Review Article

Radiotherapy in non-surgical management of esophageal cancer in the era of immuno-oncology: a narrative review

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Background and Objective: Radiotherapy is one of the key local therapeutics as non-surgical approach to esophageal cancer (EC). It has been the era of immuno-oncology for EC management. Less is more or more is more for radiation therapy? The current narrative review is to summarize the current knowledge and future perspective of radiotherapy for EC non-surgical management in immuno-oncology.

Methods: We searched PubMed up to August 6, 2022 with no language restrictions.

Key Content and Findings: The foundation of cancer immunity provides a theoretical basis for radiotherapy to participate in and plays a role in tumor immunity. It is a "double-edged sword" of radiation to the immune system, and it is critical to optimize benefits of radiation while reducing the side effects in EC radiotherapy clinical practice. In locally advanced EC, radiotherapy can be appropriately "subtracting", using accurate diagnosis to reduce unnecessary preventive irradiation to achieve accurate irradiation target area, avoiding high-dose irradiation to non-selected patients through individualized efficacy evaluation to reduce side effects, and maximizing the protection of normal tissues with the help of more advanced technical means. In advanced or metastatic EC, stereotactic radiation therapy has been expected to be the "best partner" of immunotherapy, however, it is notable that no guidelines currently recommend radiotherapy with concurrent immunotherapy in metastatic setting.

Conclusions: The development of tumor immunity has opened a new chapter for EC non-surgical management including radiation therapy. It is going on to be an inalienable and precise way for EC radiotherapy in the era of immuno-oncology.

Keywords: Esophageal cancer (EC); radiotherapy; non-surgical management; immunotherapy; immunity

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Introduction

Background

Esophageal cancer (EC) ranks seventh in terms of incidence (604,000 new cases) and sixth in mortality overall (544,000 deaths) globally, with eastern Asia exhibiting the highest cancer incidence and mortality (1). From the CONCORD database comprising 290 registries across 60 countries with 730,000 patients, a 5-year survival rate of 10–30% was reported (2).

Rationale and knowledge gap

Surgery, radiotherapy, and chemotherapy were the milestones of EC, while immunotherapy changed the paradigm in recent years (3). Radiotherapy has been one of the key local therapeutic approaches for EC treatment, which can serve as adjuvant or neoadjuvant approach for surgery, or as an organ preserve approach in definitive setting (4). Immunotherapy has demonstrated exciting outcomes in first-line and second-line treatment of advanced EC, as well as adjuvant therapy in multimodalities in locally advanced disease (5). Translational research has been conducted to explore the impact of radiation in tumor immunity, and a combination of radiotherapy and immunotherapy has been investigated in clinical studies (6,7).

Objective

It has been highlighted the synergism between immunotherapy and radiotherapy in EC from previous reviews (8,9). While the current review is to summarize the current knowledge and future perspective of radiotherapy of EC in the era of immuno-oncology. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-22-43/rc).

Methods

Relevant studies published over the last 20 years were identified via a PubMed search using different combinations of the following search terms: “esophageal cancer”, “esophageal squamous cell carcinoma”, “esophageal adenocarcinoma”, “radiotherapy”, “radiation therapy”, “stereotactic body radiotherapy”, “stereotactic ablative radiotherapy”, “chemoradiotherapy”, “multi-modality therapy”, “immunotherapy”. Most of the search formulas we used are shown in *Table 1*. Additional papers were identified by reviewing reference lists of relevant publications. Publications with relative low credibility and non-English publications were excluded. Data were extracted based on their relevance to the topic instead of implementing a systematic approach to paper selection. More details of the method are shown in *Table 2*.

