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In-Depth Analysis of the Necessity and Optimization Strategies for Adjuvant Radiotherapy Following Neoadjuvant Immunotherapy in the New Era of Esophageal Cancer Treatment

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ABSTRACT

As immunotherapy rises to prominence in cancer treatment, the therapeutic approach to esophageal cancer is undergoing significant transformations. This review emphasizes the necessity and optimization pathways for adjuvant postoperative radiotherapy after neoadjuvant therapy in patients with esophageal cancer in the immunotherapy era. Initially, we review the advancements in neoadjuvant treatment strategies. Subsequently, we evaluate the role of postoperative radiotherapy and the latest advancements in radiotherapy target volume definition and dose optimization following neoadjuvant therapy, as well as the implications of tumor immunotherapy on postoperative radiotherapy strategies. In conclusion, in the new era of immunotherapy, postoperative radiotherapy following neoadjuvant therapy for esophageal cancer holds significant value. Optimization strategies should follow individualized treatment principles and comprehensively consider tumor biology, patient status, and treatment resources to achieve optimal therapeutic outcomes and quality of life, thereby driving continuous innovation in esophageal cancer treatment.

1 | Introduction

Esophageal cancer (EC), a highly aggressive digestive tract malignancy, poses a significant global health challenge owing to its generally poor prognosis. According to 2020 global cancer statistics, EC ranks seventh in incidence and sixth in mortality, with approximately 600,000 new cases and 540,000 deaths annually [1]. Over half of all global cases of EC occur in China, where the burden is particularly heavy. Notably, esophageal squamous cell carcinoma (ESCC) dominates in high-risk regions like the Taihang mountains and Lin County in Henan and accounts for over 85% of all cases of EC [2]. Because early-stage

Abbreviations: AEs, adverse events; cCR, clinical complete response; CI, confidence interval; DFS, disease-free survival; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; JCOG, Japan Clinical Oncology Group; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; NICRT, neoadjuvant immunotherapy combined with chemoradiotherapy; NICT, neoadjuvant immune-chemotherapy; nIT, neoadjuvant immunotherapy; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; POCRT, postoperative chemoradiotherapy; PORT, postoperative radiotherapy; RT, radiation therapy.

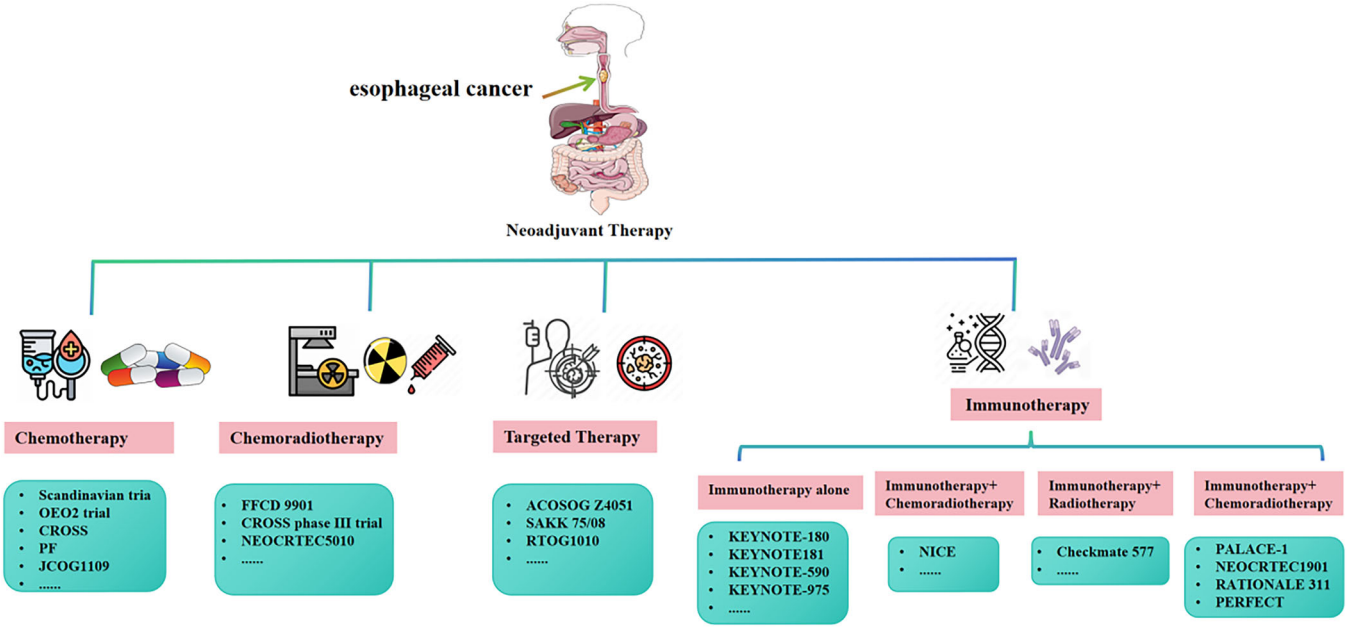

FIGURE 1 | Summary of treatment strategies for esophageal cancer.

symptoms of EC are frequently insidious, 60%–70% of patients are diagnosed at an advanced stage, which complicates treatment.

