REVIEW

Optimization of combined chemoradiotherapy and immunotherapy for locally advanced esophageal cancer

Ke Zhang,[1,5] Zongchang Nie,[1,5] Jun Wang,[3] Qingsong Pang,[1] Ping Wang,[1] Cihui Yan,[2,*] Zhihao Lu,[4,*] and Wencheng Zhang[1,*]

*Correspondence: wczhang@tmu.edu.cn (W.Z.); pppeirain@126.com (Z.L.); cihuiyan@tmu.edu.cn (C.Y.)

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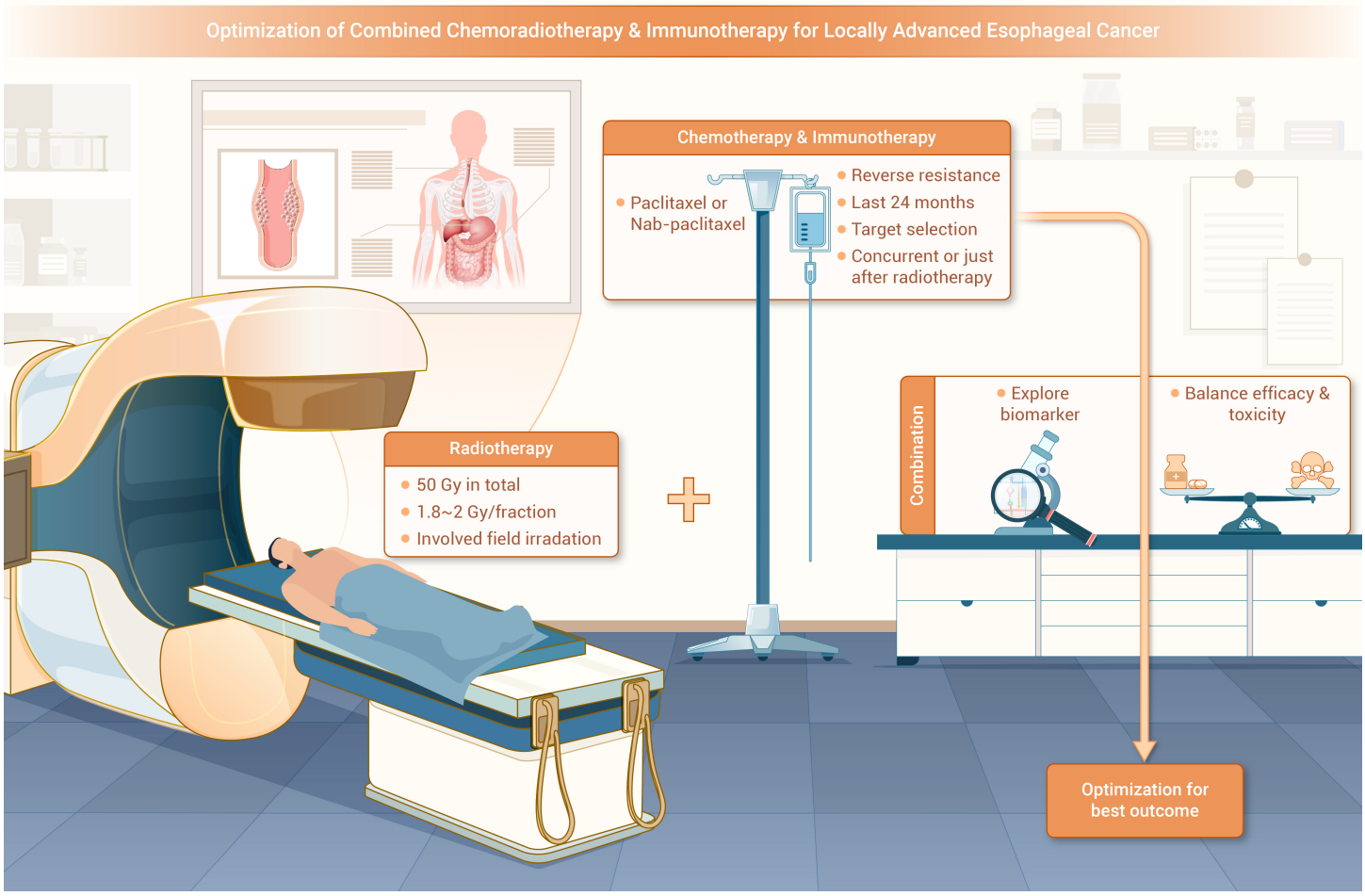
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Chemoradiotherapy is the standard treatment for locally advanced esophageal cancer with unsatisfactory efficacy.
- Combination of immunotherapy and radiotherapy has been demonstrated to elicit synergistic antitumor effects.
- Optimization of chemoradiotherapy combined with immunotherapy can result in better survival benefits.

REVIEW

Optimization of combined chemoradiotherapy and immunotherapy for locally advanced esophageal cancer

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[1]Department of Radiation Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, National Key Laboratory of Druggability Evaluation and Systematic Translational Medicine, Tianjin 300060, China

[2]Department of Immunology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Immunology and Biotherapy, Tianjin's Clinical Research Center for Cancer, Tianjin 300060, China

[3]Department of Radiation Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China

[4]Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China

[5]These authors contributed equally

*Correspondence: wczhang@tmu.edu.cn (W.Z.); pppeirain@126.com (Z.L.); cihuiyan@tmu.edu.cn (C.Y.)

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Concurrent chemoradiotherapy is the standard treatment for inoperable locally advanced esophageal cancer. However, the treatment efficacy remains unsatisfactory. The advancements in immunotherapy have greatly impacted the treatment strategies for multiple malignancies, including esophageal cancer. Several phase I/II clinical studies have shown better survival in patients who underwent immunotherapy combined with radiotherapy or chemoradiotherapy for locally advanced unresectable esophageal cancer. Phase III studies are ongoing. There is no recommended optimal combination regimen for immunotherapy combined with chemoradiotherapy. Here, we optimized the treatment regimen of immunotherapy combined with chemoradiotherapy in ten aspects in locally advanced unresectable esophageal cancer patients according to recent studies of immunotherapy and chemoradiotherapy in esophageal cancer, aiming to provide valuable clues for designing combinations of immunotherapy and chemoradiotherapy in patients with esophageal cancer.

INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors worldwide.[1] In 2022, esophageal cancer became the seventh most common cancer and the fifth leading cause of cancer death in China, with 224,000 new cancer cases and 187,500 deaths.[2] According to the histological type, EC consists of two primary subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma. Globally, ESCC subtype contributes to 85% of all EC cases[1,3,4] and more than half of the ESCC patients were diagnosed in China.[5]

As the early clinical symptoms of EC patients are not obvious, most patients are diagnosed at an advanced stage. Based on the results of RTOG8501 reported in 1999, concurrent chemoradiotherapy (CCRT) is the first-line standard treatment strategy for locally advanced unresectable ESCC.[6] However, patients' survival is still poor, with a 5-year overall survival (OS) of 26%.[6] Although modern radiotherapy techniques improve the treatment outcome of CCRT,[7-12] as indicated by the 3-year OS rate reaching 55.4% in locally advanced ESCC patients treated with paclitaxel plus fluorouracil combined with 3-dimensional conformal radiation therapy (61.2 Gy/34 fractions) in the RTOG 0113 study,[12] the efficacy of CCRT is still suboptimal.

Immunotherapy based on immune checkpoint inhibitors (ICIs) has recently shown excellent efficacy as a first-line, second-line and postoperative adjuvant treatment for advanced EC.[4] Radiotherapy can remodel the tumor microenvironment (TME), which not only promotes the antitumor immune response but also induces the expression of inhibitory immune checkpoint molecules through feedback mechanisms.[13,14] The addition of immunotherapy to radiotherapy likely synergized with antitumor effects by accelerating tumor death, and activating and maintaining antitumor immune capacity.[15,16] Moreover, the abscopal effect might be enhanced.[17] Vascular normalization during combination therapy could ameliorate cellular hypoxia, thereby enhancing the lethality of radiation.[14] As a result, combining radiotherapy and immunotherapy has the potential to further improve antitumor efficacy.

Several clinical trials have been conducted to explore the efficacy and safety of radiotherapy or CCRT combined with immunotherapy in patients with locally advanced ESCC.[18-23] The results from phase I/II clinical studies demonstrated favorable antitumor effects and tolerable safety (Table 1). Our phase Ib clinical study (NCT03671265) showed that the 12- and 24-month OS rates were 85.0% and 69.6%, respectively, and that the toxicity was manageable.[19] Encouraged by these preliminary findings, we and other researchers have launched phase III studies, which are all in the follow-up stage (Table 2). The 2024 edition of expert consensus on RT combined with immunotherapy for esophageal cancer also recommended chemoradiotherapy (CRT) combined with immunotherapy for clinical trials or selective patient treatment (evidence quality: medium; consensus level: 98%).[24]

The double-edged sword of radiotherapy on the TME is an interesting and active research field. On the one hand, RT initiates the cGAS-STING signaling pathway and type I interferon transcription, promoting T-cell activation and tumor control.[25] Tumor immunogenicity is strengthened by the upregulation of MHC class I molecule expression and exposure of calreticulin on the cell surface. Radiotherapy also stimulates the release of chemokines from tumor cells and stromal cells to increase the infiltration of dendritic cells (DCs), macrophages and T cells.[26] On the other hand, hypoxia caused by radiotherapy can remodel the TME, which induces T-cell depletion, increases the accumulation of immunosuppressive effector cells, such as M2-like tumor-associated macrophages (TAMs), regulatory T (Treg) cells, exhausted T (Tex) cells and myeloid-derived suppressor cells (MDSCs), and weakens cytotoxic T lymphocyte function.[26,27] Lymph node and blood irradiation can also lead to systemic immunosuppression due to lymph node dysfunction and lymphopenia.[26,27]

While CRT combined with immunotherapy has shown promising efficacy in treating locally advanced EC, various challenges exist in the design of this combination strategy owing to the dual immune effects resulting from radiotherapy, and to the complicated regulation of the immune system.

Herein, we first optimized the treatment regimens by combining CRT with immunotherapy for locally advanced EC in ten major aspects including: (1) dose of radiotherapy; (2) radiotherapy fractionation schedule; (3) radiation target volume; (4) selection of chemotherapy regimen and dose; (5) selection of immunotherapy agents; (6) timing and sequencing of immunotherapy; (7) maintenance time of immunotherapy; (8) balance efficacy and potential toxicity; (9) efficacy biomarkers; (10) immunotherapy resistance to further clarify the treatment regimens with the best efficacy (Figure 1).

