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Review Article

Defining disease recurrence after curative treatment of esophageal cancer: a literature review

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ABSTRACT

Background: Despite aggressive multimodal treatment, disease recurs in 30-40% of patients with esophageal cancer. In selected patients with isolated locoregional recurrence (LRR), radical treatment may lead to long-term survival. Lack of consensus on the definition of LRR complicates the selection of optimal treatment strategies. This study aimed to review the literature on the definition of LRR.

Methods: A systematic search of Embase and Medline Ovid databases was conducted to identify studies reporting on LRR after curative treatment for advanced esophageal cancer. Data on the definition of LRR, the staging system used, and the treatment strategies were extracted and tabulated. The primary outcome was the definition of LRR by anatomical site and the staging system used. Secondary outcomes included treatment strategies and outcomes for LRR.

Results: In total, 2856 studies on LRR after esophageal cancer treatment were identified, of which 44 were included and assessed. There was substantial variation in the anatomical location of LRR, with only six studies referring to TNM staging manuals for defining recurrence. Treatment and outcome for LRR were infrequently reported with considerable variation.

Conclusion: Definitions of LRR after curative treatment for esophageal cancer are inconsistent. Standardization of LRR is needed to improve comparability across studies and guide clinical management.

1. Introduction

Esophageal cancer is the eleventh most common cancer worldwide, affecting more than 500.000 people annually [1]. The prognosis of esophageal cancer is poor, with an overall 5-year survival of 20% [2], and only 50–60% of the patients can be treated with curative intent. Multimodal treatment often consists of chemo(radio)therapy plus surgery [3]. Definitive chemoradiotherapy (dCRT) without surgery is an alternative treatment in patients not fit for an operation. Despite aggressive treatment, disease recurs in 40–50% of patients, often within 3 years after treatment [4–8]. The prognosis of patients with disease recurrence is generally poor, with a median survival of only 3-10 months, given the observation that most often distant metastases are present [9–11]. Locoregional recurrence (LRR) without distant metastases is rare but may represent a subgroup that could be treated with curative intent [4]. In the CROSS study, only a small percentage of

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patients in the surgery-alone (9%) and nCRT plus surgery (3%) arms had an isolated LRR [12], as was also seen in the recent ESOPEC trial [13]. Studies on outcomes after treatment for LRR are limited and often report small numbers of patients or include only patients with squamous cell carcinoma. Secondly, there is no consensus on the definition and classification of LRR [14,15]. This limits the interpretation and comparison of studies on outcomes, and the benefit of aggressive treatment of LRR remains unclear.

The TNM Cancer Staging Manual by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) [16] and the Japanese Classification of Esophageal Cancer (JES) [17,18] are used for clinical and pathological staging of esophageal cancer. While the TNM staging system is not designed for staging recurrent disease, it is commonly used for this purpose in daily practice. In contrast, the JES includes a dedicated section on restaging after recurrence. As both classifications have changed over time, this has led to various definitions of locoregional or non-regional lymph nodes. For example, the supraclavicular and celiac lymph nodes have been considered M0, M1a, and M1b, respectively, according to the TNM system [19].

The aim of this review was to summarize definitions of LRR after treatment with curative intent reported in clinical studies. An accepted definition of LRR could improve the evaluation of treatment efficacy for LRR.

2. Methods

2.1. Search strategy and study selection

A search in Embase and Medline All was performed by a biomedical information specialist from inception until February 23rd, 2023, and updated in February 2024. A full description of the search is available in **Supplemental S1**. Inclusion criteria were: (i) retrospective, prospective, and randomized controlled studies including patients with locally advanced esophageal cancer who underwent treatment with curative intent, (ii) reporting definitions of local, regional, and distant disease recurrence, (iii) number of included patients of 100 or more, and (iv) published in or after 2010. Title and abstracts were evaluated for eligibility by J.B.S. and T.J.H. Full-text articles were then assessed on definitions of recurrence. References in included papers were manually checked for potentially missed studies.

2.2. Outcome measures and data extraction

The definition of LRR and the staging system used were extracted from all included studies. Furthermore, treatment, number of included patients, and time to first recurrence were extracted when available. The primary outcome was the definition of recurrence, including anatomic landmarks for regional lymph node stations. Secondary outcomes