Radiation therapy (RT) is a cornerstone in EC management, serving as the standard of care for both operable and unresectable locally advanced cases. RT is an important component of both preoperative neoadjuvant chemoradiotherapy (nCRT) and definitive chemoradiotherapy. Recently, immunotherapy has revolutionized EC treatment. Its integration with neoadjuvant therapy has enhanced surgical resection rates and improved patient outcomes.

Despite advancements in neoadjuvant therapy, postoperative recurrence remains a major concern. Consequently, the debate on whether to administer adjuvant RT following neoadjuvant therapy is intense, especially regarding patients who have not achieved pathological complete response (pCR). This review aims to explore the necessity and considerations for adjuvant RT after neoadjuvant therapy in the immunotherapy era, providing scientifically sound and clinically relevant guidance for practice (Figure 1).

2 | Innovations and Trends in Neoadjuvant Therapy for Esophageal Cancer

2.1 | Historical Evolution and Efficacy of Neoadjuvant Chemotherapy (nCT)

Since the introduction of nCT for EC in the landmark Scandinavian trial in 1992 [3], research has progressively refined treatment approaches. Early studies established the survival benefit of bleomycin and cisplatin combinations in locally unresectable EC (median overall survival [OS]: 12 vs. 9 months), paving the way for subsequent research. In the 21st century, the OEO2 trial, conducted by the British Medical Research Council, enrolled 802 patients randomized to surgery alone or nCT with cisplatin plus 5-fluorouracil followed by surgery. The nCT group demonstrated superior rates of disease-free survival (DFS) and OS, highlighting its significance in improving patient outcomes. After a median follow-up of 6 years [4], the nCT group showed a significantly higher 5-year survival than the surgery alone group (23.0% vs. 17.1%; hazard ratio [HR]: 0.84; 95% confidence interval [CI], 0.72–0.98; $p = 0.03$), confirming long-term benefits in both esophageal adenocarcinoma (EAC) and ESCC. Subsequently, the CROSS (carboplatin + paclitaxel) and PF (cisplatin + fluorouracil) regimens became standard nCT protocols.

While European and American studies have provided substantial evidence for nCT in EC, the predominance of ESCC in China necessitates careful interpretation and application of these data. In response, the JCOG1109 trial, initiated by the Japan Clinical Oncology Group (JCOG) in 2012, enrolled 501 ESCC patients randomized to three arms: NeoCF (two cycles of fluorouracil and cisplatin), NeoCF+D (three cycles of fluorouracil, cisplatin, and docetaxel), and NeoCF+RT (two cycles of fluorouracil and cisplatin with radiotherapy). This trial compared different chemotherapy regimens and the addition of radiotherapy, providing valuable data for neoadjuvant therapy in ESCC. Results showed a significant 3-year survival advantage for the NeoCF+D arm (72.1% vs. 62.6%; HR: 0.68; one-sided $p = 0.006$). Although the NeoCF+D arm experienced primarily grade 3 or 4 neutropenia and febrile neutropenia, these adverse events (AEs) were manageable and did not significantly increase postoperative complications or mortality. Median OS was not reached in the NeoCF+D arm, compared to 7.0 years in the NeoCF+RT arm and 5.6 years in the NeoCF arm, supporting a new standard of care for locally advanced ESCC [5]. However, balancing efficacy with minimizing AEs remains a crucial research focus.

Despite ongoing debates about the efficacy of nCT in EC, particularly ESCC, chemotherapy remains a cornerstone of treatment. With the advent of immunotherapy, the treatment

landscape of EC is undergoing transformative changes. Integrating immunotherapy into neoadjuvant therapy offers new possibilities and necessitates a reevaluation of traditional chemotherapy protocols. In the immunotherapy era, developing precise, effective, and safe treatment strategies that combine chemotherapy, radiotherapy, and immunotherapy will be a key research area. Additionally, continuous refinement of chemotherapy regimens, doses, and timing will be essential.

