 2015;15:409-25.
27. McLaughlin M, Patin EC, Pedersen M, et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. Nat Rev Cancer 2020;20:203-17.
28. Ishikawa H, Ma Z, Barber GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature 2009;461:788-92.
29. Matsumura S, Wang B, Kawashima N, et al. Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. J Immunol 2008;181:3099-107.
30. Wang Y, Kim TH, Fouladdel S, et al. PD-L1 Expression in Circulating Tumor Cells Increases during Radio(chemo) therapy and Indicates Poor Prognosis in Non-small Cell Lung Cancer. Sci Rep 2019;9:566.
31. Davis AA, Patel VG. The role of PD-L1 expression as a predictive biomarker: an analysis of all US Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors. J Immunother Cancer 2019;7:278.
32. Ngwa W, Irabor OC, Schoenfeld JD, et al. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer 2018;18:313-22.
33. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 2012;366:925-31.
34. Golden EB, Chhabra A, Chachoua A, et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncol 2015;16:795-803.
35. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895-903.
36. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
37. Chen D, Menon H, Verma V, et al. Response and outcomes after anti-CTLA4 versus anti-PD1 combined with stereotactic body radiation therapy for metastatic non-small cell lung cancer: retrospective analysis of two single-institution prospective trials. J Immunother Cancer 2020;8:e000492.
38. Hiniker SM, Reddy SA, Maecker HT, et al. A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. Int J Radiat Oncol Biol Phys 2016;96:578-88.
39. Luke JJ, Lemons JM, Karrison TG, et al. Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors. J Clin Oncol 2018;36:1611-8.
40. Rodríguez-Ruiz ME, Perez-Gracia JL, Rodríguez I, et al. Combined immunotherapy encompassing intratumoral

poly-ICLC, dendritic-cell vaccination and radiotherapy in advanced cancer patients. Ann Oncol 2018;29:1312-9.
41. Jiang H, Yu K, Cui Y, et al. Combination of Immunotherapy and Radiotherapy for Recurrent Malignant Gliomas: Results From a Prospective Study. Front Immunol 2021;12:632547.
42. Sahebjam S, Forsyth PA, Tran ND, et al. Hypofractionated stereotactic re-irradiation with pembrolizumab and bevacizumab in patients with recurrent high-grade gliomas: results from a phase I study. Neuro Oncol 2021;23:677-86.
43. Lin Z, Cai M, Zhang P, et al. Phase II, single-arm trial of preoperative short-course radiotherapy followed by chemotherapy and camrelizumab in locally advanced rectal cancer. J Immunother Cancer 2021;9:e003554.
44. Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol 2019;5:1276-82.
45. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. Asian J Surg 2018;41:210-5.
46. Watanabe M, Otake R, Kozuki R, et al. Recent progress in multidisciplinary treatment for patients with esophageal cancer. Surg Today 2020;50:12-20.
47. Deng W, Lin SH. Advances in radiotherapy for esophageal cancer. Ann Transl Med 2018;6:79.
48. Patel MA, Kratz JD, Lubner SJ, et al. Esophagogastric Cancers: Integrating Immunotherapy Therapy Into Current Practice. J Clin Oncol 2022;40:2751-62.
49. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med 2021;384:1191-203.
50. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
51. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-71.
52. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med 2022;386:449-62.
53. Chao J, He TF, D'Apuzzo M, et al. A Phase 2 Trial Combining Pembrolizumab and Palliative Radiation Therapy in Gastroesophageal Cancer to Augment Abscopal Immune Responses. Adv Radiat Oncol 2022;7:100807.
54. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
55. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.
56. Marcus L, Lemery SJ, Keegan P, et al. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clin Cancer Res 2019;25:3753-8.
57. André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020;383:2207-18.
58. Diaz LA Jr, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol 2022;23:659-70.
59. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med 2022;386:2363-76.
60. Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. J Clin Oncol 2022;40:161-70.
61. Sahin IH, Ciombor KK, Diaz LA, et al. Immunotherapy for Microsatellite Stable Colorectal Cancers: Challenges and Novel Therapeutic Avenues. Am Soc Clin Oncol Educ Book 2022;42:1-12.
62. Pelka K, Hofree M, Chen JH, et al. Spatially organized multicellular immune hubs in human colorectal cancer. Cell 2021;184:4734-4752.e20.
63. Sahin IH, Akce M, Alese O, et al. Immune checkpoint inhibitors for the treatment of MSI-H/MMR-D colorectal cancer and a perspective on resistance mechanisms. Br J Cancer 2019;121:809-18.
64. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant

chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29-42.
65. Bujko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol 2016;27:834-42.
66. Fokas E, Allgäuer M, Polat B, et al. Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12. J Clin Oncol 2019;37:3212-22.
67. Deng Y, Chi P, Lan P, et al. Modified FOLFOX6 With or Without Radiation Versus Fluorouracil and Leucovorin With Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Initial Results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial. J Clin Oncol 2016;34:3300-7.
68. Zhu J, Liu A, Sun X, et al. Multicenter, Randomized, Phase III Trial of Neoadjuvant Chemoradiation With Capecitabine and Irinotecan Guided by UGT1A1 Status in Patients With Locally Advanced Rectal Cancer. J Clin Oncol 2020;38:4231-9.
69. Parikh AR, Szabolcs A, Allen JN, et al. Radiation therapy enhances immunotherapy response in microsatellite stable colorectal and pancreatic adenocarcinoma in a phase II trial. Nat Cancer 2021;2:1124-35.
70. Yoo C, Kang J, Kim KP, et al. Efficacy and safety of neoadjuvant FOLFIRINOX for borderline resectable pancreatic adenocarcinoma: improved efficacy compared with gemcitabine-based regimen. Oncotarget 2017;8:46337-47.
71. Hosein AN, Dougan SK, Aguirre AJ, et al. Translational advances in pancreatic ductal adenocarcinoma therapy. Nat Cancer 2022;3:272-86.
72. O'Reilly EM, Oh DY, Dhani N, et al. Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. JAMA Oncol 2019;5:1431-8.
73. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828-33.
74. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.
75. Wainberg ZA, Hochster HS, Kim EJ, et al. Open-label, Phase I Study of Nivolumab Combined with nab-Paclitaxel Plus Gemcitabine in Advanced Pancreatic Cancer. Clin Cancer Res 2020;26:4814-22.
76. O'Hara MH, O'Reilly EM, Varadhachary G, et al. CD40 agonistic monoclonal antibody APX005M (sotigalimab) and chemotherapy, with or without nivolumab, for the treatment of metastatic pancreatic adenocarcinoma: an open-label, multicentre, phase 1b study. Lancet Oncol 2021;22:118-31.
77. Luchini C, Brosens LAA, Wood LD, et al. Comprehensive characterisation of pancreatic ductal adenocarcinoma with microsatellite instability: histology, molecular pathology and clinical implications. Gut 2021;70:148-56.
78. Ullman NA, Burchard PR, Dunne RF, et al. Immunologic Strategies in Pancreatic Cancer: Making Cold Tumors Hot. J Clin Oncol 2022;40:2789-805.
79. Jing W, McAllister D, Vonderhaar EP, et al. STING agonist inflames the pancreatic cancer immune microenvironment and reduces tumor burden in mouse models. J Immunother Cancer 2019;7:115.
80. Fujiwara K, Saung MT, Jing H, et al. Interrogating the immune-modulating roles of radiation therapy for a rational combination with immune-checkpoint inhibitors in treating pancreatic cancer. J Immunother Cancer 2020;8:e000351.
81. Shi F, Wang X, Teng F, et al. Abscopal effect of metastatic pancreatic cancer after local radiotherapy and granulocyte-macrophage colony-stimulating factor therapy. Cancer Biol Ther 2017;18:137-41.
82. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
83. Dawson LA, Winter K, Knox J, et al. NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937). Int J Radiat Oncol Biol Phys 2022;114:1057.
84. Li JX, Su TS, Gong WF, et al. Combining stereotactic body radiotherapy with camrelizumab for unresectable hepatocellular carcinoma: a single-arm trial. Hepatol Int 2022;16:1179-87.
85. Oh DY, Ruth HA, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022;1.
86. Faivre-Finn C, Spigel DR, Senan S, et al. Efficacy and safety evaluation based on time from completion of

radiotherapy to randomization with durvalumab or placebo in pts from PACIFIC. Ann Oncol 2018;29:viii488.
87. Brooks ED, Schoenhals JE, Tang C, et al. Stereotactic Ablative Radiation Therapy Combined With Immunotherapy for Solid Tumors. Cancer J 2016;22:257-66.
88. Pilard C, Ancion M, Delvenne P, et al. Cancer immunotherapy: it's time to better predict patients' response. Br J Cancer 2021;125:927-38.

Cite this article as: Hino C, Lee EW, Yang GY. Harnessing the abscopal effect for gastrointestinal malignancies in the era of immunotherapy. J Gastrointest Oncol 2023;14(3):1613-1625. doi: 10.21037/jgo-23-105

