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Definitive chemo-radiotherapy in cervical oesophageal cancer: a comprehensive review of literature

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Abstract

Background and objectives: Despite decades of experience with definitive chemo-radiotherapy (CRT) in cervical oesophageal cancer (CEC), the loco-regional control and survival outcomes are dismal. This review evaluated the outcomes of various treatment strategies being commonly utilized.

Materials and methods: A literature review was conducted to identify relevant articles on CEC published from years 2000–2023 addressing the predefined key questions. These questions focussed on the comparative outcomes of various primary treatment approaches

(surgery, CRT, or trimodality treatment) and the radiation dose schedules, volumes, and techniques.

Results: CRT is the standard approach for treatment for CEC so far. The potential role of surgery and trimodality approach in settings of evolving surgical approaches needs to be validated. The high dose schedules that are preferentially practiced in CEC have not shown any benefit in improving the disease outcomes over the standard dose schedule of 50.4 Gy. The target volume delineation practice of elective nodal irradiation (ENI) does not have a proven benefit over the involved field irradiation (IFU). The limited evidence on radiation techniques suggests that intensity-modulated radiotherapy/volumetric arc therapy (IMRT/VMAT) techniques can improve toxicity profile over three-dimensional conformal radiotherapy (3DCRT, but no advantage proven in disease outcomes so far.

Conclusion: This review will guide clinicians in decision-making for the management of this relatively rare entity and the directions for future research in these areas. Future large-scale multicentre prospective studies are needed for validating and standardizing our current practices and exploring potential options to improve the outcomes.

Key words: cervical esophageal cancer; radiation target volume; technique and dose; definitive radiotherapy

Introduction

The cervical oesophagus (CE) is a short segment of the proximal oesophagus, having a length of 5 centimetres and extending between the cricopharynx and thoracic inlet. CE carries certain anatomical characteristics, including a lack of serosal covering and abundant lymphatic drainage formed by two plexuses arising from the mucosal and muscular layers [1]. Owing to these peculiarities and an aggressive tumour biology [2], the primary cancer of the cervical oesophagus (CEC) is considered a distinct clinical entity [3]. CE is often involved in locally extensive hypopharyngeal cancers, and the incidence of primary CEC is merely 2–10% of all oesophageal malignancies [4].

The major underlying risk factors are alcohol consumption, tobacco use, and exposure to other carcinogens such as nitrosamines (found in certain salted vegetables and preserved

fish) [1]. Squamous cell carcinoma (SCC) is the most common histotype observed in more than 90% of cases [5]. More than half of them are diagnosed at a locally advanced stage owing to the delayed onset of symptoms, multicentricity, rich lymphatics, and lack of a defined screening protocol [2, 6]. Hence, the outcomes are quite inferior compared to other head and neck primaries, with a reported 5-year survival of only 30–40% [7–9].

In view of the paucity of high-quality evidence, the treatment approaches are broadly adapted from head and neck and thoracic oesophageal cancers [7–11]. Although definitive chemoradiation (CRT) is recommended as the standard treatment modality for CEC [10, 11], there are certain important questions about the management approach that need to be addressed. This review summarises the literature on CEC, focusing on the following key questions.

1. What should be the standard treatment approach: surgery, CRT, or a combination of these two modalities?

2. Is there any benefit of escalating the radiation (RT) dose to 66–70 Gray (Gy), analogous to head and neck cancers, over the conventional standard dose of 50.4 Gy for oesophageal cancers?
3. Does elective nodal irradiation (ENI) provide better disease control compared to involved field irradiation (IFI)?
4. Do advanced techniques such as intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) offer an advantage over three-dimensional conformal radiotherapy (3DCRT)?

Literature search

The relevant evidence focusing on the treatment approach of CEC that was published in the last two decades was screened for this review. The search was restricted to full-text articles published in English in PubMed, MEDLINE, and Scopus from the year 2000 until 2023. The references in the included articles were further searched for additional relevant studies. The search was done using predefined keywords "cervical oesophageal cancer or proximal oesophageal cancer" in combination with "surgery", "radiation", "chemoradiation", "radiation dose", "target volumes", "elective nodal irradiation", "involved field irradiation", "radiation techniques", "3DCRT", "IMRT", "VMAT". The literature search strategy is depicted in Figure 1. The minimum number of patients in a

study for inclusion in this review was kept at 25. The studies with proximal oesophageal cancer (cervical and upper thoracic) were included if at least 10% of the study population had CEC. Studies having patients with middle or lower thoracic oesophageal cancers were excluded.