Dose of radiotherapy

Accumulating studies have investigated the effects of radiation dose on treatment outcome. In combination with immunotherapy and radiotherapy, the radiation dose needs to be optimized to promote efficacy and avoid increased treatment-related adverse effects (trAEs).

Local recurrence is the main recurrent pattern in locally advanced EC. The 3- and 5-year recurrence rates were 40% and 45%, respectively, in 133

Table 1. Summary of finished clinical trials of radiotherapy combined with immunotherapy in locally advanced EC

State	Combination	Trail ID	Ph	Num	Drug name	POM
Recruiting	CRT Synchronous ICI	NCT03777813	II	120	Durvalumab: 1500 mg, Q4W	cPFS
Unknown	CRT Synchronous ICI	NCT04404491	III	240	Camrelizumab: 200 mg, Q2W	PFS, trAE (Grade 3 And Above)
Recruiting	CRT Synchronous ICI	NCT05624099	II	226	Camrelizumab: 200 mg, Q3W	ORR
Recruiting	ICI Synchronous ICI	NCT05515315	II	93	Tislelizumab: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT04481256	II	49	Bintrafusp α: 2400 mg, Q3W	Patients Finished Therapy
Recruiting	CRT Synchronous ICI	NCT04426955	III	396	Camrelizumab	PFS
Not yet recruiting	CT Synchronous ICI Then RT	NCT05183958	II	118	Camrelizumab: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT04390945	II	62	Camrelizumab: 200 mg Q2W	PFS
Unknown	CRT Synchronous ICI	NCT04821765	II	35	Tislelizumab: 200 mg, Q3W	LC
Unknown	CRT Synchronous ICI	NCT04286958	II	40	Camrelizumab: 200 mg	PFS
Not yet recruiting	CRT Synchronous ICI	NCT04494009	II	110	INCMGA00012: 500 mg, Q4W	PFS
Recruiting	CRT Synchronous ICI	NCT05520619	II	114	Tislelizumab: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT04212598	II	40	Sintilimab	2-year Progress Rate
Recruiting	CRT Synchronous ICI	NCT05919030	III	155	Tislelizumab: 200 mg, Q3W	PFS
Active, not recruiting	CRT Synchronous ICI	NCT04844385	II	83	Toripalimab: 240 mg, Q3W	2 years PFS
Not yet recruiting	CRT Then ICI	NCT05490719	II	50	QL1706: 5 mg/kg, Q3W	PFS
Active, not recruiting	CRT Synchronous ICI	NCT04550260	III	600	Durvalizumab	PFS
Unknown	CRT Synchronous ICI	NCT03817658	II	725	Camrelizumab: 200 mg Q2W	PFS, OS
Unknown	CRT Synchronous ICI	NCT04514835	II	44	Sintilimab: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT04210115	III	700	Pembrolizumab: 200 mg, Q3W	EFS, OS
Not yet recruiting	CRT Synchronous ICI	NCT05621707	II	50	Sintilimab: 200 mg, 1 Q3W	OS
Recruiting	CRT Then ICI	NCT03957590	III	370	Tislelizumab: 200 mg, Q3W	PFS
Unknown	CRT Synchronous ICI	NCT04602013	II	53	Sintilimab: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT05394415	II	30	Tislelizumab: 200 mg, Q3W	Safety
Active, not recruiting	CRT Synchronous ICI	NCT04522336	I	15	Pembrolizumab: Q2W	cCR
Not yet recruiting	CRT Synchronous ICI	NCT05547828	II	20	Tislelizumab: 200 mg, Q3W	ORR
Recruiting	CRT Synchronous ICI	NCT04821778	III	2000	Anti-PD-1/PD-L1	1-year, 2-year, 3-year and 5-year OS
Recruiting	CRT Synchronous ICI	NCT05512520	II	126	Anti-PD-1: Q3W	1-year PFS
Completed	RT Synchronous ICI	NCT02642809*	II	16	Pembrolizumab: 200 mg, Q3W	Tolerability
Recruiting	CRT Synchronous ICI	NCT06009705	II	56	Toripalimab	ORR, DCR, DOR, Safety
Recruiting	RT Synchronous ICI	NCT05817201	II	60	Toripalimab: 240 mg, Q3W	OS
Recruiting	RT Synchronous ICI	NCT05626569	II	40	Anti-PD-1	1-year PFS
Recruiting	RT Synchronous ICI	NCT06122493	II	48	Tislelizumab: 200 mg, Q3W	1-year PFS
Unknown	RT Synchronous ICI	NCT04851132	II	33	Durvalizumab: 1000 mg, Q3W	PFS
Recruiting	RT Synchronous ICI	NCT06186609	II	68	Anti-PD-1: 200 mg, Q3-4W	PFS
Not yet recruiting	CRT Then ICI	NCT06187597	II	150	Toripalimab: 240 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT06173986	II	50	Anti-PD-1: Q3W	PFS, TCR
Not yet recruiting	CRT Synchronous ICI	NCT05594914	II	47	AK104: 10 mg/kg, Q3W	ORR, DCR, DOR, TTR, AE
Enrolling by invitation	CRT Synchronous ICI	NCT06048926	II	30	Camrelizumab: 200 mg, Q3W	PFS
Unknown	CRT Then ICI	NCT04054518*	II	22	Durvalizumab: 1500 mg, Q4W	6-month PFS
Not yet recruiting	CRT Then ICI	NCT05791136	II	30	Toripalimab: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT05760391	II	100	Anti-PD-1	OS

Table 1. *(Continued)*

State	Combination	Trail ID	Ph	Num	Drug name	POM
Not yet recruiting	RT Synchronous ICI	NCT05732662	II	25	AK104: 10 mg/kg, Q3W	ORR
Recruiting	CRT Synchronous ICI	NCT06138028	II	90	Sintilimab: Q3W	PFS, OS
Recruiting	CRT Synchronous ICI	NCT05978193	II	160	Anti-PD-1: 200 mg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT06086457	III	436	Camrelizumab: 200 mg, Q3W	OS
Recruiting	CRT Synchronous ICI	NCT06084897	II	120	Anti-PD-1	1-year PFS
Not yet recruiting	ICI Then RT	NCT06143748	II	46	Cadonilimab: 10 mg/kg, Q3W	PFS
Recruiting	CRT Synchronous ICI	NCT06061146	II	136	Tislelizumab: 200 mg, Q3W	PFS
Unknown	CRT Synchronous ICI	NCT04512417*	II	63	Camrelizumab: 200 mg, Q3W	PFS
Not yet recruiting	CRT Synchronous ICI	NCT06136988	II	129	SG001: 360 mg, Q3W	DLT, RP2D, AE, sAE, PFS
Not yet recruiting	RT Synchronous ICI	NCT05628610	II	130	Tislelizumab: 200 mg, Q3W	ORR
Active, not recruiting	CRT Then ICI	NCT04543617	III	760	Tiragolumab: 600 mg, Q3W	PFS, OS
Recruiting	ICI Then CRT	NCT05713838	II	32	Durvalizumab: 1500 mg, Q4W	pCR, cCR
Unknown	CRT Synchronous ICI	ChiCTR2300070300	III	100	Toripalimab	mPFS
Unknown	CRT Synchronous ICI	ChiCTR2300072006	II	31	TQB2450	PFS
Unknown	CRT Synchronous ICI	ChiCTR2300071203	II	50	Sintilimab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2200066251	II	32	Tislelizumab	2-year OS
Unknown	CRT Synchronous ICI	ChiCTR2200056744	II	258	Sintilimab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2100055096	IV	268	Sintilimab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2000041171	II	60	Camrelizumab	ORR
Unknown	CRT Synchronous ICI	ChiCTR2000032369	II	106	Toripalimab: 240 mg, Q3W	PFS
Unknown	CRT Synchronous ICI	ChiCTR2200063345	II	90	Tislelizumab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2100046715	II	31	Toripalimab	PFS, ORR
Unknown	CRT Synchronous ICI	ChiCTR2100043004*	II	20	Camrelizumab: 200 mg, Q3W	ORR
Unknown	CRT Synchronous ICI	ChiCTR2300079055	II	49	Adelbolizumab	PFS, Safety
Unknown	CRT Synchronous ICI	ChiCTR2300071208	I	55	Tislelizumab	ORR, Safety
Unknown	CRT Then ICI	ChiCTR1900027161*	II	22	Sintilimab	trAE, Initial Tumor Response
Unknown	RT Synchronous ICI	ChiCTR2200063037	I	12	Anti-PD-1	AEr, sAEr
Unknown	CRT Synchronous ICI	ChiCTR2200062942	II	55	Envafolimab	ORR
Unknown	CT Synchronous ICI Then RT	ChiCTR2400079514	III	150	Camrelizumab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2400080389	II	31	Camrelizumab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2300076371	IV	84	Adebelizumab	1-year PFS
Unknown	CRT Synchronous ICI	ChiCTR2300075926	IV	110	Adebelizumab	1-year PFS
Unknown	RT Synchronous ICI	ChiCTR2100052444	II	20	Camrelizumab	Toxcity, PFS
Unknown	RT Synchronous ICI	ChiCTR2200057417	II	18	Camrelizumab	ORR
Unknown	CRT/RT Synchronous ICI	ChiCTR2000033338*	II	34	Pembrolizumab	PFS
Unknown	CRT Synchronous ICI	ChiCTR2000031077	II	20	Camrelizumab	PFS
Unknown	RT Synchronous ICI	ChiCTR2000040079	II	18	Camrelizumab	PFS
Unknown	RT Synchronous ICI	ChiCTR2100047579	II	20	Anti-PD-1	PFS, AE
Unknown	CRT Synchronous ICI	ChiCTR2200059190	IV	200	Tislelizumab	2-year PFS
Unknown	RT Synchronous ICI	ChiCTR2200057704	II	58	AK104	Safety
Unknown	RT Synchronous ICI	ChiCTR2400080389	I	30	Penpulimab	OS
Unknown	CRT Synchronous ICI	ACTRN12619001371189	II	54	Durvalizumab: 1500 mg, Q4W	PFS

Table 2. Summary of ongoing clinical trials of radiotherapy combined with immunotherapy in locally advanced EC