Table 1 The search terms used

Esophageal cancer
Esophageal squamous cell carcinoma
Esophageal adenocarcinoma
Radiotherapy
Radiation therapy
Stereotactic body radiotherapy
Stereotactic ablative radiotherapy
Chemoradiotherapy
Multi-modality therapy
Immunotherapy

Theoretical basis and mechanism of combined radiotherapy and immunotherapy

Tumor immunity cycle demonstrates the brief basis of tumor immunology (10): (I) antigen release from dead tumors; (II) formation of peptide major histocompatibility (MHC) complex between antigen peptide and MHC on the surface of antigen presenting cells/dendritic cells; (III) recognition of antigen peptide MHC complex by T cell receptor, binding of B7 molecule to CD28 on the surface of T cells, and activating T cells with dual signal; (IV) cytotoxic T cells reach the tumor through circulation; (V) T cells infiltrate the tumor tissue; (VI) identification of tumor cells; (VII) tumor cells killing by immunity. The foundation of cancer immunity provides a theoretical basis for radiotherapy to participate in and plays a role in tumor immunity.

How does radiotherapy play a role in tumor immunity? First, radiotherapy can induce immunogenic cell’s death and releases new antigens into the immune system, thus affecting the immune response and improving the activation of effector T cells, which is corresponding to the first, second and third steps of immune cycle. Secondly, radiotherapy can promote the release of cytokines, inducing

Table 2 The search strategy summary

Items	Specification
Date of search	2022/07/22–2022/08/06
Databases and other sources searched	PubMed/MEDLINE
Search terms used	See *Table 1* for details
Timeframe	1999–2022
Inclusion and exclusion criteria	Inclusion criteria: research articles and reviews in English about themes such as radiotherapy and immunotherapy of esophageal cancer Exclusion criteria: some papers which we considered with low reliability
Selection process	Hongcheng Zhu conducted the selection, and all authors attended a meeting to discuss the literature selection and obtained the consensus
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications

T cells to approach irradiated tumors, improving the inflow of effector T cells and enhancing the killing effect of T cells on tumor cells, and presenting new antigens to the immune system, which is corresponding to the fourth and fifth steps. Finally, radiotherapy further stimulates the expression of surface molecules on irradiated tumor cells, making them more vulnerable to cytotoxic T cell-mediated cell killing, which is corresponding to the sixth and seventh steps. The win-win model is expected as powerful combination of radiotherapy and immunity (11).

Effect of radiotherapy on tumor immunity in EC

It is a "double-edged sword" of radiation to the immune system, and it is critical to optimize benefits of radiation while reducing the side effects in EC radiotherapy clinical practice (12). It includes conventional fractionation and stereotactic radiation therapy as approaches of radiotherapy. Tumors of esophagus locate in hollow organs, thus conventional fractionated radiotherapy with 1.8–2 Gy per fraction is mostly applicated in treating esophageal primary tumor. However, the conventional fractionation radiation therapy to a total dose to 41.4 to 61.2 Gy as neoadjuvant of definitive radiotherapy often delivers a considerable amount dose to lymph node drainage area near the primary tumor and the single dose of 1.8–2 Gy is just within the range lymphatic cell killing. In this case, the drainage area of lymph nodes adjacent to the tumor is accidentally irradiated with high radiation dose, and the T cells of local lymph nodes and lymphatic vessels are damaged.

There have been studies investigating the correlation between lymphocyte changes and prognosis in patients with EC during conventional fractionated radiotherapy (9). Davuluri *et al.* found that the decline of grade IV lymphocytes in patients with EC during chemoradiotherapy was associated with poor prognosis, suggesting the role of autoimmune status in the control of EC (13). In order to further explore the relationship between lymphocyte recovery and the prognosis of EC after chemoradiotherapy, Deng *et al.* retrospectively analyzed 755 patients with stage I-III EC who received chemoradiation and found that grade IV lymphocyte decline during treatment was an independent predictor of poor overall survival, while there is no correlation between lymphocyte recovery and prognosis after treatment (14). Kroese *et al.* confirmed that grade IV leukocyte decline in EC patients receiving neoadjuvant chemoradiotherapy is closely related to survival (15). Therefore, we should adopt the treatment scheme of reducing lymphocyte damage.