2.2 | Key Advances and Benefits of nCRT for Locally Advanced EC

An in-depth analysis of the FFCD 9901 trial revealed that nCRT does not significantly enhance survival compared with surgery alone in stage I and II EC patients (47.5% in nCRT group and 53.0% in surgery alone group) (HR: 0.99; 95% CI, 0.69–1.40; $p = 0.94$) but may increase 30-day postoperative mortality (11.1% vs. 3.4%; $p = 0.049$) [6]. Given the favorable prognosis of early-stage EC, further validation is required to ascertain the suitability of neoadjuvant therapy for these patients.

Research has pivoted toward locally advanced EC, where multiple studies consistently highlight the crucial role of nCRT. The landmark Dutch CROSS phase III trial, which examined 366 EC patients, demonstrated that nCRT significantly increased the R0 resection rate (92% vs. 69%), prolonged median OS (49.4 vs. 24.0 months), and achieved a high pCR rate of 29%. A pCR was observed in 49% of ESCCs and 23% of EACs. In long-term follow-up, nCRT also reduced the rates of local recurrence (22% vs. 38%) and distant metastasis (39% vs. 48%) [7].

These findings were corroborated by China's NEOCRTEC5010 study, which randomized 451 ESCC patients to nCRT and surgery alone groups. The nCRT group exhibited a significantly higher R0 resection rate (98.4% vs. 91.2%), longer median OS (100.1 vs. 66.5 months), and longer progression-free survival (PFS; 100.1 vs. 41.7 months), with a pCR rate of 43.2% [8].

A meta-analysis of 24 studies (4188 patients) found that both nCT (HR: 0.78; 95% CI, 0.70–0.88; $p < 0.0001$) and nCRT (HR: 0.87; 95% CI, 0.79–0.96; $p = 0.005$) reduced all-cause mortality compared with surgery alone. However, nCRT did not significantly outperform nCT in reducing mortality (HR: 0.88; 95% CI, 0.76–1.01; $p = 0.07$) [9]. Although these results strongly support neoadjuvant therapy for EC, further research is needed to delineate the specific advantages of nCRT over nCT.

In conclusion, nCRT is highly recommended for locally advanced resectable EC, but its AEs and long-term toxicities necessitate individualized and meticulous adjustments to optimize therapeutic outcomes.

2.3 | Exploratory Progress and Challenges in Neoadjuvant Targeted Therapy

Neoadjuvant targeted therapies for EAC are increasingly demonstrating their potential, albeit with associated challenges. A pivotal phase II clinical trial (ACOSOG Z4051) evaluated a neoadjuvant regimen comprising docetaxel (40 mg/m^2), cisplatin (40 mg/m^2), and panitumumab (6 mg/kg) in 70 EAC patients, followed by RT (total dose 5040 cGy in 28 fractions). The trial reported a median OS of 19.4 months, a 3-year OS of 38.6% (95% CI, 24%–68%), and a pCR rate of 33.3%. Although efficacy was evident, 48.5% of patients experienced grade ≥ 4 toxicity, highlighting the effectiveness of the regimen (pCR + near-pCR = 53.7%) as well as its toxicity [10].

The application of targeted therapy has expanded beyond single histological subtypes. The SAKK 75/08 phase III trial [11] demonstrated that irrespective of EAC or ESCC, patients undergoing R0 resection after nCRT combined with cetuximab experienced significantly prolonged locoregional recurrence-free survival (HR: 0.53; 95% CI, 0.31–0.90; $p = 0.017$) without a substantial increase in AEs. These findings suggest that the incorporation of cetuximab into multimodal therapy enhances locoregional control, albeit with modest improvements in OS and PFS.

Furthermore, dual-target therapy studies combining trastuzumab and pertuzumab with nCRT have indicated that R0 resection was achieved in all surgically treated patients, with 3-year PFS and OS rates of 57% and 71%, respectively (median follow-up: 32.1 months), confirming the strategy's feasibility in improving outcome. However, the RTOG1010 trial, which integrated trastuzumab into trimodal therapy for HER2-positive EAC, did not significantly improve PFS or OS [12]. Despite these disappointing results, the way has been paved for future exploration of more effective HER2-targeted approaches. Overall, neoadjuvant targeted therapy for EC remains in a crucial phase of ongoing exploration and optimization.

2.4 | The Ascendance and Promising Prospects of Neoadjuvant Immunotherapy

2.4.1 | The KEYNOTE Trials

In 2019, pembrolizumab received approval as first- or subsequent-line systemic therapy for recurrent, locally advanced, or metastatic ESCC, particularly in patients with positive programmed cell death 1 ligand 1 (PD-L1) expression, marking a significant milestone in EC immunotherapy.

