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Tumor Immunology COMMENTARY

Rethinking how immunotherapy is combined with chemoradiotherapy in inoperable locally advanced esophageal squamous cell carcinoma

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Definitive chemoradiotherapy (CRT) has been the standard treatment for patients with inoperable locally advanced esophageal squamous cell carcinoma (ESCC) since the Radiation Therapy Oncology Group (RTOG) 8501 trial. However, the prognosis of these patients is poor, with 5-year survival rates ranging from 20% to 40%, and high rates of local recurrence or distant metastasis. The recent publication of our study examining the immunologic consequence of combining concurrent CRT with programmed death 1 (PD-1) and cytotoxic T lymphocyte associated antigen-4 (CTLA-4) double antibodies in locally advanced ESCC (LA-ESCC) adds to ongoing efforts to define how multimodal strategies should be optimally designed.[1] Yet despite this progress, the phase III trials are still ongoing and the field still lack a coherent framework to interpret the accumulating early-phase clinical evidence. Several phase I/II trials have evaluated different combinations of CRT and immunotherapy, while their designs vary in treatment sequencing, immunologic targets, and the translational analyses aimed at defining the potential responders. We here reviewed these early-phase investigations through three dimensions: treatment sequencing, immunologic targets, and responsive patient populations (Figure 1), interpreting the emerging signals in a unified manner, to inform the design of future clinical trials.

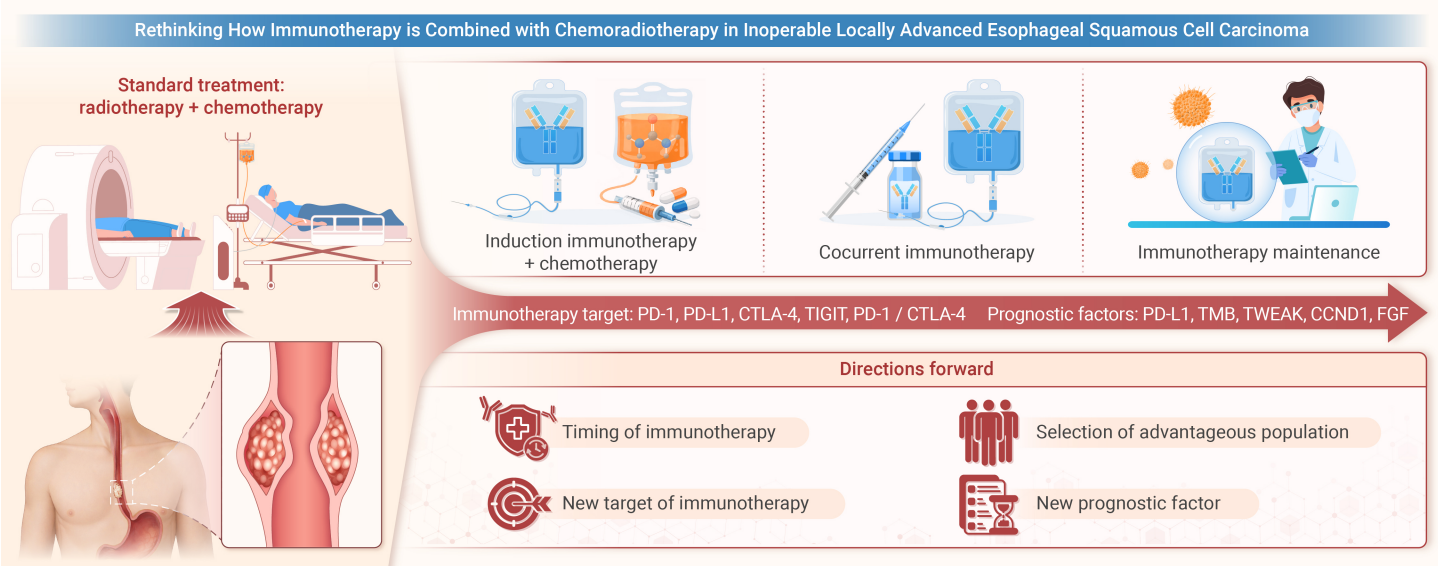

Figure 1. Rethinking how immunotherapy is combined with chemoradiotherapy in inoperable locally advanced esophageal squamous cell carcinoma The timing sequencing of ICI application needs to be further optimized. Patients with high tumor burden may benefit from induced immunotherapy. For patients with limited treatment tolerance, maintaining immunotherapy after radiotherapy may have better tolerance and potentially greater benefits. Identifying populations most likely to benefit and tailoring treatment strategies accordingly will be an important direction for future development. PD-1: programmed death 1; PD-L1: programmed death ligand-1; CTLA-4: cytotoxic T lymphocyte associated antigen-4; TIGIT: T cell immunoreceptor with Ig and ITIM domains; TMB: tumor mutational burden; TWEAK: TNF-like weak inducer of apoptosis; CCND1: Cyclin D1; FGF: fibroblast growth factor.