At the same time, stereotactic radiation therapy only irradiates tumor lesions, and there is a large dose drop from irradiated tumor to normal tissue, which can activate the release of more tumor antigens and activate T cells. Meanwhile, the single dose of 8–10 Gy which is commonly used in stereotactic radiation therapy is ideal dose to induce tumor specific antigen release (16). Ablative radiation doses stimulate immune responses and combining immunotherapy and stereotactic ablative radiotherapy (SABR) is in the hope of developments.

Radiation therapy for locally advanced EC in the era of immuno-oncology

One of approaches to reduce lymphocyte damage during EC radiotherapy is to reduce the prophylactic irradiation of lymph node drainage area by reducing the irradiation field. The debate about whether elective nodal irradiation is necessary has lasted for many years. A meta-analysis suggests that both the involved-field irradiation and elective-nodal irradiation are feasible in neoadjuvant chemoradiotherapy of EC, and involved-field irradiation is not inferior (17). In 2020, a phase III randomized controlled trial from China confirmed that involved field irradiation and the elective nodal irradiation achieved similar survival in definitive chemoradiotherapy of thoracic esophageal squamous cell carcinoma (18). In 2021, a secondary analysis of ESO Shanghai 1 phase III randomized controlled clinical trial demonstrated that EC patients receiving involved-field irradiation resulted in minimum isolated regional lymph nodes recurrence, and favorable survival outcome (19). Radiation has a direct effect on the immune system and lymphocyte. Radiotherapy for EC will not only damage lymphocytes in local lymph nodes and lymphatic vessels, but also affect circulating immune cells. Xu *et al.* (20) established and verified the effect of effective dose to circulating immune cells (EDIC) on the degree of lymphopenia and prognosis of EC after radiotherapy. It was found that the median value of EDIC was 3.6 Gy, and EDIC higher than 4 Gy was closely related to severe lymphopenia. The increase of EDIC was negatively related to overall survival, disease progression free survival and distant metastasis free survival. At the same time, the exposed dose of heart, lung and spinal cord will also affect the number and proportion of lymphocytes (21).

RTOG-8501 has established a standard radiation dose of 50–50.4 Gy for concurrent EC definitive chemoradiation (22). However, radiation dose up to 60–61.2 Gy are still used in many parts of Asia in the definitive setting of EC chemoradiation. In recent years, the ARTDECO study (23), the CONCORDE study (24), and the Chinese phase III study (25) have shown that increasing the radiotherapy dose in the definitive chemoradiotherapy of non-selected EC patients can not improve outcome. However, early evaluation of the treatment response to chemoradiation to determine the radiotherapy dose is one of the feasible methods to formulate individualized radiotherapy scheme. It is worthwhile to deliver tailored radiation dose in EC chemoradiation. The application of new technologies such as proton therapy will also provide more possibilities for the precise radiotherapy of EC and the protection of normal tissues (26,27).

Radiation therapy for advanced or metastatic EC in the era of immuno-oncology

Immunotherapy has been shown exciting results in the first-line treatment of advanced or metastatic EC, and has been established standard of care in many countries (28-35). The role of local therapy was questioned in advanced and metastatic EC (36).

A prospective phase II trial firstly explore the safety and effectiveness of stereotactic radiotherapy in the control of metastasis after EC treatment. A total of 40 oligometastases in 34 patients were included in the analysis, including 25 distant organ metastases and 15 non regional lymph node metastases. The median disease progression free survival time was 13.3 months, and the 2-year disease progression free survival time was 33.8%. The 2-year overall survival rate was 58.0%, and the 2-year local control rate was 92.1%. The results suggest that stereotactic radiotherapy combined with systemic therapy is a tolerable and effective method for the selected oligometastatic esophageal squamous cell carcinoma (37). A single arm study from China demonstrated that combining SBRT with Tα1 yielded promising treatment results in heavily pretreated metastatic esophageal squamous cell carcinoma (38). In 2022, a retrospective study of SEER database in the United States analyzed the role of local ablation in patients with metastatic esophageal squamous cell carcinoma receiving chemotherapy, and proposed that patients with esophageal squamous cell carcinoma with extrahepatic bone/liver metastasis could benefit from local ablation and systemic chemotherapy (39).