The KEYNOTE-180 trial (2017) [13] initially enrolled 121 patients with advanced metastatic EC to evaluate pembrolizumab monotherapy. The objective response rate was 9.9%, with superior outcomes in ESCC and PD-L1-positive patient subgroups. Building on this, the KEYNOTE-181 trial [14] compared pembrolizumab with chemotherapy as second-line therapy in 628 patients and showed that median OS was significantly longer in the pembrolizumab group (9.3 vs. 6.7 months; HR: 0.69; 95% CI, 0.52–0.93; $p = 0.0074$).

Subsequently, the phase III KEYNOTE-590 trial [15] investigated pembrolizumab plus chemotherapy as first-line therapy. Compared with chemotherapy alone, the addition of pembrolizumab provided significant improvements in median OS (13.9 vs. 8.8 months; HR: 0.57; 95% CI, 0.43–0.75; $p < 0.0001$) and PFS (6.3 vs. 5.8 months; HR: 0.65; 95% CI, 0.54–0.78; $p < 0.0001$). In addition, toxicity was manageable (grade 3+ treatment-related

adverse events: 72% vs. 68%). This established pembrolizumab plus chemotherapy as the standard first-line treatment.

Currently, the KEYNOTE-975 trial [16] is exploring pembrolizumab combined with concurrent chemoradiotherapy for locally advanced EC and is poised to further expand the role of immunotherapy in comprehensive treatment. Given its efficacy in advanced metastatic disease, investigating the role of immunotherapy in the neoadjuvant setting is well founded. Multiple phase I/II trials are underway to validate and optimize immunotherapy strategies for early EC intervention.

2.4.2 | Efficacy and Safety of Neoadjuvant Immunotherapy Combined With Chemotherapy in ESCC: An Exploratory Study

The phase II NICE trial enrolled 60 patients with locally advanced, resectable thoracic ESCC to assess the efficacy and safety of camrelizumab combined with albumin-bound paclitaxel and carboplatin as neoadjuvant therapy. The results revealed an impressive R0 resection rate of 98.0%, with a pCR rate of 39.2%. Although grade 3 or higher AEs occurred in 56.7% of patients, there were no in-hospital deaths or deaths within 30 or 90 days of surgery, confirming the efficacy and safety of this combination [17].

Currently, several phase III clinical trials are in progress, aiming to comprehensively evaluate the clinical benefits and safety of neoadjuvant immunotherapy combined with chemotherapy (NICT) in patients with resectable EC. Preliminary findings indicate promising efficacy and a favorable safety profile, suggesting its potential to become a pivotal component of future multimodality EC treatment.

2.4.3 | Synergistic Mechanisms and Challenges of Radiotherapy Combined With Immunotherapy

In recent years, a series of small-scale clinical trials have preliminarily unveiled the potential of nCRT combined with immunotherapy in the treatment of locally advanced EC. This combinatorial approach not only markedly elevates the pCR rate but also successfully converts initially unresectable tumors into operable ones, achieving tumor downstaging. Notably, radiotherapy synergizes with immunotherapy through multiple mechanisms, thereby broadening the therapeutic landscape.

Specifically, radiotherapy induces immunogenic cell death, leading to the widespread release of tumor-associated antigens. This process mimics the creation of an "in situ tumor vaccine," significantly enhancing the capacity of the immune system to recognize and eliminate tumor cells [18, 19]. Additionally, radiotherapy actively remodels the tumor microenvironment, facilitating CD8+ T cell infiltration and activation, increasing interferon-gamma production, and promoting macrophage polarization from immunosuppressive M2 to antitumor M1 phenotypes. These changes reshape the immune microenvironment to favor antitumor immunity [20].

Furthermore, radiotherapy activates the cyclic GMP-AMP synthase-stimulator of interferon genes pathway, triggering type I interferon production. This cascade further augments the antitumor immune response. Concurrently, radiotherapy-induced upregulation of PD-L1 on tumor cells provides more targets for PD-1/PD-L1 immune checkpoint inhibitors, thereby enhancing immunotherapy efficacy. Importantly, radiotherapy also elicits an "abscopal effect," where tumors in nonirradiated areas are attacked by the immune system, indicating the activation of a systemic antitumor immune response [21].

Another phase III randomized controlled trial (Checkmate 577) [22] evaluated nivolumab as adjuvant therapy in EC patients who had pathological residual disease after undergoing neoadjuvant chemotherapy and resection. The experimental group received intravenous nivolumab (240 mg every 2 weeks for 16 weeks, followed by 480 mg every 4 weeks) for 1 year, and the control group received placebo. The primary and secondary endpoints were DFS and OS, respectively. The trial showed that nivolumab significantly prolonged DFS (22.4 vs. 11.0 months; HR: 0.69; $p < 0.001$). This suggests that immunotherapy, as a sequential treatment after chemoradiotherapy, can significantly improve patient outcomes.

