

Advances in Immune Checkpoint Inhibitors Combined with Definitive Concurrent Chemoradiotherapy for Unresectable Locally Advanced Esophageal Squamous Cell Carcinoma

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Abstract

Definitive concurrent chemoradiotherapy (dCRT) remains the treatment backbone for anatomically unresectable locally advanced esophageal squamous cell carcinoma (ESCC), but recurrence after treatment remains relatively common. This review discusses the use of immune checkpoint inhibitors concurrently, as induction therapy, and as consolidation or maintenance therapy after dCRT. Anatomical unresectability is distinguished from medical inoperability, refusal of surgery, and organ-preservation pathways. Early studies support the feasibility of combination treatment, but differences in study populations, treatment exposure, and endpoint time origins limit comparisons across studies. EC-CRT-002 has not established a universal benefit from prolonged immunotherapy, and its historical-control comparisons should be distinguished from the randomized groups receiving different treatment durations. Studies also differ in the reporting of severe toxicity, treatment discontinuation, fistula, and treatment-related death and in the populations analyzed. Dynamic circulating tumor DNA is associated with response and survival, but no evidence has established a treatment-by-biomarker interaction for the additional benefit of immunotherapy. Confirmatory randomized studies in clearly defined target populations are still needed.

Keywords

Esophageal Squamous Cell Carcinoma, Unresectable Disease, Definitive Concurrent Chemoradiotherapy, Immune Checkpoint Inhibitor, Combination Therapy

1. Introduction

Esophageal squamous cell carcinoma (ESCC) accounts for approximately 90% of esophageal cancers in China, and some patients present with locally advanced disease at diagnosis [1]-[3]. When surgery is not appropriate, definitive concurrent chemoradiotherapy (dCRT) is a treatment option with curative intent. However, anatomical unresectability should be distinguished from other reasons for non-operative treatment when interpreting evidence for combinations with immunotherapy. In this review, immune checkpoint inhibitors are abbreviated as ICIs.

dCRT remains the backbone of curative-intent treatment for these patients, but local residual disease, recurrence, and distant metastasis limit long-term survival. The benefits of immune checkpoint inhibitors (ICIs) in advanced ESCC have prompted their investigation in the definitive treatment setting [4]-[6]. The main strategies currently include concurrent combination treatment, induction chemotherapy plus immunotherapy followed by dCRT, and consolidation or maintenance therapy after dCRT. The following sections first introduce the standard dCRT reference regimen and the rationale for combining it with immunotherapy, then review the clinical evidence for the three strategies, endpoint definitions, candidate biomarkers, and safety management.

1.1. Scope of the Review and Operational Definition of Unresectability

In this review, anatomical unresectability is defined as a thoracic surgical and multidisciplinary assessment indicating that R0 resection, namely complete tumor removal with microscopically negative margins, is not expected to be achievable with acceptable safety. Assessment should integrate contrast-enhanced imaging, endoscopy, staging investigations, and bronchoscopy when airway invasion is suspected, while considering the structures involved and the feasibility of en bloc resection. cT4b tumor invasion of the aorta, trachea or bronchi, or vertebral body is a typical anatomical reason; TNM staging alone cannot replace an assessment of surgical resectability [7] [8]. The Japan Esophageal Society guidelines explicitly state that consideration of conversion surgery after induction therapy or dCRT should be based on an expectation of R0 resection and acceptable operative risk [8]. Initial unresectability should therefore be recorded separately from resectability reassessed after treatment.

Based on eligibility criteria and baseline data, studies are classified as involving anatomically unresectable disease, mixed nonoperative populations, or insufficient information for classification. Mixed nonoperative populations may include patients with technically resectable tumors but contraindications to surgery, patients who decline surgery, and patients with cervical esophageal cancer treated for organ preservation. Nonsquamous histology, postoperative recurrence, and specific extra-regional nodal metastases are identified separately. Even if a study uses the term “unresectable”, its entire population cannot be classified as anatomically unresectable if the eligibility criteria also permit the other circumstances de-

scribed above. Overall results from mixed cohorts cannot substitute for separately reported results from the anatomically unresectable subgroup.