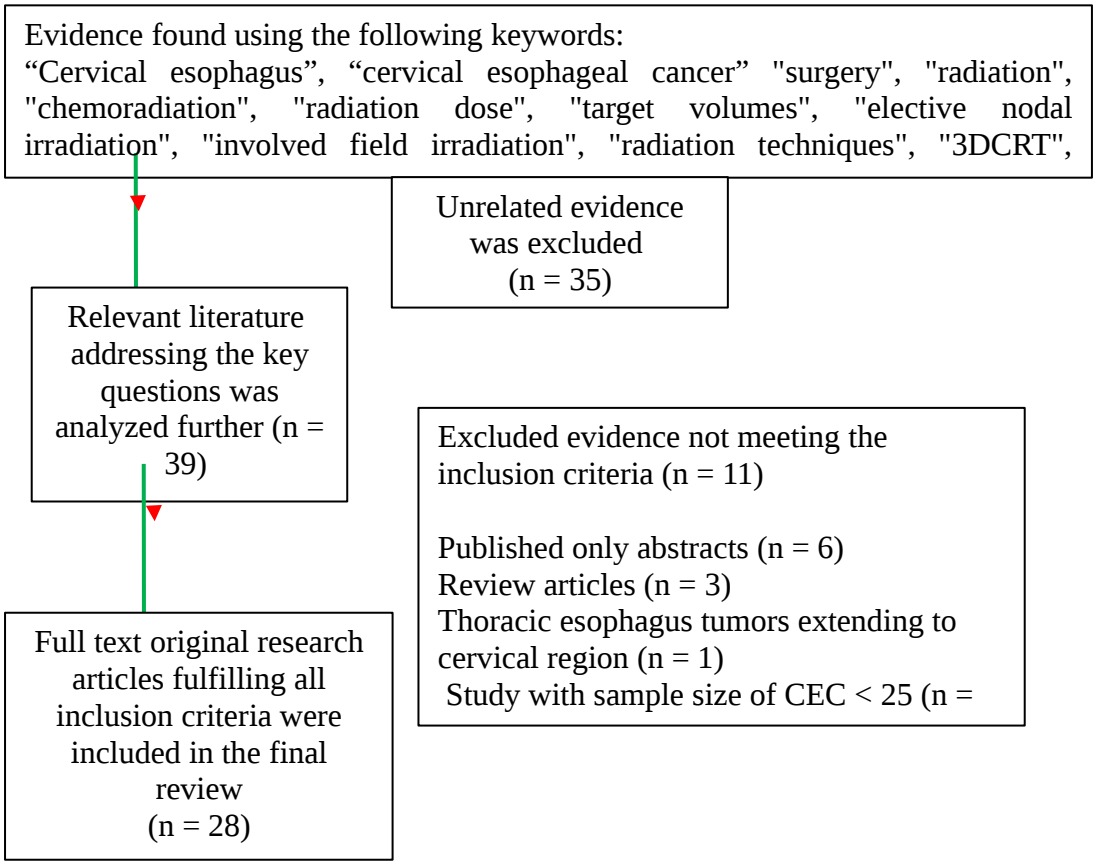

Figure 1. Figure depicting the literature search methodology. CEC — cervical oesophagus

After full text screening, only 28 articles were found suitable for inclusion in this review, all of them were retrospective series.

What should be the standard treatment approach: surgery, CRT, or a combination of these two modalities?