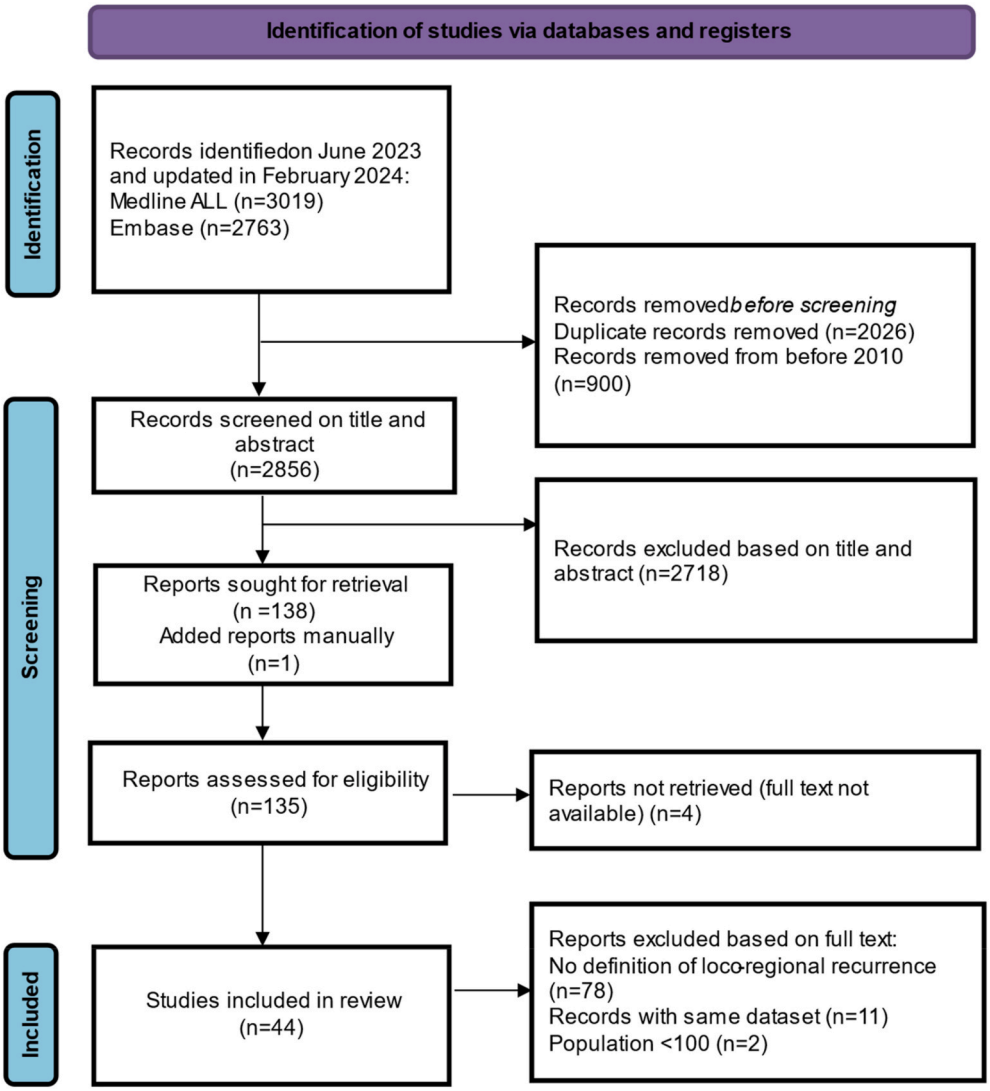

Fig. 1. Flowchart included studies.

included treatment for LRR, site of recurrence, time to recurrence, and disease-free survival (DFS). Lastly, definitions of LRR and the corresponding anatomical boundaries, as described in the well-known staging systems (AJCC/UICC and JES), were reviewed [20,21]. A comparative figure illustrating the locoregional lymph nodes stations according to these two systems was generated to facilitate direct comparison.

3. Results

3.1. Review of literature

3.1.1. Study selection

In total, 2856 studies were screened on title and abstract, and 135 were evaluated for full text. Studies without details on defining LRR, studies with overlapping datasets, and studies with fewer than 100 patients were excluded (Fig. 1). In total, 44 studies were included: 10 randomized controlled trials [3,22–31] retrospective cohort studies [4,9,31–59], and three prospective cohort studies [60–62]. Most studies focused on surgical treatment with or without (neo)adjuvant treatment (n = 37). In nine studies, patients received dCRT as curative treatment. In 39 of 44 studies, the AJCC staging manual was used for TNM-staging at the time of initial diagnosis.

3.1.2. Definitions of recurrence after surgery

Local recurrence was defined as recurrence in the remnant esophagus, the original primary tumor site, or the esophagogastric anastomosis in patients after esophagectomy, as reported in the majority of studies (98%). Regional recurrence was generally defined as recurrence in regional lymph nodes or within the area of dissection. However, details on what lymph node stations were considered locoregional disease recurrence varied. Only five studies explicitly referred to the AJCC or JES staging manual for their definition of 'regional lymph nodes'. Eighteen studies used a simplified approach, explicitly naming lymph node stations considered regional but without describing their anatomic boundaries (*e.g.*, whether they included or excluded the celiac trunk). In 12 studies, 'regional lymph nodes' were not defined by nodal stations or anatomical boundaries as advocated by the TNM staging manuals. Two studies defined regional recurrence solely as the 'surgical resection area'.

Distant recurrence after surgery was defined in 27 studies as recurrence in distant organs, non-regional lymph nodes, or any site beyond locoregional recurrence. Five studies did not provide any definition of distant recurrence, whereas another five defined it as recurrence in distant organs only. The definition of 'non-regional lymph nodes' varied across studies and was summarized in Table 1.

3.1.3. Definitions of recurrence after dCRT

Seven studies reported on patients who received dCRT only, while two studies included patients treated with dCRT or surgery (Table 2). Local recurrence was defined as recurrence at the primary tumor site or within the esophagus in all studies, at the boost area in one study, and within the radiation treatment volume in another study. Regional recurrence was defined as involvement of regional lymph nodes. However, only one study explicitly referred to the TNM staging manual for the anatomical boundaries of regional lymph node stations. The radiation field was mentioned in three studies: in two, locoregional recurrence depended on the radiation field, whereas in one it was defined independently of whether it occurred within or outside the radiation field. Distant recurrence was defined in six studies as recurrence in distant organs, non-regional lymph nodes, or any site, whereas three studies did not define it.