1.2. Information Sources and Study Selection

Information sources for this review include published or publicly available PubMed-indexed literature, original publisher reports and supplementary materials, ClinicalTrials.gov records, and professional guidelines. Targeted searches used trial names and combinations of keywords including esophageal squamous cell carcinoma, definitive chemoradiotherapy, immune checkpoint inhibitor, induction, concurrent, consolidation, and maintenance; relevant references and follow-up reports were also checked. Prospective studies of immune checkpoint inhibitors combined with curative-intent dCRT in adults with ESCC were prioritized. Greater interpretive weight was given to randomized studies, mature follow-up, and studies with clearly reported eligibility criteria and safety data. Retrospective studies, mechanistic studies, and guidelines were used for discussion of the background, biomarkers, and toxicity management.

2. Foundations of Definitive Concurrent Chemoradiotherapy and Immunotherapy

2.1. Standard dCRT Reference Regimen

dCRT refers to radiotherapy and chemotherapy delivered concurrently with curative intent, without planned routine surgery. RTOG 85-01 established the superiority of concurrent chemoradiotherapy over radiotherapy alone; INT 0123 found no improvement in survival or local control with 64.8 Gy compared with 50.4 Gy; ARTDECO likewise found no improvement in major outcomes when the primary tumor dose was increased to 61.6 Gy [9]-[11]. Therefore, 50.0 - 50.4 Gy in 25 - 28 fractions of 1.8 - 2.0 Gy can serve as an evidence-based reference for cross-study comparisons. Some regimens in Japan and China use 50 - 60 Gy for unresectable disease, particularly T4b lesions, but routine dose escalation should not be equated with better efficacy. Modern radiotherapy should use intensity-modulated radiotherapy or volumetric modulated arc therapy with image guidance and fully report the total dose, fractionation, treatment interruptions, and cardiac and pulmonary dose exposure [12].

Radiation fields are generally classified as involved-field irradiation (IFI) or elective nodal irradiation (ENI). IFI covers the primary tumor, radiographically positive lymph nodes, and a margin for subclinical extension; ENI additionally covers high-risk regional lymphatic drainage areas. Current evidence is insufficient to support the same strategy for all patients. Selection should consider tumor location, nodal distribution, normal-organ doses, and the trial protocol, and should be explicitly reported [12]. Conventional concurrent chemotherapy uses cisplatin plus fluorouracil; FOLFOX is an alternative supported by randomized studies [13], while taxane-platinum combinations are commonly used in Chinese and other Asian studies. Before evaluating the additional benefit of an immunotherapy

combination, the radiotherapy dose, radiation fields, intensity of concurrent drug treatment, and treatment completion rate should first be confirmed as comparable to those of the reference regimen.

2.2. Immune Checkpoint Inhibitor Monotherapy

Confirmatory evidence for ICI monotherapy comes mainly from advanced or recurrent disease. ATTRACTION-3 showed that nivolumab improved overall survival (OS) in patients with previously treated advanced ESCC; KEYNOTE-181 suggested that the benefit of pembrolizumab was concentrated mainly in patients with high programmed death-ligand 1 (PD-L1) combined positive scores [14] [15]. These studies established the antitumor activity of programmed cell death protein 1 (PD-1)/PD-L1 pathway blockade, but their disease stages, treatment intent, and treatment backbones differ. They therefore do not directly demonstrate the additional benefit of ICIs in unresectable locally advanced disease treated with dCRT.

2.3. Rationale for Combining Radiotherapy with Immunotherapy

Radiotherapy may enhance antitumor immunity through tumor antigen release, antigen presentation, and cytosolic DNA sensing, and may upregulate PD-L1, providing a rationale for immune checkpoint blockade. Conversely, larger radiation fields and low-dose exposure may also cause lymphopenia or immunosuppression [16]–[23]. Mechanistic studies therefore help explain treatment sequencing and target-volume optimization, but cannot replace randomized clinical evidence. Radiation dose, fractionation, and nodal irradiation may all affect immune responses, and a single immunologically optimal radiotherapy regimen cannot be assumed across different treatment settings [24].

3. Three Strategies for Combining dCRT with Immunotherapy

Clinical complete response (cCR) means that no clinically detectable tumor is found according to the combined criteria of endoscopy, biopsy, and imaging within the assessment window specified by the study; it is not equivalent to pathological complete response and has no time origin for survival analysis. Progression-free survival (PFS) is the time to progression or death, overall survival (OS) is the time to death from any cause, and event-free survival (EFS) includes protocol-defined disease-related events or death. Reports of local control should specify whether failure concerns only the primary site or also includes regional lymph nodes. Randomization, enrollment, first treatment, and initiation of dCRT are different time origins. This review retains the original study definitions without retrospective harmonization; unspecified time origins are identified in **Table 1** and are not inferred.