Historically, surgery was considered the standard of care, with reported long-term survival rates of 30–50% and treatment-related morbidity and mortality being quite high, up to 75% and 15%, respectively [12, 13]. In the early 1990s, the encouraging results from the

landmark trials led to the widespread adoption of CRT as an organ preservation approach in laryngeal and hypopharyngeal cancers [14, 15]. This paved the way for the widespread adoption of upfront CRT in CEC as an alternative to extensive radical surgery [16, 17]. (Tab. 1) In the historical series, surgery consisted of removal of the hypopharynx and oesophagus with or without larynx, depending on the disease extent, and, variably, nodal dissection. The requirement of a permanent tracheostomy and feeding tube dependency made surgery quite debilitating [12, 13]. Overall, in the past two decades, the commonest surgery utilised was total pharyngo-laryngo-esophagectomy (PLE) in 57.1% of patients, followed by partial PLE in 42.9%, with laryngeal preservation obtained in 40% of patients. The rates of conservative surgery tend to be higher in series with a relatively higher proportion of early-stage tumours. The management of lymph nodes has been rare and differently reported [18].

Most of the series have shown comparable survival rates between CRT and surgery [19–24]. In the Chinese database (1973–2018) of 500 patients, two-thirds were treated with non-surgical approaches (radiation, chemotherapy, and CRT), and the majority, 76.1%, received RT alone. The 5-year overall survival (OS) of surgical and non-surgical approaches remained comparable across various time frames, with no significant difference between the two modalities [19]. The series by Tong D.K.H. et al. also showed comparable median survival with surgery and definitive CRT (20 and 25 months, respectively) ($p = 0.39$) [20]. In a series by Cao CN et al., patients with early-stage disease were treated with primary surgery and post-operative RT if indicated [21]. Those with locally advanced CEC underwent definitive CRT, and if the interim response was deemed inadequate, then only further surgery was offered. There was no significant difference in distant failure-free survival (DFFS) and OS in matched pair analysis for primary surgery or the definitive RT group [21]. Two other small retrospective series showed comparable outcomes for both of these treatment modalities [22, 23]. Thus, data from these retrospective series have not shown any difference between CRT and surgery in survival outcomes.

The impact of treatment modalities on loco-regional control (LRC) was addressed in a few retrospective studies. Valmasoni et al. showed that the proportion of local recurrences was significantly higher in patients treated with CRT (50% for the surgery group, 84% for the CRT group, and 50% for the combined modality group) ($p = 0.024$) [24]. This may be attributable to a higher number of patients with advanced-stage disease receiving CRT (stage III, IV: 75% in CRT; 58.93% in surgery; 82.5% in the trimodality group) and a

relatively lower mean RT dose (50.44 ± 10.53 Gy) was prescribed [24]. However, the remaining studies addressing LRC rates have shown comparable outcomes [21, 22]. These studies had a uniform stage distribution in both the primary surgery and CRT arms, with a relatively higher RT dose of 60–64 Gy used [21, 22].

Few series have further analysed the role of intensification of treatment with a trimodality approach comprising surgery in combination with CRT. The largest database comes from a SEER analysis of 1371 patients reporting propensity score-matched outcomes based on the stage of the disease. Surgery was beneficial in early-stage patients with significantly improved survival compared to CRT (10-year OS: 20.7% *vs.* 11.4%, p = 0.023), and there was no additional benefit of surgery after CRT. However, for loco-regionally advanced disease, there was no significant difference in outcomes between surgery and CRT, but there was a significant improvement in the 10-year OS with surgery-based tri-modality therapy compared to CRT alone (20.4% vs. 9.0%, p = 0.031) [25]. This series uniquely highlighted the difference in treatment modalities outcomes based on the disease stage, but the major drawback was the span period of analysis, extending from 1977 to 2016 when clinical practices in this area were evolving, and also the heterogeneous treatment approach across various studies. Also, the information on dose schedule of radiation was not available. In adoption of trimodality treatment, the optimal dose of radiation to be used in preoperative settings is an important aspect to strive the balance between disease outcomes and toxicities.

Another SEER analysis done at a later time interval of 2004–2016 for stage I–III CEC patients depicted no significant benefit of trimodality over CRT [26]. Another prospective database by Valmasoni et al. showed no significant difference amongst the surgery, CRT, and trimodality groups [24]. In subgroup analysis based on the response to CRT, patients with partial response, stable disease, or progressive disease had a significantly improved survival (p = 0.023) with the trimodality approach, while those with complete response (CR) did not have an additional benefit [24].