3.1.4. Heterogeneity in the definition of regional lymph nodes

Across all included studies, the supraclavicular lymph nodes were explicitly mentioned in 16 studies. In 11 studies, they were considered as regional lymph nodes, whereas in five studies they were classified as distant nodes (metastases) (Table 1). Other regional lymph nodes explicitly mentioned by authors were mediastinal (n = 9), upper abdominal (n = 4), para-aortic (n = 7), cervical (n = 4), and celiac trunk (n = 10).

3.1.5. Outcomes and treatment of disease recurrence

Secondary outcomes included the proportion of patients with recurrence, isolated LRR, time to recurrence and DFS (Tables 3 and 4). The proportion of patients with recurrence was reported in 36/44 studies. In total, 1430 of 12,620 patients (11.3%) and 302 of 1140 patients (26.5%) were diagnosed with LRR after surgical treatment or dCRT, respectively. In two studies a total of 1036 patients received either dCRT or surgery and reported LRR in 236 (22.8%) patients [4,52]. Across all studies, the median time to recurrence ranged from 9.8 to 18.3 months.

3.1.6. Treatment of LRR

Treatment of LRR was reported in eight studies (Supplemental Table 1), with data available for a total of 520 patients. The majority of these patients (31%) received best supportive care (BSC) or no treatment, only 10.4% underwent surgery (with or without systemic treatment) and 9% received systemic treatment only. Other types of treatment were ablation, radiotherapy or chemoradiotherapy and endoscopic treatment. For a large portion of patients the treatment of LRR was unknown or not reported. Median overall survival outcomes for patients receiving no treatment or BSC were 1.5–5.6 months, compared to 2.5–21.8 months for patients receiving (chemo)radiotherapy or systemic treatment, and 9.3–33.4 months for those who underwent surgery.

3.2. Definition of LRR according to staging manuals

3.2.1. AJCC TNM 8th classification [19]

The regional lymph nodes are defined irrespective of the site of primary tumor within the esophagus. They extend from peri-esophageal cervical nodes (level VI, VII) to celiac nodes (station 20, at base of the celiac artery). Distant sites are metastases not in direct continuity with the esophagus and non-regional lymph nodes. The AJCC does not provide a definition for locoregional recurrence. For assigning stage at time of recurrence, the TNM classification uses the prefix *r* for clinical (*rc*) or pathological (*rp*) staging.

3.2.2. Japanese Classification of Esophageal Cancer 11th [17,18]

In the JES, regional lymph nodes are defined according to the primary tumor location. The JES provides a detailed definition for local and distant recurrence, but not a definition of for regional recurrence specifically. The definitions are as follows:

Local recurrence:

1. Primary lesion (esophagus)
2. Mediastinum adjacent to the primary lesion
3. Anastomotic site or esophageal stump
4. Regional lymph nodes
5. Other sites, including intramural metastases in the esophagus or stomach

Distant recurrence:

1. Lymphogenous
2. Hematogenous (distant organs)
3. Disseminated (pleura, peritoneum, pericardium)

3.2.3. Regional lymph nodes

According to the JES, supraclavicular lymph nodes are regional nodes for esophageal cancer in the cervical (Ce), upper (Ut), middle (Mt), and lower (Lt) third of the esophagus. Also, the tracheobronchial nodes are regional nodes for Ut- and Mt-esophageal tumors, as noted in

Table 1
Definitions of recurrence in patients treated surgically with or without (neo)adjuvant therapy.