TREATMENT SEQUENCING OF IMMUNOTHERAPY COMBINED WITH RADIOTHERAPY

Among the available studies, three evaluated concurrent definitive CRT combined with PD-1 blockade as first-line treatment for locally advanced or inoperable ESCC. Zhang et al reported a first phase Ib study evaluating camrelizumab administered concurrently and definitive CRT in LA-ESCC.[2] This trial demonstrated the feasibility of the combination, with 12- and 24-month overall survival (OS) rates of 85.0% and 69.6%.[2] Similarly, the EC-CRT-001 phase II trial, which incorporated toripalimab with definitive CRT, yielded a 12-month OS rate of 78.4% and high complete response (CR) rate of 62%.[3]

In QL1706-IIT-02, a novel PD-1/CTLA-4 dual inhibitor (QL1706) was administered with definitive CRT in patients with LA-ESCC.[1] The median PFS was 14.8 months, and the median OS was immature. The 1-year PFS and OS rates were 58.6% and 84.6%, respectively. QL1706 combined with CRT demonstrated potential antitumor activity and manageable toxicity, supporting further investigation. In the trials mentioned above, immune checkpoint inhibitors (ICIs) were all used in the concurrent CRT stage. The findings suggest that synchronous immune activation during CRT may promote early tumor regression, although the durability of these responses awaits confirmation in larger cohorts.

The EC-CRT-002 trial provides additional insight into the role of sequencing by comparing two immunotherapy exposure strategies.[4] In this study, patients received induction chemotherapy combined with tislelizumab followed by concurrent CRT (2 cycles each). Arm A incorporated an extended adjuvant phase of consisting tislelizumab (for a total of 16 cycles), whereas Arm B limited immunotherapy to the induction and concurrent phases. Arm B demonstrated improved 1-year PFS (73.2%) compared with both the control definitive CRT cohort (56.4%) and Arm A (52.3%). OS also favored Arm B. These observations suggest the induction of chemoimmunotherapy before CRT might result in improved treatment outcome. However, extended exposure of immunotherapy at adjuvant stage did not reach benefit. Such differences likely arise from the distinct tumor immune microenvironment shaped

by each timing scheme, resulting in less responsive to sustained checkpoint inhibition using PD-1 as the target.

A distinct perspective emerges from the SKYSCRAPER-07 trial[5] in which anti-programmed death ligand-1 (PD-L1) antibody atezolizumab monotherapy administered after CRT led to clinically meaningful improvements in PFS and OS compared with placebo. This suggests that post-radiation inflammatory window remains immunologically exploitable.

Taken together, these studies indicate that sequencing is not a binary choice between concurrent and sequential therapy but rather a nuanced determinant of therapeutic synergy. The optimal timing of immunotherapy relative to CRT likely depends on the interplay between antigen release, T-cell priming, and the evolving tumor microenvironment. Radiotherapy can induce tumor neoantigens, activate T cells in the tumor draining lymph nodes and increase leukocyte infiltrate into tumor afterward. Therefore, it would be logical to predict that the administration of radiotherapy slightly before or at the same time as immunotherapy. Other studies also suggest that addition of immunochemotherapy before radiotherapy could remove immune depressed Treg cells and enrich anti-tumor immune cells. ICI should be applied at which stage of radiotherapy remains to be further explored.

TARGET SELECTION OF IMMUNE CHECKPOINT INHIBITORS

These five studies also differ in their immunologic targets (Table S1), provides insight into how different checkpoint pathways may modulate CRT-induced immune responses. Three trials, Zhang et al.,[2] EC-CRT-001,[3] and EC-CRT-002,[4] evaluated PD-1 inhibitors. Across these studies, PD-1 blockade produced preliminary survival benefit and manageable safety profiles, supporting its role as a foundational component of CRT-based immunotherapy.