3.1. ICIs Concurrent with dCRT

Concurrent combination treatment aims to cover the window of radiotherapy-induced antigen release, and some studies continue maintenance immunotherapy

after dCRT. A phase Ib study of camrelizumab combined with docetaxel, cisplatin, and radiotherapy enrolled 20 patients with ESCC and reported 1-year OS and PFS rates of 85% and 80%, respectively; however, the original study provided limited stratification of anatomical unresectability and mainly supports treatment feasibility [25]. The population described as “inoperable” in the study of durvalumab plus tremelimumab also included patients who were medically or surgically unsuitable for surgery, had cervical tumors, or had postoperative local recurrence, while excluding T4b disease. It therefore cannot serve as direct evidence for anatomically unresectable ESCC [26].

All 42 patients in EC-CRT-001 had ESCC, but approximately 62% were considered inoperable; the remaining patients could include those who declined surgery or had cervical tumors. The overall cCR rate of 62%, 3-year OS rate of 44.8%, and PFS rate of 35.7% should therefore be interpreted as results from a mixed nonoperative cohort and cannot be directly extrapolated to a purely anatomically unresectable subgroup [27] [28]. NOBEL likewise involved a mixed population, including 25 patients with resectable and 16 with unresectable ESCC. The overall cCR rate was 73%; in the unresectable subgroup, the cCR rate was 56% and the 1-year OS rate was 81.3%, so interpretation should prioritize the subgroup results [29]. These single-arm studies suggest the feasibility of concurrent combination treatment but have not demonstrated its superiority over standard dCRT.

Another single-arm phase II study evaluated QL1706, which includes both PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade components, combined with dCRT [30]. This study extends investigation to dual-checkpoint strategies but has not demonstrated superiority over PD-1 blockade alone or standard dCRT.

3.2. Induction Chemotherapy Plus Immunotherapy Followed by dCRT

Induction chemotherapy plus immunotherapy may shrink the tumor before radiotherapy, improve swallowing, and provide early response information, but may also increase bone marrow suppression or delay dCRT. The sintilimab induction study enrolled 75 patients with locally advanced esophageal cancer receiving nonoperative treatment, predominantly ESCC; however, anatomical resectability was not stratified in a way that permits independent extrapolation. The 2-year local control rate of 81.7% should therefore be viewed only as an exploratory result of this treatment pathway [31].

ImpactCRT enrolled 49 patients with ESCC. Although the study described them as unresectable, eligibility included inoperability, contraindications to surgery, or refusal of surgery; 16 patients (32.7%) had stage IVB disease with metastasis confined to the supraclavicular lymph nodes. The study should therefore be classified as a mixed nonoperative cohort. In the intention-to-treat (ITT) population, the 1-year OS/PFS rates were 85.7%/71.4%, and the 2-year rates were 72.5%/60.5%. Its primary endpoint, the 1-year OS rate, was assessed in the per-protocol population of 46 patients, using a different denominator from the ITT

results. The single-arm design and occurrence of 1 treatment-related death warrant cautious interpretation [32].

EC-CRT-002 randomized 114 patients equally to tislelizumab maintenance or no maintenance, with 57 patients per group. The registry eligibility criteria allow nonoperative treatment for medical reasons or patient choice, so the entire population cannot be labeled anatomically unresectable [33] [34]. Both groups first received 2 induction cycles every 3 weeks: paclitaxel 135 - 175 mg/m², cisplatin 75 mg/m², and tislelizumab 200 mg. This was followed by intensity-modulated radiotherapy at 50.4 Gy in 28 fractions, with concurrent weekly paclitaxel 45 mg/m² and cisplatin 25 mg/m² for 5 weeks, and 2 additional doses of tislelizumab every 3 weeks. Group A received 12 additional maintenance cycles, for a total of 16 immunotherapy cycles; group B stopped immunotherapy after 4 cycles [33] [34].