Combination	Trail ID	Ph	Num	Drug name	POM	ORR	mPFS (months)	OS (months)	AE (3-5)
CRT Synchronous ICI	NCT04005170	II	42	Toripalimab: 240 mg, Q3W	CR	83%, 35 in 42		Not reached	86%, 36 in 42
CRT Synchronous ICI	NCT03671265	Ib	20	Camrelizumab: 200 mg, Q2W	AE, SAE	65%,13 in 20	21.13	Not reached	45%, 9 in 20
CRT Synchronous ICI	NCT03377400	II	40	Durvalumab 1500 mg and Tremelimumab 75 mg, Q3W	1-year PFS	44560	2-year PFS: 57.5%	2-year OS: 75%	No statistic
CRT Then ICI	UMIN000034373	II	50	Atezolizumab:1500 mg, Q3W	CR	cCR: 42.1%	3.2	31.0	No statistic
RT Synchronous ICI	ChiCTR2000040533	II	45	Camrelizumab: 200 mg, Q3W	PFS	41%, 20 in 49	6.93	12.8	63.3%, 31 in 49
CRT Then ICI	ChiCTR1900027161	II	36	Sintilimab: 200 mg, Q3W	Safty, OS	63.6%, 21 in 33	11.5	20.3	23.3%, 7 in 30
RT Synchronous ICI	NCT03222440	Ib	20	Camrelizumab 200 mg q2w	Safety, Feasibility	73.8%, 14 in 19	11.7	16.7	47%, 9 in 19
CRT Synchronous ICI	NCT03187314	Ib	16	Camrelizumab: 200 mg, Q2W	ORR	100%, 14 in 14	Unknown	Not reached	0
CRT Then ICI	NCT03985046	II	75	Sintilimab: 200 mg, Q3W	2-year local control rate	2-year local control rate: 81.3%	2-year PFS: 61.3%	2-year OS: 77.3%	Unknown
CRT Synchronous ICI	ChiCTR2000031544	II	110	KN046: 1/3/5 mg/kg, Q3W	ORR, DOR, 6-month PFS	44.40%	Not reached	Unknown	16.70%
RT Synchronous ICI	ChiCTR2000040533	II	49	Camrelizumab: 200 mg Q3W	PFS	40.80%	6.9	12.8	63.30%
CRT Synchronous ICI	ChiCTR2000034304	II	49	Camrelizumab: 200 mg, Q3W	1-year OS	97.60%	Not reached	Not reached	Unknown
RT Synchronous ICI	ChiCTR2100053182	II	30	Tislelizumab: 200 mg, Q3W	ORR	pCR: 66.7%	Not reached	Not reached	7.40%

CRT: Chemoradiotherapy; ICI: Immune Checkpoint Blockage; CT: Chemotherapy; RT: Radiotherapy; Ph: phase; POM: Primary Outcome Measures; Q2W: Once every 2 weeks; Q3W: Once every 3 weeks; Q4W: Once every 4 weeks; cPFS: Comprehensive Progression Free Survival; ORR: Objective Response Rate; PFS: Progression Free Survival; mPFS: median Progression Free Survival; LCR: Locoregional control rate; OS: Overall Survival; EFS: event free survival; cCR: complete Clinical Response; DCR: Disease Control Rate; DOR: Duration of Response; TCR: Treatment completion rate; TTR: Time To Resolve; DoR: Duration of overall Response; DLT: Dose-Limiting Toxicity; RP2D: Recommended Phase 2 Dose; SAE: Serious Adverse Events; AE: Adverse Events; trAE: treatment related Adverse Events; AEr: Adverse Event rate; sAEr: serious Adverse Event rate; PD-L1: Programmed death ligand 1; PD-1: Programmed death 1.

complete responders after CRT for proximal EC, two-thirds of which had locoregional failure.[28] To decrease local recurrence and improve patient survival, the radiation dose has been widely investigated. Retrospective studies have shown that a higher radiation dose (60 Gy) is associated with better survival and locoregional control than a lower radiation dose (<60 Gy) in ESCC patients with good treatment tolerance (karnofsky performance scale ≥ 80), high tumor burden (≥55.3 cm^3) and stage T3-4 or lymph node metastases.[29,30] However, several randomized clinical studies revealed that a high dose (60 Gy) not only did not improve survival but also increased the incidence of grade ≥3 trAEs compared with the standard radiation dose of 50 Gy.[31-34] Modern radiation techniques, such as 3-dimensional conformal radiation therapy, intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy and image-guided radiation therapy, have better survival benefits and similar incidences of treatment-related deaths than conventional RT for EC patients.[9,31-33] A meta-analysis indicated that modern radiotherapy techniques with high-dose radiation failed to improve OS or locoregional progression-free survival (PFS) compared with conventional radiotherapy techniques.[35]

With the development of immunotherapy, the combination of radiotherapy and immunotherapy has been widely studied for locally advanced unresectable EC. The radiation dose is an important factor associated with this combination. In our phase Ib study of camrelizumab combined with CRT in 20 patients with unresectable locally advanced ESCC (NCT03671265), a 60 Gy/30 fraction dose was used.[19] Forty-five percent of patients suffered grade 3 trAEs, including radiation esophagitis (20%) and esophageal fistula (10%). Serious trAEs occurred in 40% of patients, and 50% of patients fail to complete chemotherapy.[19] In the EC-CRT-001 study (NCT04005170), a dose of 50.4 Gy/28 fractions was applied in combination with CRT and toripalimab for untreated, unresectable, stage I–IVA ESCC. Of the 42 patients enrolled, 40 (95%) completed CRT, and 26 (62%) achieved complete response (CR). The 1-year OS and PFS rates were 78.4% (95% CI: 66.9-92.0) and 54.5 (95% CI: 41.3-72.0), respectively. The most common grade ≥3 trAEs were lymphopenia (86%) and leukopenia (19%), and one patient (2%) died of treatment-related pneumonia.[21] Several ongoing multicenter phase III clinical trials of immunotherapy combined with CCRT, e.g., KEYNOTE-975 (CCRT regimen: 84% with 50 Gy RT), ESCORT-CRT, and RATIONALE-311, have been conducted with a radiation dose of 50.4 Gy/28 fractions.

Considering the increased intensity of systemic therapy resulting from the addition of immunotherapy to CRT, a 50 Gy dose is recommended based on the current findings. Determining the optimal combined radiotherapy dose or

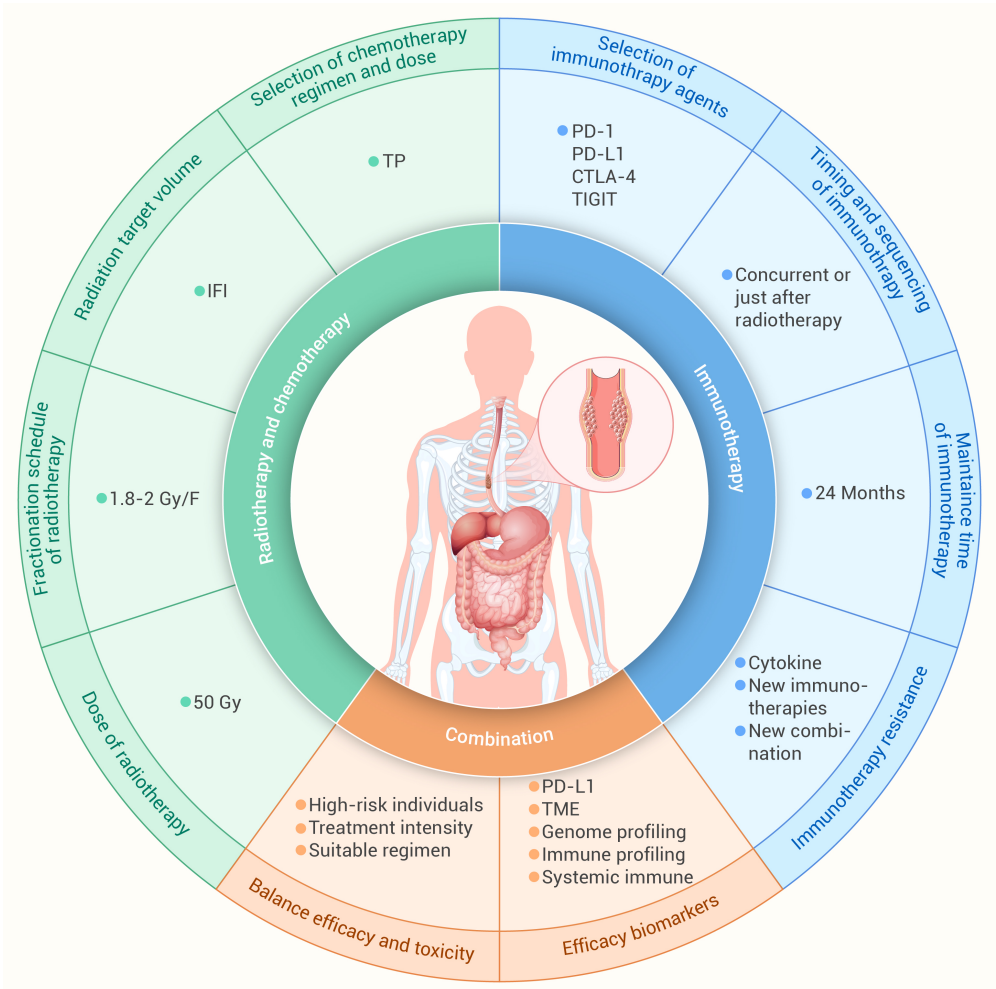

Figure 1. Optimal therapeutic regimens for locally advanced unresectable esophageal cancer We optimized the therapeutic regimens of immunotherapy combined with chemoradiotherapy in ten main aspects. The ten aspects included the dose, fraction and radiation target volume in radiotherapy and chemotherapy; immune checkpoint target selection, timing and sequencing, maintenance, and resistance in immunotherapy; balancing effect and toxicity; and potential efficacy biomarkers. IFI: Involved field irradiation; TP: Paclitaxel plus cisplatin; PD-1: Programmed death 1; PD-L1: Programmed death ligand 1; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; TME: Tumor microenvironment.

selecting the appropriate dose for different populations may require further clinical trials for confirmation.