The impact of the timing of surgery was evaluated in two series [22, 27]. In the series by Chen et al., outcomes of surgery in combination with RT (with or without concurrent chemotherapy) were compared to those of definitive CRT (n = 360) [27]. Out of the 28 patients in the surgery arm, two patients received neoadjuvant RT, 18 received adjuvant RT, and the rest underwent salvage surgery at the time of recurrence after definitive CRT. Survival was significantly improved in the combined modality group compared to definitive CRT [27]. The survival rates of salvage surgery at progression were much lower

than those of surgery and RT in the primary setting (5-year OS: 0% *vs.* 54%; p = 0.007). However, in this series, there was a large discordance in the sample sizes of the two groups. In the other series by Takebayashi et al., patients with residual disease after definitive CRT requiring salvage surgery (n = 11) had comparable outcomes to the primary surgery group (n = 13; neoadjuvant chemotherapy-6) with 5-year OS of 64.8% and 60.6%, respectively, without significant difference [22].

Treatment-related morbidities is a major concern that influences the choice of treatment modality, but unfortunately, robust data on the comparison of toxicity profiles is limited. The series by Cao et al. showed a nearly four-fold higher incidence of treatment-related mortality in surgery to CRT (p = 0.03) [21]. In the series by Valmsoni et al., the overall morbidity and mortality were higher with surgery (52.17% and 6.25%, respectively) compared (36.95% and 2.17%, respectively) with CRT [24]. Tabekayashi et al. described a 23.1% incidence of morbidity with surgery, with the major complication being anastomotic leak (15.4%), while most of the CRT induced toxicities were haematologic only (leukopenia, 50%) with no treatment related mortality observed in any groups [22]. The only functional outcome reported to have better results with surgery is immediate dysphagia relief [20, 23]. Tong et al. showed that 30% of patients after CRT had dysphagia requiring salvage surgery, while 100% of patients undergoing primary surgery had satisfactory dysphagia relief [20]. Also, in the series by Chou S. et al., the post-treatment dysphagia scoring was better with surgery than CRT, but the quality of life was nearly comparable [23].

The two recent meta-analyses show a 5-year OS of 35.3% with definitive CRT and 26.6% with surgery, but comparative data is lacking [18, 28]. The outcomes of more radical surgery involving laryngectomy were inferior to those of laryngeal-preserving surgery, attributable to an advanced stage of presentation and possibly a higher incidence of complications [18]. In the surgical series meta-analysis, 84.4% of studies reported data about post-operative complications. The perioperative mortality rate was 0.5%, but the morbidity burden was quite huge, with anastomotic leakage seen in 17% of patients, anastomotic stenosis in 6.8% of patients, and dysphagia in 7.6% of patients. Wound infection was seen in 10.5%, pulmonary complications in 9%, and recurrent laryngeal nerve injury in another 22.8% [18]. In the other meta-analysis on CRT, combined acute and late toxicity was reported in around 20 to 40% of patients, with the most frequent side effects being mucositis and leukopenia, while more severe functional complications, such

as severe dysphagia requiring feeding tubes or parenteral nutrition and fistula, were rarely reported, i.e. in around 5% of patients only [28].

Another important aspect of CRT approach is use of concurrent systemic therapy to enhance radiosensitivity. These regimens are mainly adapted from the regimens utilised in head and neck, oesophageal cancers, with the commonly utilised regimens being cisplatin as a single agent or in combination with 5-fluorouracil (5FU) or mitomycin with other combination regimens being FOLFOX, paclitaxel and carboplatin [8]. A novel approach of stratification of primary treatment approach (surgery or CRT) based on the response to combination of induction chemotherapy, immunotherapy is being tested in the SCENIC trial [29].

