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Radiotherapy for Anastomotic Recurrence and Regional Lymph Node Metastases after Esophagectomy for Esophageal Cancer: Current Evidence and Open Questions

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Abstract: Surgery remains the mainstay of curative treatment for localized esophageal cancer, yet a substantial proportion of patients relapse after esophagectomy, most often at the anastomosis or in the regional lymph nodes. For these patients, who are frequently unfit for further surgery, radiotherapy is the principal locoregional option, but the evidence base is thin and largely retrospective. This review summarizes current knowledge on the patterns and determinants of postoperative recurrence, the diagnostic work-up required before salvage treatment, and the radiotherapy strategies available for anastomotic recurrence and regional nodal disease. The roles of conventional external-beam radiotherapy, intensity-modulated radiotherapy, stereotactic body radiotherapy and particle therapy are compared, with particular attention to dose constraints in the re-irradiation setting. The toxicity–efficacy balance and the biological mechanisms underlying radioresistance are then considered; how best to combine radiotherapy with systemic agents, including immune-checkpoint blockade, remains an open question. Because prospective data specific to this setting remain scarce, treatment decisions still rest on individualized, multidisciplinary assessment.

Keywords: Esophageal Cancer; Esophagectomy; Anastomotic Recurrence; Lymph Node Metastasis; Radiotherapy; Re-Irradiation

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1. Introduction

Esophageal cancer is a leading cause of cancer-related mortality worldwide, and its incidence continues to rise in several regions [1,2]. Complete resection offers the only realistic chance of cure, but even after R0 esophagectomy with adequate lymphadenectomy, recurrence is common. Depending on the series and the intensity of postoperative surveillance, reported recurrence rates range from roughly 20% to 50%, and the great majority of failures are locoregional rather than distant [3].

Two anatomical patterns dominate. The first is recurrence at the esophagogastric anastomosis, which reflects residual microscopic disease at the resection margin or implantation of exfoliated tumor cells during surgery. The second is metastasis to regional lymph nodes—cervical, mediastinal or abdominal—that were negative or unremoved at the time of operation. These two patterns frequently coexist and share a common clinical problem: re-operation is technically demanding, morbidity is considerable, and most patients are either ineligible or decline it. Radiotherapy, alone or with systemic therapy, has therefore become the default locoregional approach for postoperative recurrence.

Despite its wide use, evidence for radiotherapy in this setting comes mainly from single-institution retrospective series.

Prospective trials have generally excluded patients with isolated recurrence, and no randomized comparison of radiotherapy with best supportive care or with surgery has been completed. This review aims to organize what is known—and what remains uncertain—about the use of radiotherapy after anastomotic recurrence or regional lymph node metastasis following esophagectomy.

2. Patterns and Risk Factors of Recurrence after Esophagectomy

2.1 Anastomotic Recurrence

Anastomotic recurrence typically presents within two years of surgery [4,5]. Its principal risk factors are a positive or close resection margin, advanced T stage, and tumor involvement of the upper or middle thoracic esophagus, where achieving a wide margin is anatomically difficult [4]. Perineural invasion and lymphovascular invasion at the primary tumor have also been linked to anastomotic failure [6]. The pathogenesis is thought to involve both incomplete microscopic excision and the seeding of viable tumor cells at the suture line during manipulation of the specimen.