Surgery with curative intent					
Author	Patients (n)	Study type	Treatment	Histologic subtype	Definition of recurrence
Lin, 2019 [34]	101	Retrospective cohort	None	SCC	(Loco)regional: primary tumor site, anastomosis, regional LN's Distant: any other
Mao, 2023 [60]	670	Prospective cohort	None	SCC	(Loco)regional: anastomosis, tumor bed or resection area Distant: distant organs, LN's outside resection area
Boonstra, 2011 [22]	169	RCT	None/nCT	SCC	(Loco)regional: primary tumor site, anastomosis and regional LN's Distant: non-regional LN's and distant organs
Bekkar, 2016 [31]	1173	Retrospective cohort	None/nCT	AC/SCC	(Loco)regional: anastomosis, area of resection, and regional LN's Distant: distant organs and SCV LN's
Liu, 2020 [26]	411	RCT	None/nCRT	SCC	(Loco)regional: esophagus, anastomosis and regional LN's Distant: non-regional LN's (SCV, para-aortic), distant organs
van Eyck, 2021 [25]	366	RCT	None/nCRT	AC/SCC	(Loco)regional: mediastinum, regional LN's (SCV, lower cervical region, celiac trunk) Distant: distant organs, LN's higher cervical and below pancreas
Chen, 2022 [23]	353	RCT	None/nCRT	SCC	(Loco)regional: esophagus, anastomosis and regional LN's Distant: distant organs, non-regional LN's (SCV, para-aortic)
Smit, 2013 [36]	150	Retrospective cohort	None/nCRT	AC/SCC	(Loco)regional: esophagus, regional LN's Distant: distant organs
Robb, 2016 [29]	170	RCT	None/nCRT	AC/SCC	(Loco)regional: esophagus, anastomosis and regional LN's Distant: non-regional LN's (SCV, para-aortic, below renal veins)
Lin, 2023 [35]	366	Retrospective cohort	None/pCT	SCC	(Loco)regional: anastomosis, regional and distant LN's (abdominal or SCV) Distant: distant organs
de Groot, 2020 [24]	104	RCT	None/nCT/nCRT	AC/SCC	(Loco)regional: anastomosis, regional LN's inside resection area Distant: other recurrence, LN's outside resection area
Hsu, 2017 [33]	426	Retrospective cohort	None/pCRT	SCC	(Loco)regional: primary tumor site, anastomosis, regional LN's (cervical, mediastinal and upper abdomen) Distant: distant organs, non-regional LN's (para-aortic, below celiac axis)
Blom, 2013 [9]	1088	Retrospective cohort	None/nCT/nCRT	AC/SCC	(Loco)regional: anastomosis and LN's neck, mediastinum, upper abdomen Distant: distant organs
du Rieu, 2013 [32]	120	Retrospective cohort	None/nCT/nCRT	AC/SCC	(Loco)regional: surgical resection site or cervical site Distant: NR
Lou, 2013 [44]	1147	Retrospective cohort	None/nCT/nCRT	AC/SCC	(Loco)regional: peri-anastomotic, LN's in mediastinum and upper abdomen (supra celiac trunk) Distant: beyond loco-regional
Altorki, 2022 [37]	242	Retrospective cohort	None/nCT/nCRT	AC/SCC	(Loco)regional: anastomosis and LN's in resection area Distant: distant organs, outside resection area
Carr, 2022 [41]	1370	Retrospective cohort	None/nCT/nCRT	AC	(Loco)regional: esophagus, anastomosis, regional LN's Distant: distant organs, non-regional LN's
Yang, 2022 [46]	298	Retrospective cohort	None/nCT/nCRT	SCC	(Loco)regional: esophagus, anastomosis, resection area, LN's according to JES 11th Distant: distant organs
Boerner, 2023 [40]	1626	Retrospective cohort	None/nCT/nCRT	AC/SCC	(Loco)regional: esophagus, anastomosis, regional LN's conform AJCC 8th + retroperitoneal LN's Distant: distant organs, non-regional LN's
Ni, 2021 [28]	172	RCT	None/pRT/pCRT	SCC	(Loco)regional: according to UICC 7th Distant: distant organs, non-regional LN's
Knight, 2017 [43]	698	Retrospective cohort	None/nCT/pCT/pCRT	AC/SCC	(Loco)regional: anastomosis, mediastinum, abdomen, regional LN's (mediastinal, left gastric celiac nodes for GEJ) Distant: distant organs non-regional LN's (SCV, para-aortic, portal and mesenteric nodes)
Moore, 2023 [61]	763	Prospective cohort	Surgery + nCT	AC	(Loco)regional: anastomosis, resection area, locoregional LN, Distant: distant organs, distant LN's
Sugimura, 2021 [30]	162	RCT	Surgery + nCT	SCC	(Loco)regional: primary site, anastomosis, regional LN's (including SCV) Distant: non-regional LN's, distant organs
Makino, 2022 [27]	180	RCT	Surgery + nCT	SCC	(Loco)regional: esophagus, anastomosis and regional LN's (including SCV) Distant: distant organs, non-regional LN's
Blackham, 2018 [39]	456	Retrospective cohort	Surgery + nCRT	AC/SCC	(Loco)regional: esophagus, mediastinal or celiac LN's Distant: distant organs and non-regional LN's
Schuring, 2023 [45]	618	Retrospective cohort	Surgery + nCRT	AC	(Loco)regional: site of primary tumor or locoregional LN's Distant: distant organs, non-regional LN's
Dorth, 2014 [42]	155	Retrospective cohort	Surgery + nCRT	AC/SCC	(Loco)regional: anastomosis and regional LN's Distant: NR
Barbetta, 2019 [38]	233	Retrospective cohort	Surgery + nCT/nCRT	AC/SCC	(Loco)regional: esophagus, mediastinal, periesophageal, gastric, celiac, SCV LN's Distant: all other sites
Sugase, 2022 [62]	325	Prospective cohort	Surgery + nCT/nCRT	SCC	(Loco)regional: primary tumor site, regional LN's (including celiac trunk, SCV region) Distant: non-regional LN's, peritoneal metastasis, distant organs

(*continued on next page*)

Table 1 (*continued*)