Given the comparable outcomes of both modalities and the higher burden of morbidity and mortality with surgery, CRT has been widely adopted as the standard approach, with the option of surgery being reserved for salvage settings the time trend of treatment approaches from 2004–2008 to 2012–2016 also depicts a declining utilisation of surgery from 14.2% to 6.2% while that of RT increased from 50.7% to 73.4% [26].
An ongoing prospective multicentric open-label clinical trial [NCT05327517] aiming to compare surgery and definitive CRT for resectable CEC, with the primary endpoint being OS and the secondary endpoint being laryngo-oesophageal dysfunction-free survival with an estimated sample size of 192 participants, aims to complete accrual by the year 2028 [30]. Such future prospective studies may provide better insight in this area regarding the potential role of surgery and the trimodality approach.

Is there any benefit to escalating the radiation (RT) dose to 66–70 Gray (Gy), analogous to head and neck cancers, over the standard dose of 50.4 Gy for other oesophageal cancers?

Even though RT is utilised as a standard approach, a strong consensus on the appropriate dose schedule is lacking. Similar dose schedules have been adopted historically due to the close resemblance to primary head and neck cancers [31, 32]. There is an inclination towards practising high-dose schedules, given the predominant pattern of relapse in proximal oesophageal cancers being loco-regional, with the majority of infield failures [33]. The studies comparing different dose schedules in CEC are summarised in Table 2.

Few series have highlighted the beneficial role of escalated dose schedules in improving LRC. Kim et al. showed significantly improved 3-year local control (LC) from 60.4% to 90% ($p = 0.001$) and 3-year LRC from 45.3% to 70.4% ($p = 0.04$) with doses $\geq$ 59.4 Gy as compared to 59.4 Gy [34]. Another series from Zhao et al. showed that a high dose of above 66 Gy to the gross tumour volume (GTV) showed significantly better LRC (96% vs. 40%, $p = 0.009$). However, the LRC benefit in both of these studies did not translate into improved progression-free survival (PFS) or OS. The probable explanations might be the small study cohort, a relatively higher number of patients in the high dose group having locally advanced disease that led to more distant failures, and the added toxicities of dose escalation outweighing the benefit of LRC [35]. An analysis of 141 patients from the Taiwan Cancer Registry depicted a trend towards improvement in survival with the escalated dose regimen (60–70 Gy) over the standard dose ($\leq$ 50 Gy) [36].

Another study conducted across four Swiss institutions proved that a total RT dose of > 56 Gy was a highly significant positive predictive factor of OS ($p < 0.006$) [37]. Another series from MD Anderson of CEC (62.9%) and upper thoracic oesophageal cancers (37.1%) showed RT dose $\geq$ 50 Gy to be the only significant factor related to local relapse-free survival ($p = 0.001$) cause-specific survival (CSS) ($p = 0.003$), and OS ($p = 0.006$). In this study, two-thirds of patients who had received less than 50 Gy received a dose of 30 Gy in 10 fractions. This dose fractionation was used because it was considered radiologically equivalent to the standard 50.4 Gy in 28 fractions. However, this dose schedule is now often used in palliative settings [38]. These studies suggest a potential role for high-dose RT in improving the LRC and survival outcomes, but a consistent relationship could not be established.

On the contrary, multiple studies have not demonstrated benefits from dose escalation [39-44]. The largest series to date in CEC testing the role of dose escalation comes from the National Cancer Database (NCDB), where 789 CEC patients treated over a period from 2004 to 2013 failed to show any OS benefit of medium (> 50.4 and 66) Gy or high dose schedules (66–74 Gy) over the standard dose (50–50.4 Gy) after adjusting for all confounding factors [39]. Despite the lack of advantage, doses higher than 50.4 Gy were delivered in 73% of patients, with no significant change in practice over the years. In 2001, the practise of dose escalation was adopted at the Princess Margaret Hospital for CEC patients. A retrospective analysis was done to compare the clinical outcomes of patients treated before 2001 with two-dimensional hypo fractionated RT (54 Gy/20 fractions) with 5FU-based chemotherapy to those treated after 2001 with conventionally

fractionated 3DCRT (70 Gy/35fractions) with high-dose cisplatin-based concurrent chemotherapy. Over a median follow-up of 3.3 years, 2-year loco-regional recurrence-free survival and OS for the older cohort were 48% and 52%, respectively, and for the recent cohort, they were 46% and 43%. However, the follow-up of the patients treated with the high dose schedules was short, and the study cohort was heterogeneous with different chemotherapy regimens, limiting further interpretation of outcomes [40].