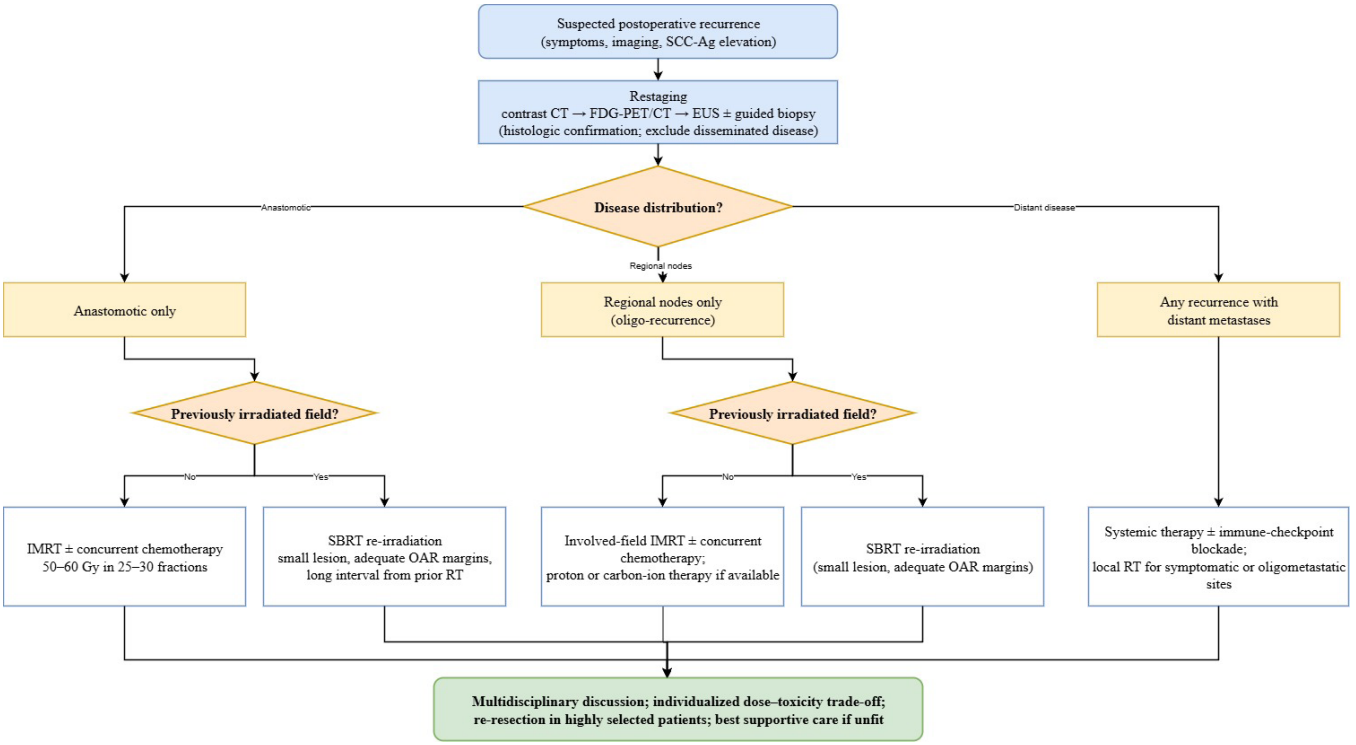
2.2 Regional Lymph Node Metastasis

The esophageal lymphatic network is dense and bidirectional, draining longitudinally along the submucosal plexus. This anatomy explains why nodal metastases can appear at stations remote from the primary tumor and why recurrence in the cervical or abdominal nodes is observed even after intrathoracic resection [7,8]. The number of metastatic nodes in the resected specimen (ypN category after neoadjuvant treatment) is the strongest predictor of subsequent nodal failure [9]. Inadequate lymphadenectomy, extracapsular nodal extension, and failure to deliver adjuvant therapy in high-risk patients further increase the risk.

3. Diagnosis and Surveillance

Accurate restaging before salvage radiotherapy is essential, both to define the target and to exclude widely disseminated disease for which locoregional treatment offers little benefit. A pragmatic diagnostic and therapeutic algorithm that integrates these considerations is presented in Figure 1.

Figure 1. Proposed diagnostic and therapeutic algorithm for patients with suspected recurrence after esophagectomy for esophageal cancer.



CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; EUS, endoscopic ultrasound; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; RT, radiotherapy; OAR, organs at risk.

3.1 Imaging

Contrast-enhanced computed tomography (CT) remains the first-line tool because of its availability, but its sensitivity for small anastomotic recurrences and for nodes sub-centimetre in size is limited [10,11]. Fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET/CT) improves detection of metabolically active recurrence, although postoperative inflammation at the anastomosis can generate false positives, particularly in the early period after surgery [12]. Endoscopic ultrasound is valuable for assessing wall-layer invasion at the anastomosis and for guided biopsy, but its utility is reduced when the gastric conduit has been pulled up into the chest [13].