At a median follow-up of 22.7 months, the 1-year PFS rate was 52.6% (95% CI 41.4 - 67.3) in group A and 71.9% (61.1 - 84.6) in group B, compared with 56.4% (44.7 - 71.1) in the historical control. The PFS hazard ratios for groups A and B relative to that historical control were 1.06 (95% CI 0.67 - 1.68) and 0.54 (0.32 - 0.94), respectively; the OS hazard ratio for group B relative to the historical control was 0.42 (0.22 - 0.82) [33]. These hazard ratios derive from historical-control comparisons and are not estimates of the effect between the randomized groups A and B. The study did not demonstrate the superiority of the immunotherapy combination through a concurrently randomized dCRT control, and its results do not support routine extension to 16 cycles. It also cannot demonstrate equivalence between the two treatment durations or establish 4 cycles as a universally optimal regimen.

3.3. Consolidation or Maintenance Immunotherapy after dCRT

The consolidation strategy includes only patients who have completed dCRT without progression, reducing the complete overlap of acute toxicities but also introducing selection of treatment completers. All 40 patients in EPOC1802 had unresectable ESCC; 95% had cT4 disease, and 25% had extra-regional M1 lymph nodes. Patients were enrolled after dCRT and received atezolizumab for 1 year. From study enrollment, median PFS and OS were 3.2 months and 31.0 months, respectively; when retrospectively measured from the start of dCRT, they were 5.5 months and 33.0 months [35]. These two time origins must not be conflated with those used in concurrent or induction studies.

A single-arm study of consolidative camrelizumab after involved-field dCRT provides additional feasibility evidence [36]. However, enrollment and follow-up were conditional on completion of the preceding treatment, and the study has not resolved the comparative benefit of the post-dCRT consolidation strategy.

SKYSCRAPER-07 randomized 760 patients after completion of dCRT without progression. Atezolizumab plus tiragolumab did not meet the primary PFS end-point versus placebo (HR 0.82, 95% CI 0.65 - 1.03; $P = 0.0947$), and the prespecified hierarchical testing therefore stopped. Atezolizumab monotherapy showed a favorable OS signal (HR 0.69, 95% CI 0.52 - 0.91; descriptive $P = 0.0085$) and PFS

signal (HR 0.74, 95% CI 0.58 - 0.93), but both are descriptive results under the prespecified multiplicity framework [37]. This qualification preserves the positive signal for monotherapy while avoiding its interpretation as confirmatory evidence that all patients should routinely receive consolidation therapy.

3.4. Pivotal Phase III Studies and Boundaries of the Evidence

KEYNOTE-975 includes squamous cell carcinoma and adenocarcinoma of the esophagus or gastroesophageal junction and therefore involves a histologically mixed population. EFS is measured from randomization, and its endpoint includes protocol-defined radiographic local, regional, or distant progression or recurrence and death [38] [39]. Before the sample size, interaction test, and results for the prespecified unresectable ESCC subgroup are formally reported, conclusions for this specific subgroup cannot be drawn solely from results in the overall or mixed-histology population. RATIONALE-311, KUNLUN, and ESCORT-CRT focus on ESCC, but “inoperability” in some protocols may still include refusal of surgery or other nonanatomical reasons [40]–[42]. Final reports should therefore present the anatomically unresectable subgroup separately and report its PFS/EFS, OS, and local control outcomes using consistent time origins.

Table 1. Representative Prospective Studies and Interpretation of Results.

Study and population	Treatment regimen	Main results	Time origin and interpretation
Camrelizumab phase Ib [25] 20 patients with ESCC; insufficient stratification of anatomical status	ICI concurrent with dCRT	1-year OS/PFS rates: 85%/80%	Time origin not specified here; single-arm feasibility evidence
EC-CRT-001 [27] [28] 42 patients with ESCC; mixed nonoperative population	Toripalimab combined with dCRT, continued for up to 1 year	cCR 62%; 3-year OS/PFS rates: 44.8%/35.7%	cCR assessed 3 months after CRT; survival measured from enrollment; mixed overall population
NOBEL [29] 25 patients with resectable and 16 with unresectable ESCC	Nivolumab combined with dCRT and maintenance	Unresectable subgroup: cCR 56%, 1-year OS rate 81.3%	Protocol-defined cCR window; survival measured from enrollment; subgroup results used
ImpactCRT [32] 49 patients with ESCC; mixed nonoperative population; 16 with M1 supraclavicular lymph nodes	2 cycles of induction chemotherapy plus immunotherapy followed by dCRT	ITT 1-year OS/PFS rates: 85.7%/71.4%	Primary endpoint assessed in 46 per- protocol patients; survival time origin not specified here; no randomized control
EC-CRT-002 [33] [34] 57 patients in each randomized group; nonoperative eligibility criteria	4 cycles of tislelizumab during induction and concurrent treatment, followed by 12 maintenance cycles or no maintenance	1-year PFS rates with/without maintenance: 52.6%/71.9%; see Section 3.2 for CIs and historical comparisons	PFS measured from randomization; historical-control HRs are not HRs between groups A and B