Radiotherapy fractionation schedule

The fractionation schedule of radiotherapy can be categorized as conventionally fractionated radiotherapy (CFRT), high-dose radiotherapy (stereotactic body radiation therapy, SBRT), low-dose radiotherapy (LDRT), or hybrid radiotherapy. CFRT schedule involves 2 Gy × 5 fractions/week for 5-8 weeks with large target volumes (>5-10 cm^3). SBRT schedule involves a >100 Gy biological equivalent dose in 2 weeks, generally <5 fractions. LDRT is typically administered at a dose of 0.5 to 2 Gy/fraction, for a total of 1 to 10 Gy. The current standard treatment option for esophageal cancer is CFRT. In addition, different segmentation patterns have various effects on the immune response in the TME.

The CFRT is the most widely used fractionation schedule for locally advanced ESCC. CFRT enhances the immunogenicity of irritated tumors and activates antitumor immune responses by inducing immunogenic cell death, increasing the release of antigens and triggering the cGAS-STING pathway.[14,36] The upregulated expression of cell adhesion molecules also contributes to the recruitment of immune effector cells into tumors.[37] However, CFRT-associated hypoxia and vasculature damage potentially result in an immunosuppressive microenvironment, such as an accumulation of immunosuppressive cells, which is negatively attributed to the antitumor immune response.[27] SBRT, an "in situ vaccine", is prone to play a positive immunomodulatory role by strongly inducing immunogenic cell death, upregulating dose-dependent MHC class I expression, recruiting polyclonal antigen-specific effector cytotoxic T lymphocytes (CTLs) into the TME and stimulating an antitumor immune response.[38-42] ICIs combined with SBRT exert immune synergistic effects, effectively increasing T-cell receptor (TCR) diversity, modulating the TME and restoring CTL effector function.[38] LDRT can mobilize both innate and adaptive immune cells, such as lymphocytes, natural killer (NK) cells, macrophages and DCs, to infiltrate the TME.[43,44] Chemokines (e.g., CXCL9, CXCL10, CXCL11, CCL4, and CCL5), which are highly induced at both transcriptional and protein levels under LDRT, recruit CD4+ and CD8+ T cells into tumors.[45] Low-dose irradiation also induces macrophages to polarize to the $iNOS^+$/M1 phenotype.[46] The DNA damage response triggered by LDRT facilitates the antigen-presenting process and CD4+ effector T cells.[44] The combination of LDRT with chemotherapy and ICIs promoted T-cell infiltration, predominantly CD4+ Th1 cells, in responsive patients in a phase Ib clinical trial.[44] For metastatic tumors, hybrid RT irradiation, in which SBRT is applied to the primary tumor and LDRT to the secondary tumor, has shown potential efficacy in several preclinical and clinical studies.[45,47,48] Combining hybrid RT irradiation with immunotherapy in a murine model upregulated the expression of T-cell-attracting chemokines, increased tumor infiltration through the activation of CD8 effector T cells and NK cells, promoted M1 macrophage polarization, and reduced transforming growth factor β (TGF-β) levels, which facilitated antitumor immune effects, with a survival rate of up to 90% in mice over a 50-day observation period.[45]

The esophagus is a cavernous organ and susceptible to complications, such as esophageal fistulae and esophagorrhagia, under a high-dose fractionation schedule. With SBRT, D1 cc (the maximum dose delivered to a volume of one milliliter) at a dose of 32.9 or 50.7 Gy in the esophagus may result in a 50% probability of complications for grade 2 or grade 3 toxicity, respectively.[49] A phase I/II radiation dose escalation trial using a simultaneous integrated boost technique with elective nodal irradiation and concurrent chemotherapy for unresectable EC showed that the maximum tolerated dose (MTD) was 95% PGTV/PTV (59.92/50.40 Gy/28 fractions) with a 2.14 dose fraction.[50] When the dose was increased to 95% PGTV/PTV (60.76/50.4 Gy/28 fractions, 2.17 Gy/fraction), grade 4 thrombocytopenia and esophageal perforation occurred in three of the six patients, and one patient developed grade 3 esophagitis.[50] Combination immunotherapy with radiotherapy for locally advanced EC, with a single dose ranging from 1.8 to 2 Gy/fraction, has a perforation rate of 10%,[19,21] which is similar to the incidence under CRT.[7] Because of the intensity of this treatment, we do not recommend increasing the single fractionation dose.

In summary, CFRT with a single irradiation dose of 1.8-2 Gy is recommended for combination with CRT for locally advanced unresectable EC. SBRT[51] and LDRT may be used in advanced esophageal cancer and require further research.

Radiation target volume

The radiation target volume is determined by the control of local regional tumors and protection of normal tissues. The 2023 National Comprehensive Cancer Network guidelines recommend applying elective nodal irradiation (ENI) for treating EC, i.e., irradiation of the primary esophageal lesion and

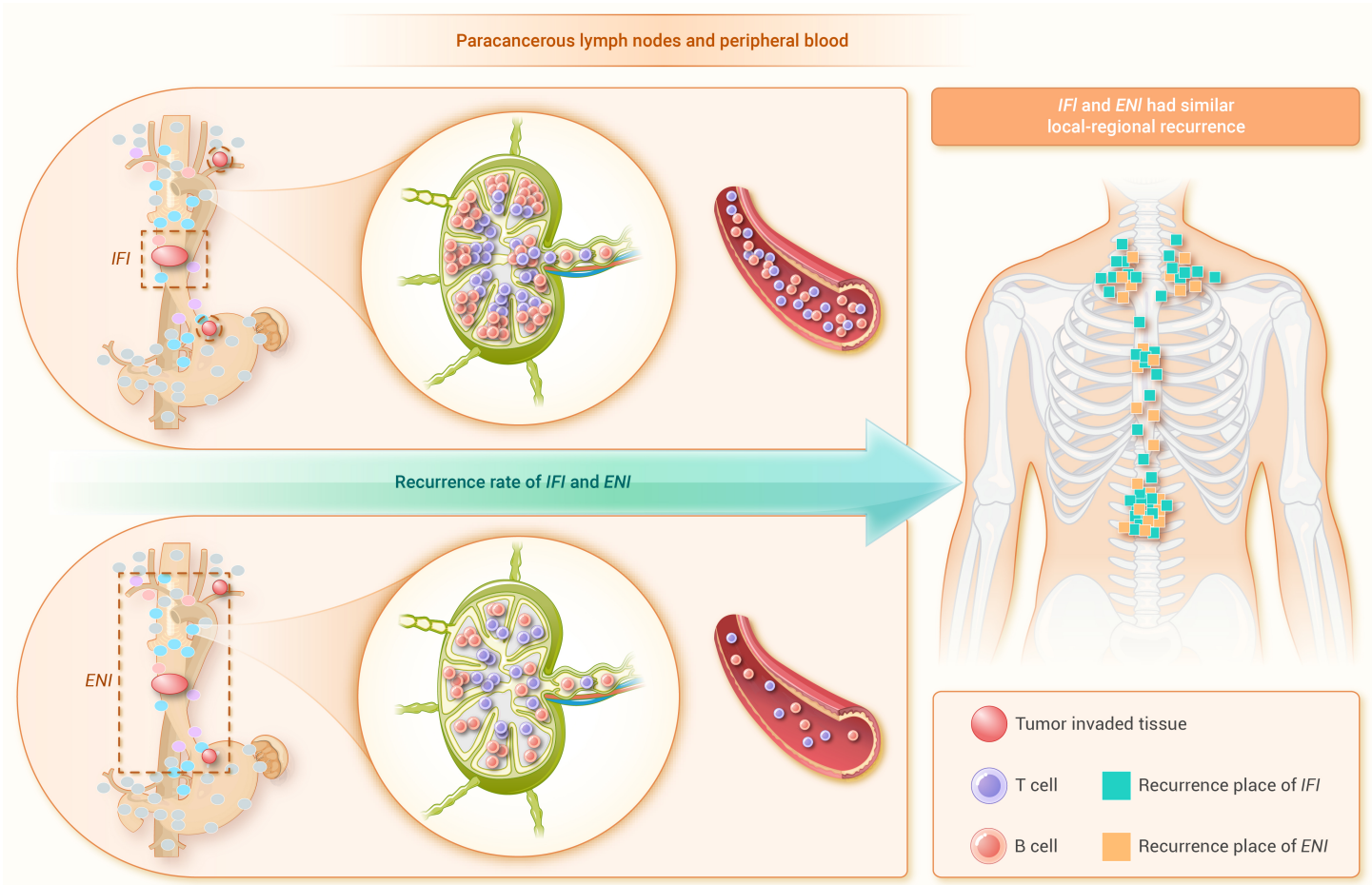

Figure 2. Involved field irradiation (IFI) may be a better choice Tumor-draining lymph nodes (TDLNs) accommodate tumor-specific memory T (Tscm) cells and progenitor exhausted T (Tpex) cells. Tscm and Tpex cells are the main cells responsive to anti-PD-1 treatment. Sparing TDLNs that are not invaded by tumors may protect against antitumor activity and further improve treatment outcomes when combined with immunotherapy, radiotherapy or chemoradiotherapy.

metastatic lymph node areas as well as the corresponding lymph node drainage areas where the lymph node metastasis rate is high.[4] However, when combining radiotherapy with immunotherapy, we suggest a smaller target area for involved field irradiation (IFI). We will elaborate upon the underlying reasons from two aspects: systemic immunity and uninvolved lymph nodes.

Systemic immunity. Excessive radiotherapy coverage might inhibit systemic immunity. The incidence of Grade 4 lymphopenia under CRT increases with the planning target volume (PTV) and whether IMRT or proton beam therapy (PBT) is used.[52] Compared with monocytes and granulocytes, lymphocytes, especially CD8+ T cells, are more vulnerable to radiotherapy.[53] The colony-forming ability of CD4+ and CD8+ T cells was reduced by 90%, and these cells were even killed under a 3 Gy dose of irradiation.[54] After radiotherapy, lymphopenia and an increased neutrophil-to-leukocyte ratio are associated with poor prognosis.[27,55,56] An increased PTV irradiation range led to a substantial decrease in peripheral lymphocytes, which was closely associated with poor survival.[57] For ESCC patients receiving CCRT and immunotherapy, a low absolute lymphocyte count (ALC) nadir during CCRT was correlated with a larger PTV, higher heart V5, and worse survival.[58] Radiotherapy-associated lymphopenia is correlated not only with organs that play a role in lymphocyte production and maturation, such as the thymus, lymph nodes, and bone marrow but also with irradiated organs with abundant blood circulation, such as the heart and lungs.[59]

PBT induced less grade ≥3 lymphopenia than photon therapy did in glioblastoma patients.[60] Compared with IMRT and CRT, PBT also significantly reduces the irradiation dose to the lungs, heart, and liver, thereby better protecting against systemic immunity.[61-63] A retrospective study indicated that stage III EC patients treated with PBT had longer OS and PFS than did those treated with IMRT, but PBT did not benefit patients with stage I/II disease.[64] A subsequent randomized clinical study of 107 EC patients (95% at stage II/III) demonstrated that, compared with IMRT, PBT reduced the risk and severity of trAEs but maintained a similar PFS.[65] Optimization of the target volume and application of new radiation techniques could alleviate radiation-induced damage to systemic immunity.