Another large multi-institutional retrospective analysis from the Netherlands compared escalated dose (> 50.4 Gy) to standard dose (41.4 to 50.4 Gy) schedules in combination with the preferred regimen of cisplatin or paclitaxel and carboplatin in proximal oesophageal cancers. No significant difference was observed in the four treatment approaches regarding CR ($p = 0.72$) and 3-year OS ($p = 0.76$). However, a trend towards higher CR was seen with paclitaxel, carboplatin, and high-dose RT, but at the cost of increased acute grade 3-5 toxicities [41]. Two other series have shown no benefit with escalating doses in terms of disease control [42, 43]. Of all these studies, the comparative data on the toxicity profile of a high-dose schedule versus a standard dose schedule is limited to a few series. Two depicted no significant difference [34, 40], while one study showed a significantly higher incidence of acute toxicities in the high dose group [41].

Despite the lack of strong evidence favouring high doses, there is continued interest among radiation oncologists in practising these schedules in CEC. This was depicted in the NCDB analysis, which showed significantly higher chances of dose escalation (> 50.4 Gy) in CEC compared to patients with other oesophageal primary sites. Overall, in oesophageal cancer, the likelihood of undergoing dose escalation significantly decreased from 2014 to 2016 compared to the years 2006 to 2013, but this was not true for CEC [44]. This is in spite of the fact that there is some emerging evidence favouring high dose schedules in oesophageal malignancies overall but substantial evidence in CEC is lacking [45, 46].

The major limitations of the existing literature are that the RT volumes, techniques and, particularly, the doses utilised were largely variable, along with other underlying and unknown confounding factors in and across these studies, leading to a potential bias in interpreting the true benefits of dose escalation.

Does elective nodal irradiation (ENI) provide better disease control than involved field irradiation (IFI)?

The target volume design in terms of including uninvolved nodal volumes in CEC remains debatable. There are broadly two types of regional nodal irradiation: involved field irradiation (IFI) and elective nodal irradiation (ENI). The ENI involves prophylactic inclusion of cervical and upper mediastinal lymph node stations in target volumes to control potential micro-metastases, while the IFI targets only the region with gross nodal disease. The choice of IFI versus ENI depends upon the trade-off between regional risk of relapses and toxicities. The NCCN guidelines recommend elective treatment of the supraclavicular nodes (SCN) and higher echelon cervical nodes, especially if the nodal stage is ≥ N1 [11]. However, the literature about this is debatable (Tab. 3).

Defining an adequate target volume in CEC is governed by studies addressing the recurrence pattern after definitive CRT. It is observed that most failures occur at the site of primary disease, which is in the high dose region. A retrospective series by Zhao L. et al. depicted the failure patterns in CEC patients after definitive CRT. Information from PET CT scan was incorporated for delineation. All observed local recurrences were in-field, with the majority being within the GTV (86.7%) and the rest being within the clinical target volume (CTV), while most of the regional failures (75%) were out of field. In patients treated by IFI, all regional failures occurred outside the CTV, with SCN being the most common site (62.5%), leading to an improvement in the regional failure-free survival in patients treated with ENI than IFI ($p = 0.025$). However, ENI wasn't a predictive factor for OS [35]. An important consideration in this series is that nearly one-third of the patients didn't receive concurrent chemotherapy, which might have impacted final outcomes. Another series by Zhang et al. analysed the failure patterns and outcomes of CEC treated with IFI. The median RT dose was 61.2 Gy (range 44–72 Gy), and 90.2% underwent PET CT at baseline. The vast majority of failures, 30.13%, were local, followed by distant in 23.7% patients, while regional relapses were the least common, with in-field failures seen in 10.26% of patients and out-field failures being extremely rare, seen in only 1.28% of patients [47].

Another study by Liu et al. highlighting patterns of relapses in patients treated by either ENI or IFI showed that the majority of failures in both groups were in the field, accounting for 60% in the IFI group and 54% in the ENI group. A total of 36.6% of the patients underwent baseline PET. ENI could delay the failures in the cervical nodal region compared to IFI, but the regional failures occurring outside the confines of involved field regions and within the area included in elective nodal region were comparable, being 6%

in IFI and 5% in ENI. This highlights no additional advantage of ENI in improving regional control [48].