3.2 Confirmation and Biomarkers

Tissue confirmation by endoscopic biopsy should be obtained whenever feasible before committing a patient to radical-intent radiotherapy. Serum markers such as squamous cell carcinoma antigen have limited sensitivity and are used mainly for surveillance rather than diagnosis [14]. On the research side, circulating tumor DNA is being explored for earlier detection of recurrence after esophagectomy; whether it can reliably distinguish anastomotic from nodal relapse before imaging changes appear is unresolved [15].

4. Radiotherapy for Anastomotic Recurrence

4.1 Conventional External-Beam Radiotherapy

Conventional three-dimensional conformal radiotherapy (3D-CRT) has historically been the workhorse in this setting. Typical palliative or salvage schedules deliver 50–60 Gy in 25–30 fractions, with retrospective series reporting symptom relief in many patients and one-year locoregional control that varies widely with tumor burden and dose [16,17]. The limiting factor has always been tolerance: the anastomosis lies adjacent to the airway, the gastric conduit and, depending on level, the spinal cord, so doses sufficient for durable control have often been constrained by the risk of stricture, fistula and pneumonitis.

4.2 Intensity-Modulated Radiotherapy

Intensity-modulated radiotherapy (IMRT) permits steep dose gradients around concave targets and has largely replaced 3D-CRT in centres with the necessary equipment. The available evidence is summarized in a 2017 meta-analysis of esophageal cancer: compared with 3D-CRT, IMRT reduced the irradiated volumes of lung and heart and improved overall survival, with no significant difference in radiation pneumonitis or esophagitis [18]. For postoperative esophageal recurrences, IMRT allows better sparing of the gastric conduit and lung, and dosimetric studies suggest that the constraints required for safe dose escalation are achievable in most patients [19]. Whether this dosimetric advantage translates into fewer fistulas or better control remains observational.

4.3 Stereotactic Body Radiotherapy and Re-Irradiation

A growing subgroup of patients presents with anastomotic recurrence in a previously irradiated field—either because neoadjuvant chemoradiotherapy preceded surgery or because salvage radiotherapy has already been given. Re-irradiation of the esophageal bed is hazardous, but stereotactic body radiotherapy (SBRT), with its hypofractionated, highly conformal delivery, has made it feasible in selected cases. SBRT was originally validated in extracranial oligometastatic disease; a 2016 series reported 94% local control for spinal metastases with acceptable toxicity [20]. Applied to small anastomotic recurrences, SBRT delivers ablative doses while respecting the low tolerance of previously irradiated organs at risk. Patient selection is everything: lesions should be small, the interval since prior irradiation reasonably long, and the cumulative dose to the spinal cord and airway carefully modelled.

4.4 Particle Therapy

Proton therapy exploits the Bragg peak to eliminate the exit dose into mediastinal structures. In postoperative non-small-cell lung cancer, proton therapy achieved local control comparable to IMRT with a lower mean lung dose (0.46 Gy vs 0.75 Gy in one 2017 analysis) [21]; the same dosimetric logic applies to the esophageal bed, where the gastric conduit and heart are the organs most likely to benefit. Carbon-ion therapy, with its high linear energy transfer, may offer biological advantages against radioresistant tumors, as suggested by phase I/II experience in recurrent nasopharyngeal carcinoma [22]. These technologies remain limited by availability and cost, and no outcome data specific to anastomotic recurrence of esophageal cancer exist.

5. Radiotherapy for Regional Lymph Node Metastasis

5.1 Target Definition and Technique

Nodal recurrence after esophagectomy raises the question of whether to treat only the involved stations (involved-field radiotherapy) or to extend elective coverage to adjacent nodal regions. Elective irradiation of uninvolved stations follows the logic of the disease's longitudinal lymphatic spread but enlarges the field into organs already compromised by surgery. Most contemporary series favour involved-field irradiation, often delivered by IMRT, reserving wider fields for cases with multiple or bulky nodal disease [23].