Uninvolved lymph nodes. Tumor uninvolved lymph nodes (uiLNs) are crucial in antitumor immunity. Elective nodal irradiation (ENI), which is always used to prevent subclinical lesions, might destroy the immunostimulatory effect of uiLNs. Tumor-draining lymph nodes (TdLNs) accommodate tumor-specific memory CD8+ T cells, which are the primary responders to programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) blockade in tumor-bearing mouse models.[66] The efficacy of immunotherapy is significantly suppressed after resection of TdLNs.[66,67] In human head and neck squamous cell carcinoma (HNSCC), progenitor exhausted CD8+ T cells (Tpex) in the uiLNs respond to anti-PD-1 therapy, which plays an important role in treatment efficacy.[68] In combination with immunotherapy and radiotherapy, TdLNs facilitated the tumor infiltration of CD8+ T cells and maintained the M1/M2 macrophage ratio, contributing to local tumor control and abscopal effects.[69]

The above findings support the pivotal role of uiLNs in immunotherapy or immune-radiotherapy (iRT). Therefore, how about the efficacy of reducing uiLN irradiation in radiotherapy? Radiation of draining lymph nodes suppressed the adaptive immune response by altering chemokine (CCL3, CCL5, CXCL10) expression, affecting CD8+ T-cell migration, and decreasing the density of tumor-infiltrating immune cells, while ENI alleviated the combination efficacy of radiotherapy combined with ICIs.[70] In NSCLC patients receiving adjuvant anti-PD-1 therapy for postoperative recurrence, an elevated dissected LN count (cutoff: 16) was associated with poor immunotherapy efficacy, especially in the immunotherapy alone group.[71]

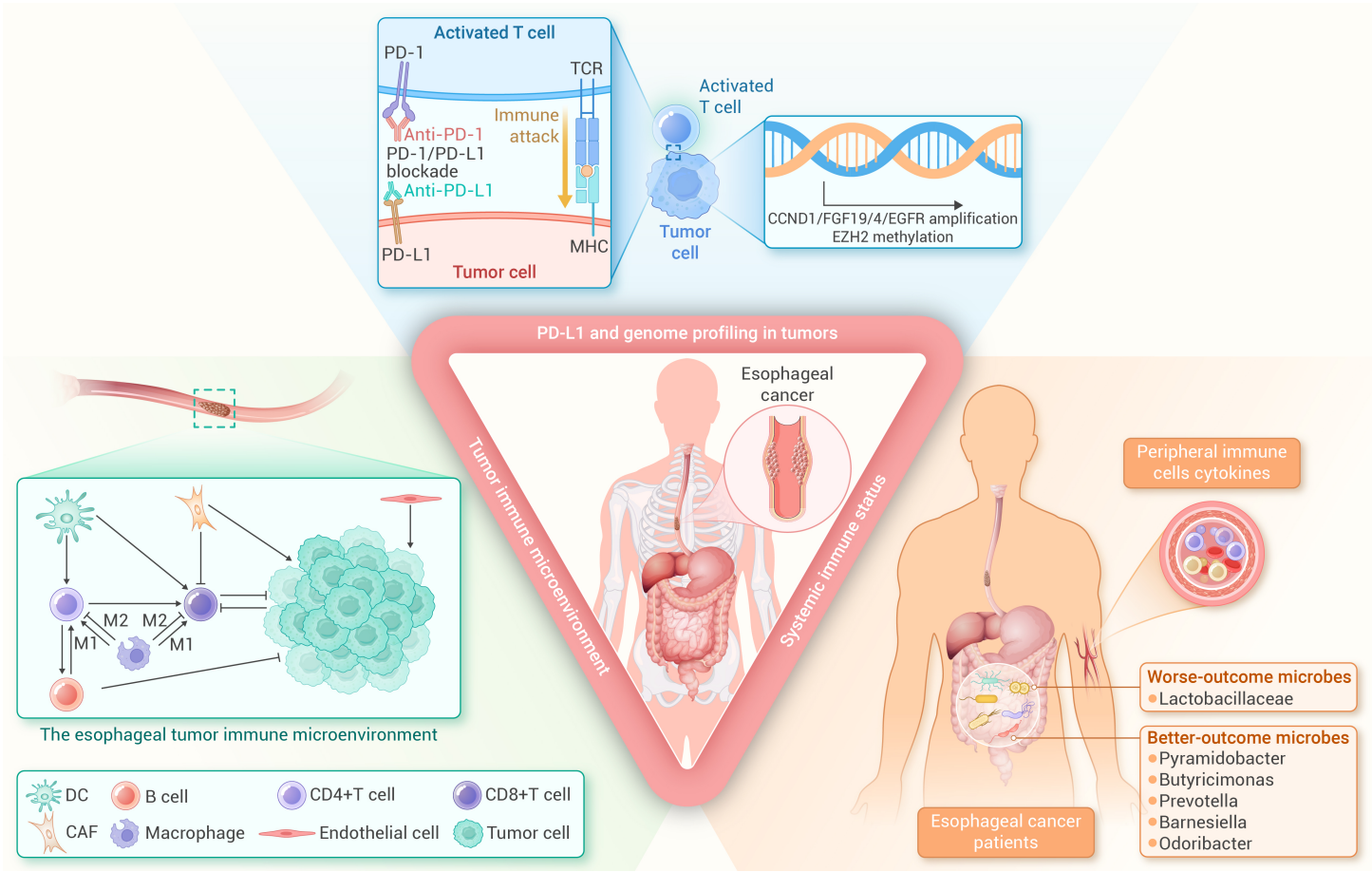

Figure 3. Selection of suitable patients Identify efficacy biomarkers in tumor cells, tumor immune microenvironment and systemic immune system.

Moreover, when radiotherapy and immunotherapy are combined for HNSCC, the ENI increases local, distant, and metastatic tumor growth by decreasing the systemic immune response.[72] A global multicenter, randomized controlled study of locally advanced NSCLC revealed that a reduced irradiation target volume determined via positron emission tomography imaging decreased the risk of locoregional progression compared with that of the conventional target group.[73] All these results demonstrated the importance of protecting against local recurrence and metastasis using antitumor immune cells in uiLNs.

By sparing TdLNs from irradiation, IFI, compared with ENI, maximizes the preservation of immune function in TdLNs. Several multicenter clinical trials have explored the feasibility and efficacy of IFI in treating EC. The IFI was associated with a low rate of elective nodal failure in locoregional ESCC patients receiving radical CRT.[74] Moreover, IFI used in combination with CRT significantly reduced the incidence of acute radiation esophagitis and grade ≥ 2 pneumonia, while patient survival was similar to that with IFI combined with the ENI.[75] Similar survival efficacy between IFI and ENI was also found in a phase III clinical study of local advanced ESCC[76] and a recently published retrospective propensity study of cervical ESCC.[77] Irradiation of uiLNs should be considered for its potential benefits and risks, with emphasis on lymphocyte protection.

In view of the above, we recommend a radiation field with IFI instead of ENI in combination with CRT and immunotherapy for locally advanced EC (Figure 2). We expect that this target design will be evaluated in clinical trials and will provide additional benefits to patients.

Selection of chemotherapy regimen and dose

Several concurrent chemotherapy regimens are available for locally advanced ESCC: paclitaxel plus carboplatin (TC), paclitaxel plus cisplatin (TP), cisplatin plus 5-fluorouracil (PF) or capecitabine or S-1, and paclitaxel plus 5-fluorouracil (TF), capecitabine or S-1. When combining CRT with immunotherapy, the selection of chemotherapy regimens with strong immune synergy is of interest.

Although there was no difference in efficacy between TF and PF (3-year OS: 55.4% vs. 51.8%; 3-year PFS: 43.7% vs. 45.5%) in CCRT for locally advanced ESCC, these two chemotherapy regimens had different toxicity spectra. Compared with PF, TF resulted in lower incidences of acute anemia but greater incidences of leukopenia and radiation pneumonitis.[12] There was still no difference in the efficacy of paclitaxel-based (TF, TP or TC) CRT regimens for locally advanced ESCC. However, compared with the TF or TC regimen, the TP regimen reduced the incidence of grade 3 or 4 esophagitis and pneumonia.[78]

The addition of immunotherapy provides us with new insight into the reasonable choice of chemotherapeutic agent for CCRT. Cross-sectional comparisons of several large multicenter clinical phase III studies of first-line chemotherapy combined with immunotherapy in advanced EC (KEYNOTE-590,[79] KEYNOTE-590 [the Chinese subgroup],[80] CheckMate-648,[81] RATIONALE-306,[82] ORIENT-15,[83] ESCORT-1st,[84] and JUPITER-06[85]) according to chemotherapy drug selection and efficacy revealed that the use of the TP schedule was associated with a greater objective response rate than was the use of the PF schedule, which suggested that paclitaxel was more likely to activate host immunity than was 5-fluorouracil. Paclitaxel promoted the immune response in the peripheral blood of NSCLC patients by impairing the inhibitory function and number of Tregs, increasing the secretion of Th1 cytokines and activating CD4+ and CD8+ T cells.[86] In modulating the TME, paclitaxel inhibits tumor angiogenesis, accelerates apoptosis and loss of function in Tregs, and enhances the release of antitumor cytokines (interleukin-2 and interferon-gamma).[87] Several studies have shown that even low-dose paclitaxel can deplete Tregs, disrupt tumor immune tolerance and promote the antitumor effect of systemic immunity.[88] Nab-paclitaxel (albumin-bound formulation) is water-soluble and delivered in a nanoparticle form, contributing to hypoallergenic traits and different pharmacokinetics

compared with paclitaxel.[89] Nab-paclitaxel internalized by tumor-associated macrophages facilitated M1 polarization in pancreatic cancer model.[90] In the ESCORT-NEO/NCCES01 (ChiCTR2000040034) study, which is the first phase III trial evaluating neoadjuvant immunotherapy plus chemotherapy versus chemotherapy for locally advanced resectable ESCC, patients receiving camrelizumab, nab-paclitaxel and cisplatin exhibited significant improvement in pathologic complete responses compared with those receiving nab-paclitaxel and cisplatin (28.0% vs 15.4%),[91] In our pilot trial of CCRT for inoperable locally advanced EC, the 3-year OS and PFS for patients who received weekly nab-paclitaxel plus cisplatin with concurrent intensity-modulated radiotherapy were 17% and 35%, respectively.[92] Nab-paclitaxel as well did not require hormonal pretreatment and showed low toxicity compared with paclitaxel.[93] Nab-paclitaxel in chemotherapy regimen in combination of immunotherapy and radiotherapy might have promising outcome in locally advanced ESCC, which yet need to be clarified. Finally, the ambivalent effects of 5-fluorouracil on immunity, such as depletion of MDSCs, elicitation of Th17 cells and Tregs, and interference with the differentiation of naïve cells to memory CD8+ T cells, have also been reported.[94]