Discussion

Checkmate 577 has been stablished the role of checkpoint inhibitor as adjuvant therapy in EC patients receiving neoadjuvant chemoradiotherapy and surgery (40). Nowadays, there are several phase III clinical trials in progress, including KEYNOTE-975 (41), RATIONALE-311 (42), ESCORT-CRT (43), KUNLUN (44), etc., for definitive chemoradiotherapy of locally advanced EC. The key research will certainly open a new pattern for the treatment of locally advanced EC (*Table 3*). In locally advanced EC, radiotherapy can be appropriately "subtracting", using accurate diagnosis to reduce unnecessary preventive

Table 3 Ongoing phase III trials of dCRT combined with immunotherapy for locally advanced esophageal cancer

Study	Phase	Histology	Population	Number of patients	IO drug	Concurrent chemotherapy	Radiation dose (Gy)	Primary end points
KEYNOTE-975 (41)	III	SCC/AC	Global	600	Pembrolizumab	PF or FOLFOX	50 or 60	OS, EFS
RATIONALE-311 (42)	III	SCC	Asian	366	Tislelizumab	TP	50.4	PFS
ESCORT-CRT (43)	III	SCC	Asian	396	Camrelizumab	TP	50.4	PFS
KUNLUN (44)	III	SCC	Global	600	Durvaluzumab	PF or XP	50-64	PFS

dCRT, definitive chemoradiotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; IO, immune oncology; PF, cisplatin + 5-fluorouracil; FOLFOX, oxaliplatin + leucovorin + 5-fluorouracil; XP, capecitabine + cisplatin; TP, paclitaxel + cisplatin; OS, overall survival; EFS, event-free survival; PFS, progression-free survival.

Table 4 Ongoing randomized trials of local therapy for oligometastatic esophageal cancer

Study	Phase	Center	Country	Study period	Histology	Oligometastatic definition	Local therapy	Systematic therapies	Primary end points
NCT04248452 (46)	III	Multi	USA	2020–2023	AC	Synchronous	SBRT	FOLFOX or XELOX	OS
NCT03161522 (47)	II	Single	USA	2018–2023	AC	Synchronous	Resection	CAP + 5-Fu	OS
NCT04512417 (48)	II	Single	China	2020–2022	SCC	Synchronous/ metachronous	SBRT	Camrelizumab	PFS
NCT03904927 (49)	II	Multi	China	2019–2022	SCC	Synchronous/ metachronous	SBRT or RFA or resection	PF or DTX or IRI with or without IO drug	PFS

AC, adenocarcinoma; SCC, squamous cell carcinoma; SBRT, stereotactic body radiation therapy; RFA, radiofrequency ablation; FOLFOX, oxaliplatin + leucovorin + 5-fluorouracil; XELOX, capecitabine + oxaliplatin; CAP, capecitabine; 5-Fu, 5-fluorouracil; PF, cisplatin + 5-fluorouracil; DTX, docetaxel; IRI, irinotecan; IO, immune oncology; OS, overall survival; PFS, progression-free survival.

irradiation to achieve accurate irradiation target area, avoiding high-dose irradiation to non-selected patients through individualized efficacy evaluation to reduce side effects, and maximizing the protection of normal tissues with the help of more advanced technical means.

As the "best partner" of immunotherapy, stereotactic radiation therapy has been explored in the treatment practice of advanced or metastatic cancers (45). However, it is to be noted that radiotherapy with concurrent immunotherapy is not recommended by major international guidelines currently. Randomized clinical trials have been in progress for investigating the role of local therapy (mainly SABR) in oligometastatic EC, and the results are expected to guide the future management of EC (46-49) (*Table 4*).

Summary and future directions

The development of tumor immunity has opened a new chapter for the comprehensive treatment of EC. Radiotherapy is an important non-surgical treatment for EC, and the combination of immunotherapy and radiotherapy has gradually changed from theory to practice. Back to the question of less is more or more is more? Our answer is that radiotherapy is going on an inalienable and precise way to the era of immuno-oncology.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pcm.amegroups.com/article/view/10.21037/pcm-22-43/coif). The 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.

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