Continued

EPOC1802 [35] 40 patients with unresectable ESCC; 95% cT4	Atezolizumab for 1 year after dCRT	Median PFS/OS: 3.2/31.0 months	Measured from enrollment after dCRT; 5.5/33.0 months when retrospectively measured from the start of dCRT
SKYSCRAPER-07 [37] 760 patients with ESCC without progression after dCRT	Atezolizumab ± tiragolumab or placebo	Dual-immunotherapy group: PFS HR 0.82 (95% CI 0.65-1.03); P = 0.0947	Measured from randomization after dCRT; first primary endpoint not met; monotherapy results descriptive

Note: Abbreviations: cCR, clinical complete response; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not explicitly reported in the reviewed materials. Population classification follows Section 1.1. The cCR assessment window differs from the time origin of survival endpoints; NR does not mean that the study did not collect the endpoint. This review did not calculate pooled effects or indirect comparative effects.

4. Response Assessment and Candidate Biomarkers

cCR should be assessed within a prespecified time window by integrating contrast-enhanced CT, PET/CT, endoscopy, and biopsies from multiple sites, with reporting of the assessors, criteria, and missing data. Inflammation after radiotherapy may cause wall thickening or increased metabolic uptake, and negative superficial biopsies cannot completely exclude residual disease within the wall. Therefore, cCR cannot replace PFS/EFS, OS, or local control. Cross-study comparisons should first align the populations, treatment completion status, and endpoint time origins.

An association between a biomarker and response or survival in a cohort receiving the same treatment may suggest prognostic or monitoring value. Predicting differences in benefit between treatments is a stronger conclusion and requires comparative treatment data and a well-designed treatment-by-biomarker interaction analysis. PD-L1 remains a candidate marker in the setting of dCRT combined with an ICI. Among the 35 patients in EPOC1802 with evaluable PD-L1 tumor proportion scores (TPS), cCR rates were 44.4% and 41.2% for TPS < 1% and ≥ 1%, respectively, with no significant association [35].

The title of the EC-CRT-001 translational study did use the term “predictive role” for circulating tumor DNA (ctDNA) [43]. Its design was an exploratory analysis of a single-arm trial: 42 patients provided 118 blood samples and 35 tissue samples. Patients who were ctDNA-negative after CRT had a higher cCR rate than those who were positive, at 21/27 (78%) and 3/10 (30%), respectively, P = 0.017; post-CRT ctDNA positivity was associated with worse PFS (HR 2.88, 95% CI 1.21 - 6.83) and OS (HR 3.67, 95% CI 1.41 - 9.55). The study had no dCRT-alone control and did not demonstrate differential benefit from toripalimab through a treatment-by-ctDNA interaction. It therefore supports prediction of outcomes within the cohort receiving combination treatment and dynamic monitoring, but does not validate ctDNA for determining the additional benefit of adding an ICI or deciding treatment duration. PET/CT response and systemic inflammatory markers likewise remain investigational for treatment selection [44]-[47].

5. Safety and Management of Major Adverse Events

5.1. Safety across Treatment Strategies

Table 2 compares reported severe toxicity, treatment delivery, fistula, and treatment-related death. These data are descriptive observations and cannot be used to rank the safety of the three strategies. Concurrent studies include the acute CRT phase, induction studies add an earlier period of treatment exposure, and consolidation studies begin counting events only after further selection among patients who have completed dCRT. Differences in the extent of T4b invasion, radiation dose, laboratory monitoring, adverse-event attribution, and safety-analysis denominators can substantially affect the reported incidence. In particular, the incidence of severe lymphopenia must not be equated with the overall incidence of clinically symptomatic severe toxicity.

Table 2. Descriptive Safety Comparison of Representative Treatment Strategies.