There are few relevant studies on the optimal chemotherapy dose for patients receiving CRT combined with immunotherapy. Nevertheless, based on the findings of other cancer types,[95-99] low-dose chemotherapy has shown advantages in eliminating immunosuppression, increasing immunotherapeutic sensitivity and reducing trAEs during combination therapy. Therefore, for the selection of chemotherapeutic agents in combination with immunotherapy for locally advanced EC, the TP (especially nab-paclitaxel based) regimen is more widely accepted than the other regimens and seems to be safer and to have synergistic effects, and nab-TP might be alternative to TP regimen.

Selection of immunotherapy agents

Platinum-based chemotherapy was previously the standard treatment for advanced ESCC.[4] However, its prognosis is unsatisfactory, with a median survival time of only 7-13 months.[100-102] Currently, ICIs, especially those used in combination with second-line therapy, have demonstrated significant antitumor activity in patients with advanced EC.[103-107] Immunotherapy combined with chemotherapy has also become the first-line standard treatment for advanced ESCC. Anti-PD-1 antibodies, such as pembrolizumab, nivolumab, camrelizumab, teraplizumab, and sindilizumab, are all approved as first-line agents for advanced EC. Anti-PD-1 antibodies are the most widely studied immunotherapeutic agents in combination with radiotherapy or CRT for locally advanced EC. Clinical results from phase I/II trials showed that either teraplizumab or camrelizumab combined with radiotherapy or CRT was efficacious and safe.[18-22] Several phase III clinical trials of ICIs targeting PD-1 or PD-L1 in combination with CRT, such as KEYNOTE-975, ESCORT-CRT, RATIONALE-311, SHR-1210-III-323, YO42137, and KUNLUN, are underway.

Combinations of immunotherapeutic drugs and antivascular drugs (e.g., envolizumab combined with Endostar) or double immunotherapeutic drugs (e.g., PD-L1 plus cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1 plus CTLA-4, PD-1 plus TGF-β, and PD-L1 plus TIGIT) are also being investigated. Moreover, CTLA-4/PD-L1 double blockade combined with definitive CCRT improved the treatment efficacy (1-year PFS: 57.5% vs. 42.6%; 1-year OS: 75.0% vs. 59.2%; historically compared). Patients could tolerate the intensity of the combination therapy, as indicated by a low incidence of grade ≥3 radiation pneumonitis. PD-L1-positive patients had significant clinical benefits compared with PD-L1-negative patients receiving durvalumab and tremelimumab with CCRT.[23] The feasibility of inhibiting TGF-β and PD-L1 combined with CCRT has been investigated in a phase II clinical study.[108] The phase III trial SKYSCRAPER-07, about the application of atezolizumab plus tiragolumab after definitive concurrent chemoradiotherapy in patients with unresectable locally advanced ESCC, is also ongoing.[109]

Overall, PD-1 inhibitors are currently the most widely studied ICIs for combination immunotherapy and CRT. To achieve better efficacy, especially for patients with primary or adaptive resistance, optimization of the ICI dose and combination with other drugs are needed. However, the combination of the most suitable ICIs and drugs with CRT is still being evaluated in clinical studies. Notably, combining novel radiosensitizers, such as nanomaterials, with iRT alleviated iRT-induced tumor hypoxia, which could enhance the therapeutic benefits and is one of the directions of our future research.[110,111]

Timing and sequencing of immunotherapy

As the expression of checkpoint molecules is dynamically modulated by both the TME and treatment, the timing of adding ICIs to the CRT treatment duration is critical for promoting antitumor immunity and improving treatment outcomes.

The following three treatment regimens were evaluated in most mouse models: immunotherapy after radiotherapy, concurrent radioimmunotherapy, and radiotherapy after immunotherapy. In a colorectal cancer (CRC) mouse model, compared with earlier anti-PD-1 therapy before irradiation, anti-PD-1 therapy administered one day after irradiation had superior systemic antitumor immunity and an abscopal effect. PD-1 blockade after radiotherapy results in the expansion of multifunctional CD8+ T cells and reinvigoration of CD8+ Tpex cells.[112] Inconsistently, anti-PD-1 therapy administered four days before irradiation had synergistic efficacy over monotherapy in $Kras^{G12D}p53^{-/-}$ NSCLC model mice.[113] In addition, in colon carcinoma tumor-bearing mice, concurrent radiotherapy (10 Gy/5 fractions) and an anti-PD-L1 antibody (on day 1 or day 5 of radiotherapy) strongly improved long-term survival compared to radiotherapy alone. However, it was also reported that concomitant but not sequential administration of anti-PD-L1 antibody was critical for the therapeutic outcome of radiotherapy in breast, colon cancer mouse models,[114,115] colon cancer mouse models,[114] melanoma,[116,117] and CRC.[116] A real-world study of PACIFIC-R (NCT03798535) revealed that when CRT plus immunotherapy was administered, stage III NSCLC patients who started consolidation of durvalumab ≤42 days after finishing radiotherapy had improved OS compared with >42 days (2-year OS rate: 74.8% vs 71.2%, 3-year OS rate: 66.0% vs 61.8%).[118]

The timing of immunotherapy was also closely associated with treatment safety. Interstitial pneumonia is one of the most common trAEs in EC patients receiving radiotherapy or immunotherapy. Both the occurrence and severity of interstitial pneumonia are intimately related to the prognosis and survival of EC patients. Compared with patients with limited-stage unresectable lung cancer (including NSCLC and small cell lung cancer),[119,120] locally advanced EC patients rarely develop grade 3 or 4 radiation pneumonitis while receiving traditional CCRT.[10,11,121] Because of the better pulmonary condition and lower incidence of radiation pneumonitis, adding immunotherapy to CCRT has greater therapeutic safety in EC patients than in lung cancer patients.

The proportion of patients who completed sequential treatment is low in clinical practice due to factors such as physical condition (e.g., occurrence of radiation pneumonitis, radiation esophagitis, and disease progression) and personal wishes. Hence, immunotherapy administered as soon as possible after or concurrently with CRT may provide additional survival benefits. Multiple phase III clinical trials of CRT combined with immunotherapy for locally advanced EC, including KEYNOTE-975, NCT04426955, KUNLUN and RATIONAL 311 for concurrent immunotherapy with CRT and SKYSCRAPER 07 for immunotherapy after CRT, are currently underway. Moreover, the efficacy and safety of immunotherapy following CCRT[22,122] or induction of chemoimmunotherapy before CCRT[123] have also been preliminarily confirmed, with 12-month OS rates of 65.8%[122] and 85%,[123] respectively.

There is still a lack of definitive preclinical and clinical data supporting the optimal timing of immunotherapy combined with radiotherapy or CRT. The divergent combination treatment outcome reported in different mouse models probably result from the TME heterogeneity in various tumors, the characteristic dynamics of specific effective memory T cells during treatment, and the different immunotherapeutic agents used. Because of the altered immune TME, increased recruitment of tumor-specific T cells into tumor sites, and the activation of systematic immune response induced by CRT, we suggest that the regimen of concurrent immunotherapy combined with CRT is suitable for locally advanced EC and that earlier application of immunotherapy after radiation possibly controls tumor recurrence well and achieves better efficacy. The treatment sequence that best benefits patients will ultimately be determined by the results of clinical trials.

Maintenance time of immunotherapy

Multiple phase II/III trials demonstrated that the median PFS was 9.4-24.3 months in EC patients who underwent CCRT treatment,[10-12] and progressive disease occurred within two years in approximately 50% of ESCC patients.[12] In our two phase 1b clinical trials of anti-PD-1 therapy combined with RT or

CRT in patients with local advanced ESCC, anti-PD-1 therapy was administered six months after the completion of CRT. While only 10-20% of patients suffer progressive disease during anti-PD-1 therapy maintenance, 20-50% of patients experience progressive disease six months after the completion of immunotherapy.[18,19] Therefore, the appropriate duration of immunotherapy combined with CRT plays an important role in determining treatment outcomes.

Since approximately 75% to 84% of patients experience recurrence within two years after surgery,[124,125] it is better to maintain ICI treatment for two years. In advanced NSCLC, two years (35 cycles) of anti-PD-1 treatment demonstrated impressive antitumor efficacy.[126,127] A recent clinical trial in NSCLC patients proved that an indefinite duration of ICI treatment (receiving immunotherapy ≥760 days) did not provide more survival benefits than maintaining ICI treatment for two years (700 - 759 days), and PD patients who continued immunotherapy after suspension still showed a response.[128] As the duration of ICI treatment increases, common adverse effects (AEs), including hypothyroidism, hypophysitis, pneumonia and potentially lethal cardiovascular diseases, need to be closely monitored.[129] When combining CRT and immunotherapy for EC, we recommend a maintenance phase of immunotherapy covering the period of high risk of recurrence but not extending through two years.