Surgery with curative intent					
Author	Patients (n)	Study type	Treatment	Histologic subtype	Definition of recurrence
Surgery with curative intent – recurrence only cohort					
Cai, 2010 [48]	140	Retrospective cohort[b]	None	SCC	(Loco)regional: anastomosis, SCV, mediastinal, upper abdominal LN's Distant: non-regional LN's
Li, 2013 [51]	134	Retrospective cohort[b]	None	SCC	(Loco)regional: primary tumor site, anastomosis, regional LN's Distant: NR
Cui, 2021 [49]	428	Retrospective cohort[b]	None/pRT	SCC	(Loco)regional: anastomosis and regional LN's conform JES 9th Distant: distant organs (such as liver, lung) and non-regional LN's
Xu, 2023 [53]	335	Retrospective cohort[b]	None/nCT/pCT	SCC	(Loco)regional: primary tumor site, anastomosis regional LN's according to AJCC/UICC 7th Distant: NR
Kang, 2023 [50]	321	Retrospective cohort[b]	None/nCRT/pCT	SCC	(Loco)regional: anastomosis, mediastinal, upper abdominal LN's Distant: distant organs
Butter, 2017 [47]	212	Retrospective cohort[b]	Surgery + nCT/nCRT	AC/SCC	(Loco)regional: esophagus, anastomosis and regional LN's (according to tumor location) Distant: all other sites
Sugawara, 2023[a] [52]	136	Retrospective cohort[b]	None/nCT/nCRT	AC/SCC	(Loco)regional: primary tumor site, anastomosis, regional LN's (including SCV) Distant: distant organs, non-regional LN's (including para-aortal)
Pape, 2022[a] [4]	645	Retrospective cohort[b]	None/nCT/nCRT/ pCT/pCRT	AC/SCC	(Loco)regional: primary tumor site, regional LN's Distant: NR

Abbreviations: AC, Adenocarcinoma; LN, Lymph node; nCT, Neoadjuvant chemotherapy; nCRT, Neoadjuvant chemoradiotherapy; NR, Not reported; pCT, Postoperative chemotherapy; pCRT, Postoperative chemoradiotherapy; pRT, Postoperative radiotherapy; SCC, Squamous cell carcinoma; SCV, Supraclavicular nodes.
[a] Included patients treated with dCRT or surgery.
[b] Included patients with recurrence only.

Table 2
Definitions of recurrence in patients treated with definitive chemoradiotherapy with curative intent.

Definitive chemoradiotherapy					
Author	Patients (n)	Study type	Treatment	Histologic subtype	Definition of recurrence
Versteijne, (2015) [57]	184	Retrospective cohort	dCRT	AC/SCC	(Loco)regional: primary tumor site, regional LN's (up to SCV and celiac trunk) Distant: NR
Sudo, 2018 [56]	204	Retrospective cohort	dCRT	SCC	(Loco)regional: primary tumor site, regional LN's Distant: distant organ, non-regional LN's conform AJCC 6th
de Vos-Geelen, 2021 [54]	133	Retrospective cohort	dCRT	SCC	(Loco)regional: primary tumor site and regional LN's up to SCV Distant: other recurrence
Hulshof, 2021 [3]	260	RCT	dCRT	AC/SCC	(Loco)regional: site of boost area, LN's from SCV to celiac trunk, esophagus outside primary tumor area, independent of in/outfield area Distant: any other site
Zhang, 2023 [59]	120	Retrospective cohort	dCRT	SCC	(Loco)regional: primary tumor site or LN's in the neck within radiation field Distant: NR
Welsh, 2012 [58]	239	Retrospective cohort	dCRT + nCT	AC/SCC	(Loco)regional: within radiation treatment volume Distant: any recurrence outside RTF
Smit, 2013 [55]	287	Retrospective cohort	dCRT/dRT	AC/SCC	(Loco)regional: esophagus, regional LN's Distant: distant metastasis
Definitive chemoradiotherapy – recurrence only cohort					
Sugawara, 2023[a] [52]	42	Retrospective cohort[b]	dCRT	AC/SCC	(Loco)regional: primary tumor site, anastomosis, regional LN's (including SCV) Distant: distant organs, non-regional LN's (including para-aortal)
Pape, 2022[a] [4]	213	Retrospective cohort[b]	dCRT	AC/SCC	(Loco)regional: primary tumor site, regional LN's Distant: NR

Abbreviations: AC, Adenocarcinoma; LN, Lymph node; nCT, Neoadjuvant chemotherapy; nCRT, Neoadjuvant chemoradiotherapy; NR, Not reported; pCT, Postoperative chemotherapy; pCRT, Postoperative chemoradiotherapy; pRT, Postoperative radiotherapy; SCC, Squamous cell carcinoma; SCV, Supraclavicular nodes.
[a] Included patients treated with dCRT or surgery.
[b] Included patients with recurrence only.

the JES classification. This contrasts with the AJCC, where both the supraclavicular and tracheobronchial lymph nodes are considered as non-regional lymph nodes.

Regional lymph nodes in the abdominal compartment also differ between AJCC and JES. The AJCC considers lymph nodes along the common hepatic artery, splenic artery, and celiac trunk as regional nodes only when located at the base of the vessels. In contrast, the JES considers lymph nodes along the entire course of these vessels as regional nodes. A direct head-to-head comparison of lymph node stations between the AJCC and JES, adapted from these systems, is provided in Fig. 2.

4. Discussion

The current review shows substantial heterogeneity in definitions of LRR after curative treatment for esophageal cancer. While most studies consistently report on local and distant recurrence sites, a comprehensive definition of regional recurrence is highly variable.