The impact of RT volumes on survival was reported in two series. A study by Wang J. et al. compared the long-term outcomes of ENI and IFI [49]. PET CT was done at baseline if feasible. Although nodal involvement proved to be a significant predictor of OS, there was no significant difference in LRC, regional failures, distant failures, or 8-year OS between the two groups after propensity score matching. In the series by Liu et al. for cervical and upper thoracic oesophageal cancers, there was no significant difference in terms of distant failures ($p = 0.728$) and OS ($p = 0.741$) [48]. The major acute and long-term reported toxicities in these series were minor, with no discernible difference between the two techniques [48, 49].

It is proposed that the incidental radiation dose delivered and the effect of chemotherapy can potentiate the LRC, which may be sufficient to control microscopic disease in electively draining lymph node regions [50, 51]. In oesophageal malignancies, including all subsites, emerging evidence supports IFI with better local control, OS, and toxicity profile [52, 53]. However, robust data in CEC still lacks the ability to curtail the volumes from the preferential practise from ENI to IFI. While practising IFI, it is crucial to incorporate PET-CT during radiation planning as it can have a significant impact on target volume delineation in (20–94% patients) resulting in either decrease or increase in target volumes relative to CT scans [54]. In addition, PET-CT can detect areas of abnormal FDG uptake in the regional nodal area and distant metastatic sites that are not evident on CT scan [55, 56]. Alongside the inclusion or omission of nodal volumes in the target region, several other underlying factors like RT dose, technique, the use of diagnostic PET CT, and chemotherapeutic regimens can affect the risk of regional failure, which needs to be tested in a well-designed prospective setting.

Do advanced techniques such as intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) offer an advantage over three-dimensional conformal radiotherapy (3DCRT)?

Owing to the close proximity of CE to various critical structures, the steep dose gradient of commonly utilised conformal techniques (IMRT, VMAT) offers an advantage in improvising the dose distribution to the target volume. However, the data regarding the efficacy of advanced RT techniques in CEC is still limited (Tab. 4).

The dosimetric results of existing studies favour advanced techniques. Comparison by Chen NB et al. showed IMRT significantly improved the mean dose of GTV ($p = 0.001$), D5% of planning target volume (PTV) ($p = 0.007$), over 3DCRT with comparable lung V20 (volume receiving 20% of dose) lung ($p = 0.479$), higher V5Gy ($p = 0.032$), and lesser spinal cord Dmax (maximum dose) ($p < 0.001$) [57]. In the study by Yang et al., IMRT/VMAT techniques consistently reduced the dose to organs at risk (OAR) over 3DCRT, with significant reductions in lung V20 ($p = 0.001$) and Dmean (mean dose) ($p = 0.041$), brachial plexus D max ($p = 0.001$), and spinal cord Dmax ($p = 0.001$) [58]. Another study by Chen et al. of cervical and upper thoracic oesophageal cancer also favoured IMRT, with the conformity index ($p < 0.001$) and the V20 of the lung ($p < 0.001$) being significantly better while the PTV mean, minimum and maximum doses were comparable [59]. However, advanced techniques have failed to show a meaningful clinical outcome as compared to conventional techniques, with comparable reported response rates, PFS, and OS. Correlating with a better sparing of OARs, the toxicity profile seems to favour the IMRT/VMAT technique over the 3DCRT.