Balance efficacy and potential toxicity

Considering the balance between the efficacy and potential toxicity of combination therapy, the FDA pooled and analyzed 16835 cancer patients and found that immunotherapy given within 90 days following radiotherapy did not increase serious adverse eventss.[130] Radiotherapy or CRT plus ICIs may be both safe and feasible for treating EC,[131] for which the incidences of esophageal fistula, esophageal hemorrhage and grade 3-5 pneumonitis are 6%-10%,[19,84] 2.5%-10%[84,132] and 0.8%,[7,18,84,132-134] respectively. Although single-arm clinical trials have shown no significant increase in the risk of radiation pneumonitis, esophageal fistula or esophageal hemorrhage when iRT is applied for EC,[18,20] identifying and screening patients at high risk of complications, such as esophageal fistula, esophageal hemorrhage and radiation/immune pneumonitis, are necessary.

Esophageal fistula is a common and severe complication of EC. As both the esophagus and the trachea develop from the embryonic foregut, they maintain an intimate relationship in the upper mediastinum and are separated from each other only by 4 mm of connective tissue.[135] This unique structure provides an anatomical basis for the formation of esophageal fistulas associated with radiotherapy. In a small-sample prospective study of CRT combined with immunotherapy, the incidence of esophageal fistula reached 10 -14%.[19,21] Esophageal fistula usually occurs approximately 3 - 4 months after radiotherapy begins.[136,137] Patients with advanced esophageal cancer and esophageal fistula only have a median postoperative survival of 3.63 months,[138] and up to 65% of patients die from esophageal fistula within two months after they develop esophageal fistula.[139] The occurrence of esophageal fistula is closely related to the tumor site, treatment methods, individual nutritional status and inflammatory factor levels. An increased incidence of esophageal fistula was always found when the tumor significantly invaded the major blood vessels or the membranous wall of the trachea, when obvious necrosis developed and when the tumor was in the T4 stage.[138,140,141] A maximum transverse diameter of gross tumor volume >2.45 cm (P = 0.009, HR = 3.805) in CCRT was a risk factor for esophageal fistula and bleeding.[142] To reduce the occurrence of esophageal fistula, patients should be assessed for the risk of esophageal fistula before treatment. The pretreatment platelet-to-lymphocyte ratio (PLR)[137] and nutritional status also need to be verified. For patients screened at high risk of esophageal fistula, it is necessary to lower the dose of a single radiation (maximum tolerated dose: 59.92 Gy/2.14 Gy/28 fractions).[50] It is important to avoid re-radiotherapy if possible[143] and to continuously monitor tumor changes. In summary, patients with a high risk of esophageal fistula or tumor invasion of the thoracic aorta should avoid intensive CRT, especially in combination with immunotherapy.

Radiation/immune pneumonitis is another severe complication requiring attention. Radiation-induced cytotoxic damage to type II pneumocytes and vascular endothelial cells results in radiation-related pneumonia.[144] However, ICI-induced T-cell dysregulation and increased antibody and inflammatory cytokine levels might lead to ICI-associated pneumonia.[145] Activated cytotoxic self-reactive T cells can exert off-target effects in healthy tissues.[146] The risk of pneumonitis was also strongly enhanced in patients who had preexisting pulmonary dysfunction (chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, pneumothorax, asthma and pleural effusion), a low karnofsky performance scale, a female sex, a smoking history, were older than 65 years old and who were receiving thoracic radiation.[145,147-149] However, EC patients tolerated ICIs plus CRT better than patients with locally advanced NSCLC did (grade 3-5 pneumonia: 0.8% vs. 8%).[131,150] Although simultaneous or sequential immunotherapy combined with CRT or RT increased the incidence of Grade 3-5 pneumonitis (1.9% vs 0.8%),[131] the addition of immunotherapy was tolerable for EC patients. Each tumor has a high incidence of trAEs, which is closely associated with the relevant system.[151-153] However, the difference in toxicity profiles between PD-1 and PD-L1 antibodies in patients with EC is less known. Because of the tolerable and manageable efficacy of immunotherapy combined with CRT in treating EC, a greater emphasis should be placed on efficacy rather than toxicity. Moreover, the radiation dose applied to normal tissues should be strictly limited to reduce damage in off-target healthy tissues. Adopting precise target-area outlining and optimized radiotherapy plans to minimize the irradiation dose to normal lung tissue and the proportion of lung volume irradiated >20 Gy (V20)[154] to reduce lung injury is important.

Taken together, by screening high-risk individuals, strictly limiting the intensity of treatment, and designing optimized treatment regimens, we can greatly reduce serious trAEs and balance efficacy and toxicity.

Efficacy biomarkers

Biomarkers that can predict immunotherapy efficacy, such as PD-L1 expression, microsatellite status and tumor mutation status, have been widely studied but have limited utility.[155] Patients have shown heterogeneous sensitivity to combination therapy with CRT and ICI, but predictors that are strongly associated with combination therapy outcome have been less frequently reported in patients with EC. Therefore, novel predictors need to be explored to identify patients who may benefit from these combination therapies. Here, we summarized the predictive biomarkers identified in the tumor cells, TME and systemic immune system to screen patients.

A meta-analysis of eleven phase III randomized controlled trials involving 6267 patients with ESCC suggested that PD-L1 expression could be used as a predictor of survival benefit from anti-PD-1 therapy.[156] Similar results were found in advanced gastroesophageal cancer.[157] There are currently two methods for evaluating PD-L1 expression: the combined positive score (CPS) and the tumor proportion score (TPS). High PD-L1 expression is usually defined as a TPS ≥ 1% or a CPS ≥ 10. The CPS is currently used more widely for gastrointestinal cancer, but its cutoff value of 1 or 10 points is inconclusive. Multiple clinical trials, regardless of whether they received first- or second-line immunotherapy, have demonstrated that patients with high PD-L1 expression (TPS ≥ 1% or CPS ≥ 10) have longer OS than patients with low PD-L1 expression.[156,158,159] In the clinical trial RATIONALE-306, which used PD-L1 tumor area positivity (TAP) scoring, the results demonstrated that tislelizumab plus chemotherapy improved OS compared with placebo plus chemotherapy, independent of TAP level.[82] In summary, after first- or second-line treatment with either ICI monotherapy or dual-ICI therapy (PD-1 or PD-L1 plus CTLA-4), patients with high PD-L1 expression would experience a survival benefit.[81,156,159] Consistent with the findings above, phase I/II clinical trials of radiotherapy or CRT combined with immunotherapy in locally advanced ESCC patients also showed that tumor tissue PD-L1 expression was associated with improved survival.[18,19,23] Patients with PD-L1-high tumors may benefit from combination immunotherapy.

High microsatellite instability/mismatch repair deficiency (MSI-H/dMMR) and high tumor mutational burden (TMB-H) have also been demonstrated to be effective positive predictors for immunotherapy in multiple solid tumors.[160] The frequency of MSI-H and TMB-H tumors is low in EC, at 0-3.3%[161] and 3-3.5%,[162,163] respectively. Xi et al. reported that ESCC patients with higher blood-based TMB (>1 mutations/mb) detected during CRT were associated with a favorable OS (HR=0.33, log-rank p=0.027).[164] The associations between EC genetic phenotypes and the efficacy of immunotherapy or combination therapy were explored recently. Based on multiomics profiling, Liu et al. classified

ESCC into four molecular subtypes: the cell cycle pathway activation (CCA) subtype, NRF2 oncogenic activation (NRFA) subtype, immune suppression (IS) subtype and immune modulation (IM) subtype. Patients in IM subtype group having abundant CD8+ T cell, NK cell and macrophage infiltration were sensitive to immunotherapy. The others were resistant to immunotherapy alone.[165] Patient in IS subtype group having high B and NK CD56^{high} infiltration, low mutation burden and ERBB2 overexpression responded to combination of ICIs combined with ERBB2 therapy. Since radiotherapy induced tumor infiltration of immune cells and remodeled TME, patient with IS subtype might respond when radiotherapy was added in ICIs and ERBB2 therapy. Patients in CCA subtype group having CCND1 amplification and CDKN2A/B deletion were sensitive to CDK4/6 inhibitors. Our premilitary study showed that CCND1/FGF19/FGF4 amplification was related to poor survival in ESCC patients receiving immunotherapy plus CCRT.[19] Addition of CDK inhibitors in CRT combined with immunotherapy might benefit these CCA patients. Chen et al. analyzed the genomic characteristics of the treatment-naive ESCC patients and established the EC genome-based immuno-oncology classification (EGIC) scheme which incorporated the immunogenic featurea and oncogenic alterations to predict the treatment efficacy of combination of chemotherapy and PD-1 blockade. The combination achieved clinical significance in patients with EGIC1 (immunogenic feature-favorable and oncogenic alteration-negative) or EGIC2 (either immunogenic feature-favorable or oncogenic alteration-negative), but not in patients with EGIC3 (either immunogenic feature-unfavorable or oncogenic alteration-positive). PIK3CA oncogenic alteration was negative associated with the outcome of the combination.[166] Mutations enriched in PI3K signaling pathway was correlated with improved survival in locally advanced ESCC patients receiving radiotherapy and PD-1 blockade.[18] On the contrary, MCL1 amplification reduced tumor sensitivity to cisplatin[167] and had potential predictive value for ESCC patients receiving immunotherapy plus CRT, who had increased infiltration of PD-L1+CD8+ T cells and PD-L1+ macrophages and reduced survival.[21]

According to tumor infiltration of immune cells, tumors are classified into three dominant immune phenotypes: immune-inflamed, immune-excluded, and immune-desert. Tumors with an immune-excluded or immune-desert phenotype, also known as cold tumors, are characterized by rare clinical responses to anti-PD-1 and anti-PD-L1 ICIs.[168] Notably, chemotherapy (e.g., anthracyclines, platinum, antimetabolites and alkylating agents) and radiotherapy may improve response to immunotherapy by converting cold tumors into hot tumors through several mechanisms, including increasing tumor inflammation, inducing immunogenic cell death, modulating the TME and enhancing antigen presentation.[168] When combined with radiotherapy, ICIs can further unleash the immune response against tumor cells and normalize the tumor vasculature, improving blood flow and oxygenation, which can enhance the efficacy of radiotherapy.[14] These mechanisms work together to create a synergistic effect. As a result, patients who are resistant to immunotherapy because of the immune-excluded, immune-desert phenotype or genomic characteristics in tumors might benefit from combination when CRT was added.