However, the application of radiotherapy must be approached with caution because of its potential to induce immunosuppressive side effects (increased secretion of transforming growth factor-beta, suppression of CD8+ T cell function, induction of regulatory T cells) that may compromise immunotherapy effectiveness [23]. Therefore, future research should focus on determining the optimal radiation dose, fractionation schedule, and timing of combination with immunotherapy to maximize synergistic effects while minimizing potential adverse impacts. Ultimately, the goal is to offer more precise and effective treatment options for patients with locally advanced EC.

2.4.4 | Preliminary Outcomes of Neoadjuvant Immunotherapy Combined With Chemoradiotherapy

In China, the phase I PALACE-1 trial pioneered the investigation of pembrolizumab combined with nCRT for locally advanced ESCC. This study enrolled 20 patients with surgically resectable ESCC. The rates of pCR and R0 resection were 55.6% and 94.4%, respectively. Even though 65% of patients experienced grade ≥ 3 AEs, the regimen demonstrated promising efficacy with manageable toxicity [24]. Similarly, the NEOCRTEC1901 trial, which evaluated toripalimab plus nCRT for locally advanced ESCC, reported an R0 resection rate of 98% and a pCR rate of 50% (95% CI, 35–65); the incidence of grade 3/4 AEs was only 20% [25]. These studies suggest the potential of neoadjuvant immunotherapy in enhancing pCR rates, albeit definitive evidence from large-scale, multicenter trials is currently lacking.

Another phase III clinical trial (RATIONALE 311) [26] also confirmed the efficacy and safety of immunotherapy combined with concurrent chemoradiotherapy in patients with locally advanced, unresectable ESCC. This study enrolled patients who had not received prior systemic treatment. The experimental group received tislelizumab (200 mg every 3 weeks for 1 year)

combined with concurrent chemoradiotherapy (50.4 Gy in 28 fractions + cisplatin + fluorouracil). The control group received placebo plus concurrent chemoradiotherapy. The primary endpoint was PFS; secondary endpoints were OS and objective response rate. The experimental group demonstrated longer PFS (10.3 vs. 6.7 months; HR: 0.56; $p < 0.001$), showing the effectiveness of immunotherapy combined with concurrent chemoradiotherapy in the treatment of unresectable locally advanced ESCC.

However, the combined use of multiple preoperative treatments carries a risk of toxicity accumulation. In a meta-analysis of 38 trials which compared the efficacy and safety of neoadjuvant immunotherapy combined with chemoradiotherapy (NICRT) versus NICT [27], the NICRT group showed a higher pCR rate (38% vs. 28%; p. A similar trend was observed in main pathological response rate (67% vs. 57%; $p = 0.181$). Notably, the incidence of grade ≥ 3 treatment-related AEs was significantly higher in the NICRT group (58% vs. 18%; $p < 0.001$), although considered generally acceptable.

The single-arm phase II PERFECT trial assessed the efficacy of integrating the CROSS regimen (carboplatin + paclitaxel) with atezolizumab in the treatment of EAC. However, it did not show significant improvements in pCR rates (25% vs. 29%) or median OS (29.7 vs. 34.3 months) compared with the CROSS trial, although the safety profile was comparable. Nonetheless, the unique immune-related toxicities associated with PD-L1 inhibitors observed in PERFECT require close attention [28].

In conclusion, the application of NICRT in EC treatment is in its early exploratory phase. Preliminary results suggest its potential for enhancing pCR rates with manageable adverse effects, but larger-scale, rigorous phase III randomized controlled trials are necessary to validate its efficacy and safety. Additionally, in-depth research on managing and optimizing treatment-related toxicities is crucial to ensure patients can safely and effectively benefit from this innovative treatment approach.

2.5 | Innovative Organ-Preserving Treatment Modalities Under Neoadjuvant Therapy: Practices and Reflections

2.5.1 | Emergence of Neoadjuvant Therapy Regimens: Addressing Limitations of Traditional Surgical Treatment

Traditional surgical methods of EC treatment, though effective, frequently result in substantial trauma and postoperative complications, including anastomotic leakage, stenosis, pulmonary infection, reflux esophagitis, gastrointestinal discomfort, and malnutrition, which can markedly diminish quality of life. Advances in immunotherapy have led to neoadjuvant therapy regimens that significantly enhance clinical complete response (cCR) rates, offering new pathways to prolong survival and improve quality of life. The Chinese Society of Clinical Oncology guidelines recommend considering a "wait-and-see" approach for patients achieving cCR after preoperative chemoradiotherapy, reserving salvage surgery for local tumor recurrence during follow-up. This strategy is particularly advantageous for EC patients who are highly responsive to chemoradiotherapy and can achieve long-term survival rates comparable to those of surgical patients while preserving quality of life.