5.2 Combination with Systemic Therapy

Radiotherapy for nodal recurrence is rarely delivered alone in fit patients. Concurrent chemotherapy, most commonly platinum-based regimens, is extrapolated from the definitive chemoradiotherapy literature for inoperable esophageal cancer [24,25]. More recently, immune-checkpoint inhibitors have entered this space. The biological rationale is direct: irradiation upregulates programmed death-ligand 1 (PD-L1) on tumor cells, and PD-L1 expression in esophageal squamous cell carcinoma specimens correlates with advanced T stage ($p = 0.004$), lymph node metastasis ($p = 0.012$), and higher locoregional failure rates ($p = 0.0001$) [26]. Blocking this axis could plausibly convert irradiated, antigen-releasing tumor into an in situ vaccine. Clinical evidence specific to postoperative nodal recurrence is still preliminary, but results from adjuvant and advanced-disease trials are encouraging [27,28]. The randomized trials that currently underpin this strategy are summarized in Table 1.

Table 1. Randomized trials informing the combination of radiotherapy and immune-checkpoint blockade in esophageal cancer

Trial, year [ref]	Population	Intervention	Primary result	Relevance to postoperative recurrence
CheckMate 577, 2021 [27]	Resected esophageal / GEJ cancer with residual pathologic disease after neoadjuvant CRT	Adjuvant nivolumab vs placebo	Median DFS 22.4 vs 11.0 mo (HR 0.69)	First positive perioperative immunotherapy trial; defines the high-risk postoperative population
ESCORT-1st, 2021 [28]	Advanced or metastatic ESCC, first line	Camrelizumab + chemotherapy vs placebo + chemotherapy	Median OS 15.3 vs 12.0 mo (HR 0.70)	Establishes PD-1 inhibitor plus platinum chemotherapy as the backbone for systemic combination

GEJ, gastroesophageal junction; CRT, chemoradiotherapy; DFS, disease-free survival; HR, hazard ratio; mo, months; OS, overall survival; ESCC, esophageal squamous cell carcinoma.

5.3 Outcomes and Prognostic Factors

Reported survival after salvage radiotherapy for postoperative recurrence is heterogeneous, which reflects case-mix more than technique. Consistent adverse prognostic factors include a short disease-free interval after surgery, bulky recurrence, weight loss at presentation, and failure to achieve a complete metabolic response on interim imaging [29,30]. Where recurrence is truly oligometastatic and all visible disease can be encompassed in a radical field, selected series report outcomes approaching those of primary radical treatment—an observation that has fueled interest in aggressive local therapy for limited nodal relapse [31,32]. Because these series differ in case-mix, dose and endpoints, their findings are not directly comparable; a structured summary is provided in Table 2.

Table 2. Principal studies of salvage radiotherapy for postoperative recurrence of esophageal cancer

Study, year [ref]	n	Recurrence site	Dose / fractionation	Concurrent therapy	Survival outcome	Grade ≥3 toxicity
Zhang J, 2012 [17]	50	Local (postoperative)	50.4–64 Gy	FP/TP-based CCRT	MST 13.3 mo; 1-y OS 56%; 3-y OS 14%	—
Ito, 2022 [16]	51	Locoregional (postoperative)	60 Gy / 30 f (3D-CRT)	5-FU / platinum	Median OS 23.1 mo; 3-y OS 40.7%	No grade ≥3 late toxicity