Strategy and study	Severe toxicity	Treatment delivery or discontinuation	Fistula	Treatment-related death
Concurrent combination EC-CRT-001 [27] n = 42	G $\geq$ 3 lymphopenia: 36/42 (86%); an individual toxicity, not the overall AE rate	40/42 (95%) completed planned CRT; the abstract did not separately report the rate of discontinuation due to toxicity	G2-3 fistula: 6/42 (14%)	1/42 (2%); pneumonia
Induction followed by dCRT ImpactCRT [32] n = 49; full-course safety n = 46	G $\geq$ 3 lymphopenia: 46/46 (100%); G $\geq$ 3 esophagitis: 2/46 (4.3%)	Radiotherapy stopped early in 1/46 (2.2%) due to endotoxic shock; concurrent chemotherapy stopped early in 2/46 (4.3%)	No cases reported	1/46 (2.2%); infection after bone marrow suppression
Post-dCRT consolidation EPOC1802 [35] n = 40	G $\geq$ 3 pneumonitis: 2/40 (5%); overall G $\geq$ 3 AE rate not reported in the main text	11/40 completed; 23/40 stopped due to progression; the main text did not separately report the rate of discontinuation due to AEs	1 patient with post-CRT tracheal fistula excluded before enrollment; post-enrollment incidence not separately reported in the main text	0/40
Post-dCRT consolidation SKYSCRAPER-07 [37] Safety n = 755	G3-4 TRAEs: 16.1% with dual immunotherapy, 9.6% with atezolizumab, 9.6% with placebo	Rates of treatment withdrawal due to AEs: 9.1%, 6.8%, and 4.0%, respectively	Not reported as a separate endpoint in the reviewed abstract	1.2%, 0.8%, and 1.6%, respectively

AE, adverse event; TRAE, treatment-related adverse event; G, grade; NR, not separately reported in the main text or available abstract. NR does not equal 0. Percentages retain the analysis populations of the original reports, and overall adverse events are distinguished from individual toxicities. Failure to complete treatment cannot invariably be attributed to toxicity; events occurring before enrollment for

consolidation cannot be counted as events during consolidation treatment.

In EC-CRT-002, $G \geq 3$ adverse events occurred in 86.0% of the maintenance group and 80.7% of the nonmaintenance group, with corresponding rates of severe lymphopenia of 77.2% and 73.7% [33]. These data alone cannot establish the reasons for the difference in efficacy. Safety after dCRT is also affected by eligibility criteria: before atezolizumab was initiated, EPOC1802 excluded 1 patient with a tracheal fistula after CRT and some patients with persistent, unresolved CRT-related toxicity [35]. The absence of fistula in a small, selected cohort cannot demonstrate that immunotherapy prevents fistula.

5.2. Assessment and Management

Safety data should retain the version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) used in each original study; historical v4.0 or v5.0 events should not be retrospectively regraded using a later version [48]. Management should distinguish CRT-related injury, immune-related adverse events (irAEs), infection, and tumor progression. Table 3 summarizes the main differential diagnoses and the basis for management.

Table 3. Major adverse events and management principles.

Event	Main manifestations or risks	Differential assessment	Management principles
Esophagitis and nutritional injury	Odynophagia, inadequate intake, obstruction, malnutrition	Infection, progression, drug-related inflammation	Grading, analgesia, mucosal protection, nutritional screening, and enteral nutrition when necessary [49] [50]
Fistula or bleeding	T4b, ulceration, airway/aortic invasion; choking, fever, hemoptysis	Contrast-enhanced CT; contrast studies, endoscopy, or bronchoscopy as needed	Stop the relevant treatment; no oral intake, anti-infective treatment, nutritional support, and urgent multidisciplinary assessment [51] [52]
Pneumonitis	Cough, dyspnea, hypoxemia; in-field or multifocal opacities	Infection, embolism, heart failure, progression; correlate with the radiotherapy plan	Grade-based ICI withholding, corticosteroids, and specialist assessment; permanent ICI discontinuation for G3-4 immune-related pneumonitis [53]-[56]
Bone marrow suppression and lymphopenia	Decreased leukocytes, platelets, or lymphocytes	Chemotherapy, radiation exposure, other drugs, infection	Monitor blood counts, reduce the dose or withhold treatment according to grade, manage infection, and optimize radiation exposure
Endocrine irAEs	Thyroid, pituitary, or adrenal dysfunction, or hyperglycemia	Drug effects and pre-existing endocrine disease	Stabilize emergencies and replace deficient hormones; controlled endocrinopathies do not invariably require permanent ICI discontinuation [55] [56]
irAEs in other systems	Hepatitis, colitis, rash; uncommon myocarditis or neurological injury	Infection, underlying disease, and other drugs	Grade according to the affected organ; withhold ICI, administer corticosteroids, and provide specialist management when necessary [55] [56]