A pivotal 2007 randomized controlled trial involving 444 operable T3N0-1M0 patients with thoracic EC in Europe and the United States provided early insights. Following two cycles of fluorouracil and cisplatin chemoradiotherapy, patients were randomized to nCRT plus surgery or chemoradiotherapy alone, with the chemoradiotherapy group receiving three additional cycles. Although the nCRT plus surgery group showed a slightly higher local control rate (66.4% vs. 57%), the chemoradiotherapy group demonstrated superior 2-year OS (HR: 0.9; $p = 0.44$) and a significantly lower 3-month mortality (0.8% vs. 9.3%) [29], suggesting the potential of organ-preserving treatment.

Furthermore, results of the 2018 Japanese JCOG 0909 prospective study strongly support the "wait-and-see" strategy. Patients achieving cCR after chemoradiotherapy, followed by two cycles of consolidation chemotherapy, were managed expectantly. Notably, half of the patients avoided surgery yet achieved 3- and 5-year OS rates of 74.2% and 64.5%, respectively, with 5-year DFS and resection-free survival rates of 48.3% and 54.9%, respectively. Safety data showed only 9.6% of patients experienced grade III late toxicity compared to 19% of those undergoing salvage surgery. The JCOG 0909 outcomes were non-inferior to the classic CROSS study (5-year OS and DFS of 47% and 43%, respectively, in the nCRT plus surgery group), and esophageal function was preserved in 55% of patients [30]. Domestic studies have also validated the feasibility and efficacy of this strategy [31], marking a paradigm shift in EC treatment toward individualized care and quality of life optimization.

2.5.2 | International Advances in Personalized Treatment Pathways: The SANO Trial

At the 2023 European Society for Medical Oncology Congress, a late-breaking abstract presented the SANO trial, marking a significant advancement. This study randomized patients with resectable locally advanced esophageal and esophagogastric junctional cancers (25% squamous cell carcinoma, 75% adenocarcinoma) to either surgery or active surveillance following concurrent chemoradiotherapy. The randomization was based on a rigorous response assessment, the preSANO protocol, which included endoscopy, bite-on-bite biopsy, and fine-needle aspiration.

For patients achieving cCR post-chemoradiotherapy, irrespective of tumor histology, the study evaluated the feasibility of a "wait-and-see" approach. After approximately 30 months of follow-up, the 2-year OS in the active surveillance arm was non-inferior to that of the surgical arm (HR: 1.14; 95% CI, 0.75–1.78; $p = 0.55$), although the median DFS was shorter in the surveillance group (35 months; 95% CI, 31–41) than in the surgical group (49 months; 95% CI, 38–NA).

Notably, of the 198 patients under active surveillance, 33 (17%) developed distant metastases, while 69 (35%) maintained sustained cCR. This suggests that 35% to 52% of patients avoided

potentially unnecessary esophagectomy, despite a local–regional recurrence rate of 48% (96 cases). However, 86% of patients with recurrence underwent timely salvage surgery with complication rates comparable to those of standard surgery. Furthermore, health-related quality of life assessments at 6 and 9 months of follow-up demonstrated significantly better outcomes in the surveillance group ($p < 0.01$) [32].

Currently, esophageal-preserving strategies are in the early stages of exploration, and the advent of immunotherapy has opened new avenues for nonsurgical management of EC. Several ongoing phase III clinical trials have preliminarily confirmed that neoadjuvant immunotherapy can significantly increase the proportion of patients achieving cCR. Future research endeavors will focus on extending patient survival and optimizing long-term quality of life, heralding profound transformations in EC treatment paradigms.

3 | Postoperative Radiotherapy in EC: Necessity, Controversy, and Practice Variations

3.1 | Neoadjuvant Therapy and Postoperative Radiotherapy: Balancing Efficacy and Controversies

Despite the notable benefits of neoadjuvant therapies in reducing tumor size and enhancing resectability, with immunotherapy further elevating pCR rates to between 20% and 30%, a significant proportion of patients still grapple with residual tumor or micrometastases. Consequently, postoperative radiotherapy (PORT) has emerged as a vital consolidative treatment to eradicate residual disease, enhance local control, and improve survival outcomes. However, the necessity of PORT for EC remains internationally debated. Notably, Japan, which has 5-year postoperative survival rates superior to those of China, along with Western countries, favors neoadjuvant therapy followed by surgery over postoperative chemoradiotherapy (POCRT), highlighting the importance of early intervention and surgical optimization.