Variability is highest in defining lymph node stations, particularly the supraclavicular and abdominal nodes, as regional or distant. Only 16 of 44 studies explicitly specified whether the lymph nodes were regional or non-regional, while many others were unclear, suggesting that the extent of heterogeneity may be underestimated. Interestingly, only six

Table 3
Timing and proportion of recurrence (distant, locoregional, mixed) and isolated locoregional recurrence after surgical treatment for esophageal cancer. Median time to recurrence refers to the overall recurrence group, not specifically to isolated locoregional recurrence. DFS/RFS/PFS and OS refer to the overall study cohort, unless stated otherwise.

Surgery with curative intent							
Author	Patients (n)	Treatment	Median follow-up (months)	Numbers of patients with recurrence (%)	Number of patients with isolated LRR (%)	Median time to recurrence (months)	DFS/RFS/PFS
Lin, 2019 [34]	101	None	41	19 (18.8)	11 (10.9)	*NR*	3-year RFS 81.9%
Mao, 2023 [60]	670	None	71.2	*NR*	*NR*	*NR*	3-year DFS 60.6–69.8%
Boonstra, 2011 [22]	169	None/nCT	14.0–15.0	66 (39.1)	37 (21.9)	*NR*	*NR*
Bekkar, 2016 [31]	1173	None/nCT	47.8	*NR*	*NR*	*NR*	5-year DFS 36.1–44.9%
Liu, 2020 [26]	411	None/nCRT	38.4	166 (40.4)	50 (12.2)	10.6–10.8	3-year RFS 61.2%
van Eyck, 2021 [25]	366	None/nCRT	147	213 (58.2)	48 (13.1)	NR	*NR*
Chen, 2022 [23]	353	None/nCRT	67.6	159 (45.0)	43 (12.2)	11.5–12.5	*NR*
Smit, 2013 [36]	150	None/nCRT	20	*NR*	*NR*	*NR*	3-year DFS 24–53%
Robb, 2016 [29]	170	None/nCRT	94.2	67 (39.4)	34 (20.0)	*NR*	*NR*
Lin, 2023 [35]	366	none/pCT	80	199 (54.0)	33 (9.0)	*NR*	*NR*
Hsu, 2017 [33]	426	None/pCRT	20.8	126 (29.6)	42 (9.9)	5.9	2-year RFS 65–70%
de Groot, 2020 [24]	104	None/nCT/nCRT	60	57 (54.8)	4 (3.8)	10.0	5-year DFS 42%
Blom, 2013 [9]	1088	None/nCT/nCRT	21.0	493 (45.3)	68 (6.3)	10.5	*NR*
du Rieu, 2013 [32]	120	None/nCT/nCRT	47	53 (44.2)	30 (25.0)	10.3	5-year RFS 51%
Lou, 2013 [44]	1147	None/nCT/nCRT	46	435 (37.9)	121 (10.5)	*NR*	*NR*
Altorki, 2022 [37]	242	None/nCT/nCRT	151.4	115 (47.5)	20 (8.3)	11.3	5-year DFS 37%
Carr, 2022 [41]	1370	None/nCT/nCRT	36	531 (38.8)	155 (11.3)	9.8–12.4	*NR*
Yang, 2022 [46]	298	None/nCT/nCRT	30.6	95 (31.9)	44 (14.8)	12.1	*NR*
Boerner, 2023 [40]	1626	None/nCT/nCRT	92.4	595 (36.6)	160 (9.8)	11.0	*NR*
Ni, 2021 [28]	172	None/pRT/pCRT	56.4	*NR*	*NR*	*NR*	3-year DFS 36.7–57.3%
Knight, 2017 [43]	698	None/nCT/pCT/pCRT	19.4	326 (46.7)	76 (10.9)	*NR*	3-year DFS 53.1%
Moore, 2023 [61]	763	Surgery + nCT	*NR*	348 (45.6)	45 (5.9)	*NR*	*NR*
Sugimura, 2021 [30]	162	Surgery + nCT	69.8	76 (46.9)	47 (29.0)	*NR*	5-year RFS 40.7–59.9%
Makino, 2022 [27]	180	Surgery + nCT	39	45 (26.8)	16 (9.5)	*NR*	2-year PFS 71.1–71.4%
Blackham, 2018 [39]	456	Surgery + nCRT	50.1	167 (36.6)	27 (5.9)	10.6	*NR*
Schuring, 2023 [45]	618	Surgery + nCRT	*NR*	278 (45.0)	31 (5.0)	11.3	*NR*
Dorth, 2014 [42]	155	Surgery + nCRT	15.6	21 (13.5)	9 (5.8)	*NR*	*NR*
Barbetta, 2019 [38]	233	Surgery + nCT/nCRT	42.4	61 (26.2)	17 (7.3)	11.6	5-year DFS 53%
Sugase, 2022 [62]	325	Surgery + nCT/nCRT	25.6–37.8	126 (38.8)	36 (11.1)	*NR*	3-year DFS 39.1–56.8%
Surgery with curative intent – recurrence only cohort							
Cai, 2010 [48]	140	None	*NR*	*NA*	93 (66.4)	18.3	*NR*
Li, 2013 [51]	134	None	*NR*	*NA*	*NR*	12.0	*NR*
Cui, 2021 [49]	428	None/pRT	*NR*	*NA*	*NR*	*NR*	*NR*
Xu, 2023 [53]	335	Surgery alone/pRT	48.6	*NA*	*NR*	14.6	*NR*
Kang, 2023 [50]	321	None/nCRT/pCT	*NR*	*NA*	110 (34.3)	10.7	*NR*
Butter, 2017 [47]	212	Surgery + nCT/nCRT	*NR*	*NA*	23 (10.8)	10.4	*NR*
Sugawara, 2023 [52]	178	None/nCT/nCRT/dCRT	*NR*	*NA*	75 (42.1)	10.8	*NR*
Pape, 2022 [4]	645	None/nCT/nCRT/pCT/pCRT	*NR*	*NA*	61 (37.9)	10.5	*NR*