Study, year [ref]	n	Recurrence site	Dose / fractionation	Concurrent therapy	Survival outcome	Grade ≥3 toxicity
Zhang C, 2021 [29]	103	Lymph node (postoperative)	IMRT-based; 61% >60 Gy	RT alone (38%) or CRT (62%)	Median OS 22.5 mo; 1/3/5-y OS 80.6 / 37.0 / 25.8%	Grade ≥3 toxicity 16.5%; grade 3 anastomotic stenosis and grade 4 gastric-bronchial fistula confined to 64–66 Gy subgroup
Yamashita, 2017 [31]	237	Lymph node oligo-recurrence	Median 60 Gy (45–70); involved-field or elective	CRT 84%	MST 21.6 mo; 3-y OS 36.7%; 3-y local control 45.1%	—
Ihara, 2023 [32]	—	Solitary postoperative recurrence (PET-detected)	Definitive RT (≥50 Gy)	—	1/2/3-y OS 85.2 / 62.6 / 47.3%	—
Mummudi, 2022 [33]	1,553	Locoregional postoperative recurrence	Median 60 Gy	CRT 57%	1/2/3-y OS 67.9 / 35.9 / 30.6%	Acute grade 3/4 mucositis 8%; pneumonitis 5%

MST, median survival time; FP, 5-fluorouracil/cisplatin; TP, paclitaxel/platinum; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; 5-FU, 5-fluorouracil; f, fractions; OS, overall survival; y, year; GEJ, gastroesophageal junction; PET, positron emission tomography. —, not reported in the original publication.

6. Limitations and Controversies

6.1 The Efficacy–Toxicity Balance

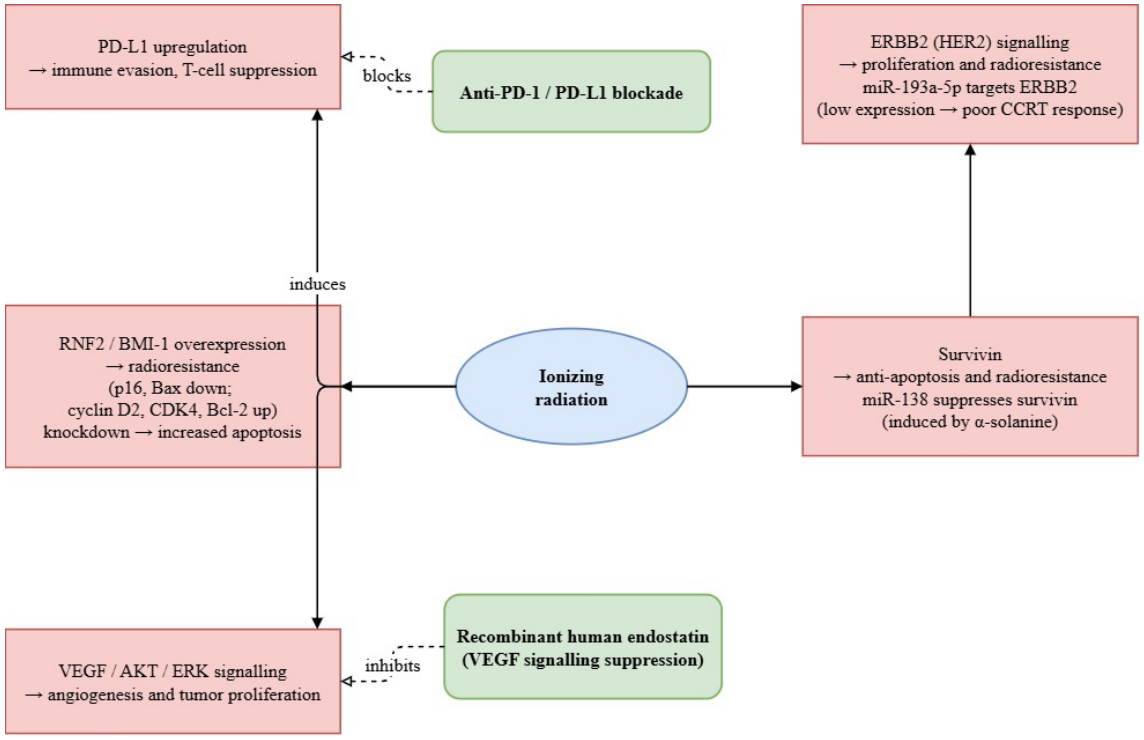
The central dilemma is that the doses needed for durable local control approach the tolerance of the reconstructed esophagus and the surrounding mediastinum. Anastomotic stricture requiring dilation, tracheo- or broncho-esophageal fistula, and conduit necrosis are the feared complications, each potentially fatal in a patient whose nutritional reserve is already compromised [16,29]. Retrospective series almost certainly under-report grade 4–5 events; prospective registries with standardized toxicity capture are needed before firm dose recommendations can be made.