The spatial ecology of TME also plays a critical role in the treatment response to immunotherapy combined with radiotherapy. We illustrated the spatial distribution of tumor-infiltrating immune populations and their underlying interactions based on paired tumor biopsies collected at baseline and during treatment from our two phase Ib clinical trials. We found that tumor-infiltrating CD4+/CD8+ T cells, DCs and macrophages predominantly accumulated at a distance of 5-10 μm from tumor cells. PD-1-negative T cells were located closer to tumor cells than PD-1-positive T cells were. Interestingly, DCs and macrophages migrated closer to tumors with iRT. The distributions of T cells, DCs, and macrophages in tumors were positively correlated, and tumors with a high TMB (>5 mutations/MB) had a closer distribution of T cells, DCs, and macrophages.[169,170] Additionally, TCR richness and clonal expansion were also observed with iRT in our study.[171] With further studies, the intertumoral, intratumoral, and spatial heterogeneity of ESCC, as well as the dynamic changes during combination therapy, could guide optimized treatment strategies.

Finally, the immune status of the immune system, including immune subsets and cytokines, is highly important in the immune response. A low absolute lymphocyte count was closely related to the poor prognosis of ESCC patients who received CRT plus anti-PD-1 therapy.[58] The percentage of CD4+ and CD8+ central memory T cells greatly decreased in ESCC patients who experienced disease progression with CRT plus nivolumab therapy.[172] Our study also revealed that a higher baseline peripheral TCR diversity was associated with better survival in ESCC patients receiving iRT, and the peripheral TCR clonality and the extent to which TCRs were shared with tumor cells significantly increased during combination therapy.[171] These results indicated that peripheral T cells not only were activated during iRT but also served as a T-cell pool to promote T-cell infiltration into local tumor sites for antitumor effects. Additionally, the levels of IL-15, IL-27, eotaxin-3 and IL-22 in peripheral blood are closely related to OS in these patients.[19] Earlier research also revealed that the functional IL-15RA rs2228059 A>C variant contributed to a low risk of ESCC.[173] Another meta-analysis indicated that the IL-27 rs181206 T>C allele increased the risk of EC.[174] IL-27 induces the activation of NK cells and T-cell renewal and stimulation.[175] IL-15 stimulated the JAK1-STAT3 pathway and JAK3-STAT5 pathway. Phosphorylated STAT3 and STAT5 are translocated to the nucleus and activate the transcription of BCL-2 and MCL-1, which play key roles in the survival of NK cells in both quiescent and proliferating states.[176]

Taken together, identifying biomarkers that could predict treatment efficacy greatly helps in selecting suitable patients who are sensitive to a specific treatment strategy (Figure 3). Compared with tumor tissue, biomarkers from peripheral blood provide more convenient sources for efficacy prediction and deserve further confirmation in future studies.

Immunotherapy resistance

Although first-line immunotherapy combined with chemotherapy for advanced EC has significant clinical benefit, only approximately 20% of patients have long-term survival, and up to 80% of patients develop immunotherapy resistance and distant metastases. The median survival was only 5.7-7.3 months.[79-85] In our phase 1b clinical study of CRT combined with camrelizumab, tumor recurrence occurred in 30% (6/20) of patients; 5% had local failure, 15% had distant metastasis, and 10% had concurrent regional failure and distant metastasis, with a median time to recurrence of 8.25 months.[19] In Xi's phase II clinical trial of CRT combined with toripalimab, the 1-year PFS was 54.5%, and 38% (16/42) of patients who had not achieved a complete response at three months experienced progression after 14 months of radiotherapy.[21] Therefore, immune resistance after immunotherapy combined with CRT remains a critical challenge to improve the combination efficiency.

While the mechanism of immune resistance after immunotherapy combined with CRT is little reported, its mechanisms in other treatment regimens have been widely studied. Two main mechanisms contribute to the immune resistance: primary and acquired resistance,[177] which involves in both internal and external factors. The internal factors include 1) MAPK signaling pathway mutation, PTEN loss or WNT/β-catenin signaling pathway mutation, 2) abnormal IFN-γ signaling pathway activity, 3) lack of tumor antigen, 4) defects in antigen processing and presentation, and 5) abnormal PD-L1 expression. The external factors include 1) Tregs, 2) MDSCs, 3) TAMs, 4) the mechanism of immunosuppression caused by antitumor immune signs, 5) immunosuppressive cytokines, and 6) chemokines and their receptors.[177]

Several methods have been developed to overcome immune resistance. Cancer vaccines, therapies targeting immunosuppressive myeloid programs and ICI combination strategies could alleviate resistance to immunotherapy in patients with dMMR tumors.[178] A recent study reported that a novel IL-12 mRNA therapy alone was sufficient to overcome anti-PD-1 resistance in a melanoma mouse model.[179] IFN-α/β activate downstream IFN signaling to enhance antigen presentation by tumor cells and facilitate tumor-antigen recognition by T cells.[180] The phase III SKYSCRAPER08 study of atezolizumab plus tiragolumab (anti-PD-L1 plus anti-TIGIT) in combination with chemotherapy and our phase II study of QL1706 (anti-PD-1 plus anti-CTLA4) combined with CRT for first-line treatment of advanced ESCC are also being performed. Furthermore, antiangiogenic drugs in combination with immunotherapy or chemotherapy have also shown promising results.[181-183] The modulatory effect of the gut microbiome on immunity has been widely studied in recent years. Melanoma patients responding to anti-PD-1 therapy had higher alpha diversity and a greater relative abundance of bacteria in the

Ruminococcaceae family, and fecal microbiota transplantation during the response showed an enhanced antitumor immune response in a mouse model.[184] An elevated ratio of Prevotella/Bacteroides was correlated with response in gastrointestinal cancer patients.[185] Combinations of other ICIs, intratumoral therapies, costimulatory checkpoint agonists, targeted therapies, vaccines and adoptive T-cell therapies may be considered if immune resistance persists despite combination therapy with CRT.[186] Additionally, because the subsets of immune cells mobilized and activated, and the anti- or proinflammatory factors secreted are not always consistent under different strategies of CRT, such as the dose of CRT and fractions of radiotherapy. It is important to select matched regimens of CRT and immunotherapy agents based on their mechanisms and influence on the TME, with the purpose of alleviating, avoiding or delaying the occurrence of immune resistance.

In recent years, immunotherapy has become a hot topic in the field of cancer treatment, and multiple clinical trials have been carried out to test PD-1/PD-L1 inhibitors (for monotherapy or in combination with other therapies).[187] However, studies are rare on immune resistance after combination of immunotherapy and radiotherapy for EC, and we are always focusing on this topic in the future.

CONCLUSION

Overall, by summarizing the results of recent studies, we optimized ICIs combined with radiotherapy to achieve a greater curative effect in locally advanced EC patients. First, we made delicate adjustments to the details of the regimens used for radiotherapy, chemotherapy, and immunotherapy. The selection of radiotherapy dose, segmentation mode and fields, selection of ICI regimen and timing of addition and maintenance, and selection of the optimal chemotherapeutic agent and dose have a great impact on the efficacy and tolerability of treatment in EC patients. Furthermore, it is important to select a population with potential beneficial effects based on PD-L1 expression, tumor mutation status, genomic phenotype, TME characteristics and the systemic immune status of the patients, and to exclude patients who cannot tolerate the combination therapy. Finally, we also present our own views on the efficacy-toxicity balance and immune resistance associated with immunotherapy combined with CRT.

Considering the important roles of systemic immunity and uninvolved lymph nodes in the immune response, we recommend a smaller range of IFIs instead of the traditional ENI in iRT for locally advanced EC. In addition, compared with photon therapy, PBT significantly reduces the irradiation dose to the lungs, heart and liver, demonstrating the ability to protect immune cells. Radiation therapists are exploring the possibility of enhancing the precision and reducing the field of radiotherapy targets for EC.

Although many questions remain unresolved, immunotherapy has revolutionized EC treatment, and immunotherapy combined with radiotherapy or CRT has shown impressive efficacy in the treatment of locally advanced EC. We look forward to the ten optimization points summarized here being validated or modified in subsequent preclinical and clinical studies.

ABBREVIATIONS

ALC: absolute lymphocyte count; CCA: cell cycle pathway activation; CCRT: concurrent chemoradiotherapy; CFRT: conventionally fractionated radiotherapy; CPS: combined positive score; CRC: colorectal cancer; CRT: chemoradiotherapy; CTL: cytotoxic T lymphocyte; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; DC: dendritic cell; EC: esophageal cancer; EGIC: esophageal cancer genome-based immuno-oncology classification; ENI: elective nodal irradiation; ESCC: esophageal squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; ICI: immune checkpoint inhibitor; IFI: involved field irradiation; IM: immune modulation; IMRT: intensity-modulated radiation therapy; iRT: immuno-radiotherapy; IS: immune suppression; LDRT: low-dose radiotherapy; MDSC: myeloid-derived suppressor cell; MSI-H/dMMR: high microsatellite instability/mismatch repair deficiency; MTD: maximum tolerated dose; NK: natural killer; NRFA: NRF2 oncogenic activation; NSCLC: non-small cell lung cancer; OS: overall survival; PBT: proton beam therapy; PD-1: programmed death 1; PD-L1: programmed death ligand 1; PF: cisplatin plus 5-fluorouracil; PFS: progression-free survival; PGTV: planning gross target volume; PLR: platelet-to-lymphocyte ratio; PTV: planning target volume; RT: radiotherapy; SBRT: stereotactic body radiation therapy; TAM: tumor-associated macrophage; TAP: tumor area positivity; TC: paclitaxel plus carboplatin; TCR: T-cell receptor; TdLN: tumor-draining lymph node; Tex: exhausted T cell; TF: paclitaxel plus 5-fluorouracil; TGF-β: transforming growth factor β; TMB-H: high tumor mutational burden; TME: tumor microenvironment; TP: paclitaxel plus cisplatin; Tpex: progenitor exhausted T cell; TPS: tumor proportion score; trAE: treatment-related adverse effect; Treg: regulatory T cell; T_{TSM}: tumor-specific memory CD8+ T cell; uiLN: uninvolved lymph node.

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DECLARATION OF INTERESTS

The authors declare no competing interests, including financial and nonfinancial interests.

DATA AND CODE AVAILABILITY

Not applicable.

LEAD CONTACT WEBSITE

Wencheng Zhang: https://tutors.eol.cn/web/index/details?service_id=1&tutor_id=11099

Cihui Yan: https://tutors.eol.cn/web/index/details?service_id=1&tutor_id=19409

Zhihao Lu: https://teach.bjcancer.org/Html/Teachers/Index/387.html