In contrast, clinical practice in China typically involves direct definitive surgery, predominantly via left thoracotomy, and the use of preoperative therapy is limited. This underscores the pressing need to refine patient selection for PORT and define appropriate irradiation fields. Currently, EC guidelines from the Chinese Society of Clinical Oncology [33], the National Comprehensive Cancer Network [34], the European Society for Medical Oncology [35], and those from Japan uniformly recommend PORT for patients with R1 or R2 resection margins. Nonetheless, the application of PORT after R0 resection has been achieved remains controversial.

3.2 | From Classic Research to Emerging Perspectives: Accumulating Evidence for Postoperative Radiotherapy

A 2012 update of the landmark INT0116 clinical trial with over a decade of follow-up demonstrated a significant and sustained benefit of POCRT on patient survival. Specifically, the HR for OS was 1.32 (95% CI, 1.10–1.60; $p = 0.0046$), and that for recurrence-free survival was 1.51 (95% CI, 1.25–1.83; $p < 0.001$). However, it is important to note that only 20% of participants had adenocarcinoma of the esophagogastric junction, while 80% had gastric adenocarcinoma [36], limiting the clarity of these findings for EAC. Consequently, despite National Comprehensive Cancer Network guidelines recommending PORT for pT2-4aN0, N+M0 EAC, the specific subpopulation benefiting from the INT0116 trial remains undefined.

Focusing on ESCC, multiple studies have accumulated crucial evidence [37] suggesting that stage III and node-positive patients are the primary beneficiaries of PORT. In a prospective randomized controlled trial, 495 patients undergoing esophagectomy were randomly assigned to surgery alone or surgery plus radiotherapy (radiation dose, 50–60 Gy). The trial showed that PORT improved the 5-year OS rate from 14.7% to 29.2% ($p = 0.0698$) in node-positive patients, but statistical significance was not reached; however, this effect was more pronounced in stage III patients, in whom 5-year OS increased from 13.1% to 35.1% ($p = 0.0027$) [38]. Nonetheless, these conclusions are largely derived from retrospective studies utilizing two-dimensional irradiation, which has inherent limitations in precision and target delineation.

With advancements in precision radiotherapy technologies, such as three-dimensional conformal radiotherapy and intensity modulated radiation therapy, recent studies have provided new insights into PORT indications. Notably, a study of T2-3N0 thoracic ESCC patients undergoing R0 resection and comprehensive lymph node dissection, followed by intensity-modulated radiation therapy within 3 months, showed a significantly higher 3-year DFS in the surgery plus radiotherapy group than the surgery alone group (75.1% vs. 58.7%; $p = 0.03$) [39]. Although the OS difference was not statistically significant, these findings suggest that PORT may benefit pT2-3N0M0 ESCC patients.

A pivotal phase III randomized controlled trial published in 2021 further refined postoperative treatment strategies for ESCC [37]. It not only confirmed the rationale for PORT in IIB-III stage ESCC but also explored the differential effects of various treatment strategies. Notably, among patients with IIB-III stage ESCC undergoing left thoracotomy resection, both PORT and POCRT effectively prolonged DFS and OS, with the POCRT group showing the most significant improvement in prognosis [40]. These findings provide a solid foundation for optimizing postoperative treatment regimens. A summary of trials regarding PORT/POCRT is shown in Table 1.

3.3 | Recent Advances in Defining Postoperative Radiotherapy Target Volumes and Dose Optimization

Addressing the challenges and controversies in defining target volumes and optimizing doses for PORT in EC necessitates a tailored approach to irradiation field planning, given the skip metastasis characteristic and the preponderance of local recurrence and distant metastasis in treatment failure. The recurrence patterns, heavily influenced by surgical techniques,

TABLE 1 | Postoperative radiotherapy/chemoradiotherapy clinical trials and studies.

References	Phase	Stage	Histology	CT/RT	Technique	Survival
[36]	III	IB–IV	GC/GEJ	5–Fu/45 Gy	3DCRT	35 months vs. 27 months (OS)
[37]	III	IIB–III	ESCC	FP/45–50.4 Gy	IMRT	28.5 months vs. 16.2 months (DFS)
[38]	Retro	III	ESCC	FP/50.4 Gy	IMRT/3DCRT	21.3 months vs. 11.8 months (DFS)
[39]	III	II	ESCC	50.4 Gy	IMRT/3DCRT	78.5% vs. 63.2% (DFS)
[40]	III	IIB–III	ESCC	FP/50.4 Gy	IMRT	44.3% vs. 31.2% (OS)
[41]	Retro	II–III	ESCC	FP/50–54 Gy	IMRT	52.3 months vs. 41.6 month (OS)

Abbreviations: 3DCRT, 3-dimension conformal radiation therapy; DFS, disease-free survival; ESCC, esophagus squamous cell cancer; FP, cisplatin plus 5-Fluorouracil; IMRT, intensity modulated radiation therapy; OS, overall survival; Retro, retrospective study.

tumor sites, and postoperative pathological stages, demand meticulous attention.