The QL1706-IIT-02 study introduces a second mechanistic dimension of combining definitive CRT with PD-1/CTLA-4 dual inhibitor.[1] The dual PD-1/CTLA-4 inhibitor was administered currently with definitive CRT and subsequently maintained for one year. The most common grade 3 or 4 treatment related adverse events were lymphopenia (79.5%) and leukopenia (46.2%), respectively. No grade 3 radiation esophagitis or radiation pneumonia occurred, while grade ≤ 2 events were observed in 59.0% and 12.8% of patients, respectively, which was comparable to previous CRT combined with mono immunotherapy studies. The use of a relatively low radiation dose (50.4 Gy/28 fractions), involved field irradiation instead of elective nodal irradiation, prophylactic nutritional tube placement in most patients (69.2%) may have contributed to the low incidence of severe esophagitis. These findings suggest that dual-checkpoint modulation may offer a distinct immunologic strategy when integrated with CRT.

A third target strategy was evaluated in the SKYSCRAPER-07 trial, which assessed both PD-L1 inhibition and T cell immunoreceptor with Ig and ITIM domains (TIGIT) co-blockade following definitive CRT in patients with locally advanced ESCC.[5] Although the TIGIT and PD-L1 combination did not demonstrate a survival advantage over placebo, atezolizumab monotherapy produced clinically meaningful improvements in PFS and OS. However, in MORPHEUS-EC study, investigator-assessed confirmed objective response rate was 67.7% in TIGIT plus PD-L1 and chemotherapy group, 53.8% in the PD-L1 and chemotherapy group, and 47.8% in the chemotherapy group. The two studies differed in the treatment backbone (CRT vs chemotherapy) and enrolled patients at different disease stages, which can shape distinct tumor immune microenvironments and influence treatment interpretation.

Collectively, these studies illustrate that target selection is not a pharmacologic choice but a determinant of how immunotherapy interfaces with CRT-induced immune modulation. Understanding these mechanistic distinctions will be crucial for designing rational combinations and sequencing strategies.

POTENTIAL RESPONDER POPULATION FROM IMMUNOTHERAPY COMBINED WITH CRT

Although the sample sizes of these early-phase trials are modest, several convergent signals point toward potential biomarkers of response. PD-L1 expression is currently the most used and important predictive indicator. High tumor PD-L1 expression was associated with improved survival in Zhang's study[2] and QL1706-IIT-02 study.[1] However, in the ATTRACTION-3 and EC-CRT-001 study,[3] survival or CR rates did not differ significantly between the higher and lower PD-L1 expression groups. Differences in immune targets, combination, and antibody clones can elicit distinct immune responses, which may help explain the divergent association between PD-L1 expression and clinical outcomes observed across studies.

Tumor mutational burden (TMB) reflects the potential load of tumor-derived neoantigens, which may be exposed and released under CRT, thereby enhancing responses to added immunotherapy. In QL1706-IIT-02, higher tissue-based TMB independently correlated with longer PFS.[1] The EC-CRT-001 study similarly demonstrated the elevated blood-based TMB levels during CRT was associated with improved OS.[3] The optimal TMB threshold in other cancer types or clinical scenarios is still under discussion. Beyond global mutational load, recurrent alterations in Cyclin D1 (CCND1) and fibroblast growth factor (FGF)-family genes are frequent in ESCC, and amplification of CCND1, FGF19, or FGF4 has been linked to shorter OS.[2] These genomic features suggest that targeted approaches for CCND1/FGF-amplified tumors may warrant further exploration. The QL1706-IIT-02 study also identified baseline plasma TNF-like weak inducer of apoptosis (TWEAK) and fas ligand (FASLG) levels as positively associated with PFS and OS,[1] indicating the potential value of proteomic markers.

CONCLUSION

The concurrent evidence from early-phase studies does not yet define a standard of care, but it offers a valuable framework for understanding how CRT and immunotherapy may be synergistically combined in LA-ESCC. By examining these studies through sequencing, target selection, and patient stratification, a clearer illustration of the principles that should guide future clinical development. Based on these observations, the timing sequencing of ICI application needs to be further optimized. Patients with high tumor burden may benefit from induced immunotherapy. For patients with limited treatment tolerance, especially the elderly, maintaining immunotherapy after radiotherapy may have better tolerance and potentially greater benefits. Identifying populations most likely to benefit and tailoring treatment strategies accordingly will be an important direction for future development.

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All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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