6.2 Radioresistance at the Molecular Level

Radioresistance in esophageal cancer is multifactorial, and several molecular nodes have been characterized in preclinical models. Recombinant human endostatin sensitizes esophageal cancer xenografts to irradiation by suppressing vascular endothelial growth factor signaling: at 5 mg/kg it reduced relative tumor proliferation by up to 40% by day 15, lowered microvessel density, and downregulated VEGF, AKT and ERK pathways [34]. BMI-1, a polycomb-group protein overexpressed in esophageal squamous cell carcinoma in association with tumor size, nodal metastasis and poor survival, also modulates the radiation response: silencing of BMI-1 in esophageal carcinoma cells increased apoptosis, altered cell-cycle distribution and enhanced radiosensitivity in preclinical models [35]. MicroRNAs add another layer—miR-193a-5p targets ERBB2, and its overexpression enhances radiosensitivity, whereas low expression predicts poor response to concurrent chemoradiotherapy [36]; α-solanine, a steroidal glycoalkaloid, upregulates miR-138 and thereby suppresses survivin, again sensitizing tumor cells [37]. Whether any of these targets will yield clinically useful radiosensitizers is unresolved, but they supply a rational basis for combination trials. An integrated view of these mechanisms and of the strategies that target them is presented in Figure 2.

Salmon boxes, pathways implicated in radioresistance; green boxes, radiosensitizing interventions characterized in preclinical models. Solid arrows indicate induction or modulation by ionizing radiation; dashed open arrows indicate inhibition or suppression. PD-L1, programmed death-ligand 1; VEGF, vascular endothelial growth factor; CCRT, concurrent chemoradiotherapy.

Figure 2. Molecular mechanisms of radioresistance and radiosensitization in esophageal squamous cell carcinoma.



6.3 Unresolved Clinical Questions

Three questions stand out. First, is radiotherapy after recurrence genuinely life-prolonging, or does it chiefly palliate? No trial has answered this. Second, what is the optimal integration with immunotherapy—concurrent, sequential, or triggered by response? Third, how should clinicians weigh aggressive local treatment against systemic therapy alone for patients with simultaneous nodal and distant failure? Multidisciplinary tumor boards remain the only practical forum for weighing these trade-offs case by case.

7. Future Directions

Technical progress will continue: adaptive radiotherapy, guided by repeat imaging during treatment, may better accommodate the shifting anatomy of the postoperative mediastinum; magnetic resonance imaging–guided delivery may improve soft-tissue visualization at the anastomosis; and proton facilities are expanding in Asia, where esophageal squamous cell carcinoma predominates. Biologically, the combination of radiotherapy with PD-1/PD-L1 blockade is the most promising avenue, and the molecular radiosensitizers described above offer a pipeline of hypotheses. Methodologically, what the field most needs is a prospective registry, or preferably a randomized trial, enrolling patients with isolated postoperative recurrence and comparing radiotherapy strategies with standardized endpoints for control, toxicity and quality of life. Until such data exist, guidelines will continue to be built on retrospective experience, and individualized judgment will carry more weight than protocol.

8. Conclusions

Anastomotic recurrence and regional lymph node metastasis after esophagectomy are common, difficult to re-operate, and amenable to radiotherapy in most cases. IMRT is now the technical standard where available, and SBRT has made re-irradiation possible for a selected minority; particle therapy, by contrast, remains an unproven but dosimetrically attractive option. The evidence, however, is retrospective and heterogeneous, and the integration of radiotherapy with chemotherapy and immune-checkpoint blockade is only beginning to be explored in this setting. Careful restaging, realistic discussion of toxicity, and multidisciplinary decision-making remain essential.

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No

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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