Abbreviations: dCRT, Definitive chemoradiotherapy; DFS, Disease Free Survival; LRR, locoregional recurrence; nCT, Neoadjuvant chemotherapy; nCRT, Neoadjuvant chemoradiotherapy; NA, Not applicable (recurrence only cohort); NR, Not reported; pCT, Postoperative chemotherapy; pCRT, Postoperative chemoradiotherapy; pRT, Postoperative radiotherapy; PFS, Progression Free Survival; RFS, Recurrence Free Survival.

Table 4
Timing and proportion of recurrence (distant, locoregional, mixed) and isolated locoregional recurrence after treatment with definitive chemoradiotherapy
Median time to recurrence refers to the overall recurrence group, not specifically to isolated locoregional recurrence. PFS/LRFFS and OS refer to the overall study cohort, unless stated otherwise.

Definitive chemoradiotherapy							
Author	Patients (n)	Treatment	Median follow-up (months)	Numbers of patients with recurrence (%)	Number of patients with isolated LRR (%)	Median time to recurrence (months)	PFS/LRFFS
Versteijne, 2015 [57]	184	dCRT	22.8	115 (62.5)	40 (19.6)	9.6	*NR*
Sudo, 2018 [56]	204	dCRT	75.7	80 (39.2)	41 (20.1)	*NR*	*NR*
de Vos-Geelen, 2021 [54]	133	dCRT	64.7	58 (43.6)	32 (24.1)	*NR*	3-year PFS 49%
Hulshof, 2021 [3]	260	dCRT	50.3	140 (53.8)	66 (25.3)	*NR*	3-year PFS 23–35%
Zhang, 2023 [59]	120	dCRT	*NR*	91 (75.8)	74 (61.2)	*NR*	5-year LRFFS 21.7%
Welsh, 2012 [58]	239	dCRT + nCT	52.6	165 (69.0)	49 (20.5)	*NR*	14.7
Smit, 2013 [55]	287	dCRT or dRT	*NR*	*NR*	*NR*	*NR*	8.0
Definitive chemoradiotherapy – recurrence only cohort							
Sugawara, 2023 [52]	178	dCRT	*NR*	*NA*	75 (42.1)	10.8	*NR*
Pape, 2022 [4]	213	dCRT	*NR*	*NA*	100 (62.1)	10.5	*NR*

Abbreviations: dCRT, Definitive chemoradiotherapy; dRT, Definitive radiotherapy; LRFFS, Locoregional Failure Free Survival; LRR, Locoregional recurrence; nCT, Neoadjuvant chemotherapy; NA, Not applicable (recurrence only cohort); NR, Not reported; PFS, Progression Free Survival.