Currently, surgical strategies for EC encompass a spectrum from incomplete two-field dissection via left thoracotomy to comprehensive three-field dissection involving the neck, thorax, and abdomen, with notable variations in the extent of upper mediastinal and supraclavicular clearance. The intricate neural, lymphatic, and vascular networks in the lower neck and upper mediastinum often render these regions susceptible to recurrence following incomplete dissection. A retrospective study of 414 patients who underwent R0 resection for thoracic EC without adjuvant radiotherapy reported a 50% recurrence or metastasis rate; the location of locoregional failure was the neck in 24.9% of patients and mediastinum in 44.5%, underscoring their importance in target volume delineation [41].

Recurrence patterns vary by tumor location: upper esophageal cancers tend to recur in the neck/supraclavicular area and upper mediastinum, while middle esophageal cancers predominantly recur in the mediastinum, with variable neck/supraclavicular and abdominal lymph node involvement. Lower esophageal cancers primarily recur in the mid-to-lower mediastinum and abdomen. Some argue that the abdomen, with its clear surgical field and thorough dissection, experiences a lower recurrence rate, and given the radiotherapy-associated toxicity, prophylactic irradiation may not be justified. Anastomotic recurrence rates after EC surgery are generally low (< 5%) and do not exceed 8.5% even in T3-4 patients, thus obviating routine prophylactic irradiation of the anastomosis [42].

Although the overall recurrence rate in the tumor bed after surgery is low, patients with an advanced T-stage cancer are at increased risk. Regarding dose optimization for PORT, while phase III randomized controlled trials have not definitively confirmed its benefits, multiple retrospective analyses support its positive impact on survival. Notably, both the Dutch ARTDECO study [43] and a Chinese phase III trial [44] demonstrated comparable outcomes between 50 and 60 Gy radiation doses. For patients with potential tumor residual (R1/2), a total dose not exceeding 60 Gy is recommended.

Therefore, delineating the clinical target volume for PORT requires a comprehensive consideration of the primary tumor site, surgical details, preoperative imaging, postoperative pathological staging, and patient condition to achieve individualized and precise target volume planning. Dose prescription should align with the latest research and clinical practice guidelines to ensure treatment safety and efficacy.

3.4 | Impact of Tumor Immunotherapy on Postoperative Radiotherapy Strategies and Future Directions

In the evolving landscape of tumor immunotherapy, adjuvant treatment strategies for EC after surgery are undergoing significant shifts. Although clinical research on PORT or cRT combined with immunotherapy is still scarce, immunotherapy has shown impressive efficacy in select patient cohorts, heralding a new era in treatment paradigms. Importantly, for patients in whom R0 resection has been achieved, but not pCR after neoadjuvant therapy, adjuvant nivolumab has become a standard treatment option, which is supported by robust clinical evidence.

However, these advancements also present novel challenges to the field of postoperative adjuvant RT. With nivolumab established as a standard in adjuvant therapy, the implementation of randomized controlled trials for adjuvant RT alone faces unprecedented ethical dilemmas. Specifically, the ethical rationale for randomly assigning patients to a group that may exclude immunotherapy is questioned when a clear therapeutic benefit is evident.

4 | Conclusions

Future research should focus on exploring combined strategies of radiotherapy/CRT with immunotherapy, aiming to enhance therapeutic outcomes through synergistic effects. Concurrently, there is a need to delve into optimizing radiotherapy protocols within the current immunotherapy framework for more precise and individualized treatment. Additionally, conducting dedicated radiotherapy studies targeting specific subsets of patients with suboptimal responses to immunotherapy represents an important avenue worth exploring.

In conclusion, despite the myriad challenges faced by randomized controlled trials of postoperative adjuvant radiotherapy, these challenges also present opportunities to advance EC treatment toward a more personalized and integrated direction. Through continuous exploration and innovation, we anticipate opening up new avenues with improved prognoses for EC patients.

Author Contributions

Guohui Liu: conceptualization (lead), funding acquisition (lead), writing – original draft (lead), writing – review and editing (lead). **Yao Su:** writing – review and editing (supporting). **Yunlong He:** writing – review and editing (supporting). **Hanqing Hu:** conceptualization (lead), funding acquisition (lead), funding acquisition (lead), writing – review and editing (lead), writing – review and editing (lead).

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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