Suspected immune-related pneumonitis should first be graded according to CTCAE. Grade 1 refers to radiographic changes without symptoms and requires close monitoring; ICIs may be temporarily withheld, with reassessment of symptoms, oxygen saturation, and chest CT. For grade 2 pneumonitis with symptoms requiring medical intervention, ICIs should be withheld; prednisone 1 - 2 mg/kg/day or an equivalent dose is commonly used and tapered over at least 4 - 6 weeks after improvement. If infection has not been excluded, pathogen testing should be performed concurrently, with empirical anti-infective treatment when appropriate. Grade 3 pneumonitis involves severe symptoms, impairment of self-care, or a need for supplemental oxygen; grade 4 is life-threatening. Both require hospitalization, permanent discontinuation of ICIs, and intravenous methylprednisolone 1 - 2 mg/kg/day. If there is no improvement within 48 - 72 hours, a multidisciplinary team should consider second-line immunosuppressive treatment such as mycophenolate mofetil or intravenous immunoglobulin [55] [56]. Rechallenge may be considered on an individual basis only after a grade 2 event has completely or substantially resolved to grade ≤ 1 , corticosteroids have been reduced to a physiological or low dose, and infection has been excluded. Reuse of ICIs is generally avoided after grade 3 - 4 pneumonitis.

Endocrine irAEs are an exception to the general principle of permanent discontinuation. Emergencies such as adrenal crisis or severe hyperglycemia should first be stabilized; thyroid, pituitary, or adrenal insufficiency is managed primarily with appropriate hormone replacement. Resumption of ICIs may be considered once the condition is stable, and treatment should not be permanently discontinued solely because long-term hormone replacement is needed [55] [56]. High-dose corticosteroids are generally not used for isolated hypothyroidism. When adrenal insufficiency is suspected, glucocorticoid deficiency should be corrected before thyroid hormone replacement is initiated.

Radiation esophagitis and nutritional support likewise require standardized, evidence-based management. Body weight, intake, and swallowing function should be assessed continuously before and during treatment. Initial measures include individualized dietary guidance, analgesia, acid suppression and mucosal protection, and oral nutritional supplements. Enteral nutrition is preferred when gastrointestinal function is intact but oral intake remains inadequate; parenteral nutrition is considered only when enteral nutrition is not feasible or remains insufficient [49] [50]. Esophageal stents should not routinely be placed during dCRT to prevent obstruction. The European Society of Gastrointestinal Endoscopy (ESGE) recommends covered self-expanding metal stents to seal malignant tracheoesophageal or bronchoesophageal fistulas, but placement before or during definitive chemoradiotherapy may increase adverse events. Establishing a route for nutritional support is generally prioritized, with individualized decisions made by a multidisciplinary team [52].

6. Conclusions

Standardized dCRT remains the treatment backbone for anatomically unresec-

table locally advanced ESCC. Cross-study comparisons should first align with the evidence-based reference dose of 50.0 - 50.4 Gy, or explicitly describe the 50 - 60 Gy regimen, IFI/ENI strategy, concurrent chemotherapy regimen, and completion rate. Only then can the observed benefit be discussed as potentially attributable to ICIs rather than differences in radiotherapy or chemotherapy.

Concurrent, induction, and consolidation or maintenance immunotherapy remain under evaluation. Existing studies differ in anatomical eligibility criteria, endpoint time origins, toxicity reporting, and selection after dCRT. EC-CRT-002 did not establish a universal benefit from prolonged maintenance therapy; although SKYSCRAPER-07 showed a favorable descriptive monotherapy signal, it did not meet the primary endpoint tested first in the hierarchy [33] [37]. Future studies should report the anatomically unresectable ESCC subgroup separately, include randomized dCRT controls where appropriate, fully report treatment exposure and severe safety outcomes, and validate treatment-by-biomarker interactions before using biomarkers to select or prolong immunotherapy.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

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