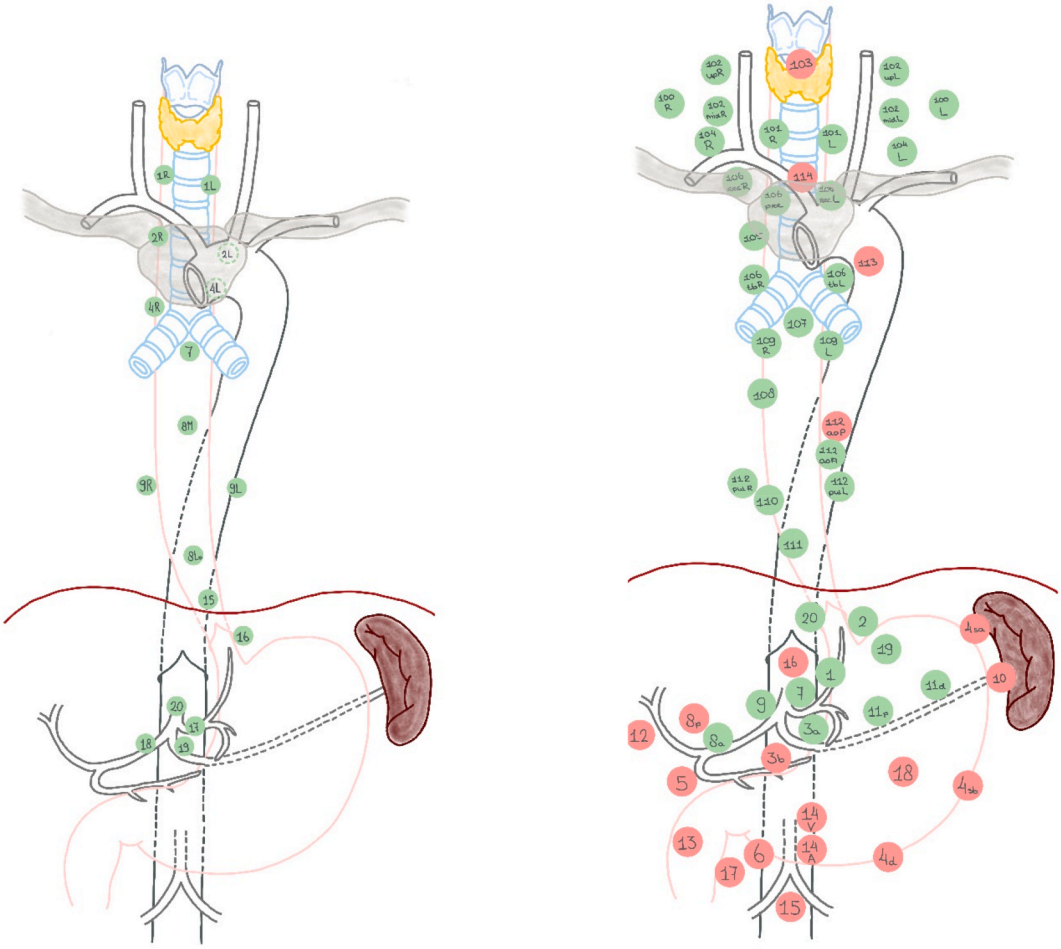

Fig. 2. A head to head comparison of (non)-regional lymph nodes
The color green indicates 'regional' lymph nodes, the color red indicates 'non-regional' lymph nodes. According to the AJCC classification 8th edition (left) and JES classification 11th edition (right). Note that JES represents lymph nodes that can be considered locoregional, depending on the location of the primary tumor. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

studies stated that they defined recurrence according to an established staging system (AJCC, JES), underscoring the need for greater transparency and comprehensive criteria to improve uniformity and comparability across studies.

Further complicating this issue is the inconsistency in how LRR is defined relative to the radiation field in patients after dCRT. Some studies define LRR based on whether recurrence occurs within or outside the radiation field, while others classify LRR independently of the radiation field [3,58,59]. This raises the question of whether the radiation field should be incorporated into the standard definition of LRR for patients who were treated with radiotherapy, either as dCRT or in combination with curative resection.

Differences between staging systems further contribute to inconsistent definitions of regional recurrence. The AJCC and JES differ not only in which lymph node stations are considered regional, but also in how the anatomical boundaries of these stations are defined [17–19]. These differences include the supraclavicular nodes, cervical and upper mediastinal lymph node stations, and lymph nodes in the upper abdomen, relative to vascular structures. Moreover, the JES considers the primary tumor site when classifying lymph nodes as regional and provides guidance on staging disease recurrence, whereas the AJCC does not. Schuring et al. addressed these differences and proposed a mapping between the two commonly used systems using the TIGER classification [63,64]. However, a single classification system does not resolve the issue of inadequate compliance and individual interpretation. Furthermore, definitions within AJCC and JES evolve, further hindering comparability between older and newer studies.

Although distant recurrence is more often seen in patients after treatment with curative intent and remains the most important cause of death in esophageal cancer, isolated LRR still occurs in a substantial proportion of patients (11.3% after curative resection and 26.5% after dCRT). A standardized definition of LRR could help identify patients with isolated LRR who might benefit from potentially curative interventions. However, the current lack of uniformity hinders both the identification of these patients, and the development of effective treatment strategies.

This review has several limitations. The main limitation is that the definitions of recurrence were often incomplete or poorly defined, limiting the ability to fully capture and compare heterogeneity in definitions across studies and, thereby, likely underestimating the true variability. Second, included studies varied not only in study design and patient characteristics, but also in treatment regimens (*e.g.,* curative resection or dCRT, with or without neoadjuvant therapy) [4,39,45]. This resulted in a wide range not only in the incidence of isolated LRR but also in estimated survival afterward across the included studies. Last, follow-up procedures, timing, and type of imaging (PET-CT, CT), and cytological confirmation of recurrence varied between the studies. In addition, the majority of studies on recurrence after dCRT did not formally assess cCR, leaving uncertainty as to whether the observed recurrence represented true recurrence or residual disease in patients who did not adequately respond to treatment. Only a limited number of studies reported survival outcomes after treatment for LRR, and detailed information on the specific treatments administered was mostly lacking. Consequently, it is difficult to provide reliable estimates or to compare outcomes across studies.

Despite these limitations, this is the first review to provide an overview of how LRR after curative treatment for esophageal cancer is defined across studies. In an effort to address this issue, the Dutch Upper GI Cancer Group (DUCG) held an initial meeting to review the literature and discuss the definition of recurrence after curative treatment for esophageal cancer with curative intent (surgical and non-surgical). Although an important first step, it was not a formal consensus meeting. Future efforts may benefit from a structured Delphi process, ideally involving international experts, to achieve a widely accepted, evidence-based definition that can guide clinical decision-making in the management of recurrent esophageal cancer.

DOI statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2026.111841.

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