Chen NB et al. showed that the incidence of esophagitis, pneumonitis, and haemorrhage was comparable between the two techniques. The incidence of stricture was nearly twice as high in the 3DCRT group (21.4%) compared to the IMRT group (12.5%), but this difference was not statistically significant. The only significant difference reported was in tracheostomy rates, which were significantly higher in IMRT compared to 3DCRT (14.3% versus 1.8%; $p = 0.032$), which was attributed to a higher dose per fraction (median 2.13 Gy) delivered using simultaneous integrated boost [57]. The study by Yang H. et al. showed that the IMRT and VMAT groups had a significant reduction in grade 1 pneumonitis on radiological assessment, while the rest of the toxicities were nearly comparable (dysphagia, brachial plexopathy, bleeding). Brachial plexopathy was reported in six (7.7%) patients, and it was found that the maximum doses to the brachial plexus were higher than the constraint of 66 Gy and could be reduced to < 62 Gy after re-planning by the IMRT/VMAT technique, suggesting the potential role of these techniques in preventing plexopathy [58]. Chen F et al. also favoured IMRT, with the post-treatment thyroid function tests being significantly higher and the incidence of acute esophagitis (65% *vs.* 28.3%; $p < 0.001$) and pneumonitis (40% *vs.* 20%; $p = 0.028$) being far less in IMRT than 3DCRT [59].

A prospective series by Laskar et al. (27.5% of patients — upper oesophageal cancer; 60% — post-cricoid cancer) analysed the outcomes of CRT in patients treated with the VMAT

technique. The major acute ≥ grade 2 odynophagia was observed in 55%, and the most common late toxicities were strictures requiring dilatation in 45%, followed by long-term feeding tube requirements in 37%, symptomatic aspiration in 17.8% of patients, and tracheoesophageal fistula in 5%. In terms of quality of life, at 6 months after treatment, this series depicted significant improvement from the baseline in terms of pain ($p = 0.043$), appetite scores ($p = 0.021$), and swallowing function ($p = 0.029$), but significant worsening in xerostomia ($p = 0.017$), along with increased feeding tube dependency ($p = 0.047$) [60]. Overall, the IMRT and VMAT techniques seem to have some role in improving the therapeutic ratio, toxicity profile, and functional outcomes, but an improvement in terms of LRC or OS has not been elicited so far [57–59]. Nevertheless, this benefit is also dependent on the target volume delineation, dose prescription, planning objectives, and various other patient and treatment-related factors that need to be accounted for. But there is some data from radiobiological models suggesting that 3DCRT delivers higher Equivalent Uniform Dose that translates to a significant improvement in tumor control probability over IMRT & VMAT [61].

The study offers a comprehensive examination of recent literature regarding the treatment strategies for CEC, effectively tackling key inquiries and presenting a structured framework for understanding the treatment considerations associated with CEC. Furthermore, it acknowledges the variability present in the existing literature concerning treatment protocols, patient demographics, and clinically significant outcomes. However, the review is constrained by its heavy reliance on retrospective studies due to the absence of robust prospective evidence, thereby limiting the ability to fully account for various baseline confounding factors related to patient populations and treatment approaches. Additionally, certain crucial aspects of treatment, such as nutritional rehabilitation and quality of life, remain unaddressed in the current review. Although long-term nutrition therapy for patients approaching refractory cachexia has been demonstrated to mitigate the severity of acute radiation reactions [62, 63] and enhance quality of life, this aspect is not thoroughly explored in the review.

Conclusion

Based on this review, we suggest the following interpretation with the hope of gaining future insight to explore the areas that seem to have some potential benefit.

Definitive CRT is widely accepted as the standard approach in CEC given the comparable outcomes to those of surgery, the potential for organ preservation, and less morbidity and mortality. Few studies with evolving surgical techniques showed improved outcomes with the trimodality approach compared to CRT, requiring its further validation.

There is limited evidence favouring the preferential practice of high dose schedules over standard ones. The major limitation is that the high-dose regimen lacks a common consensus definition which limits the generalisation of results.

The evidence is more in favour of IFI than ENI, but the impact of other confounding treatment-related factors on improving regional control must be considered to curtail the delineation volumes.

Based on the very limited data on the comparison of the conformal techniques, the IMRT/VMAT technique seems to reduce the dose to the OARs, improving the toxicity profile over 3DCRT, while loco-regional control and survival rates are comparable. Given the large heterogeneity among various studies, retrospective nature and inclusion of four studies with combination of CEC and upper third esophageal cancer, a strong conclusion cannot be derived on the effect of various therapeutic approaches. Being a rare entity, recruiting patients in a multicentric prospective study is strongly recommended to determine the underlying prognostic and predictive factors and tailor the treatment approaches.

Conflict of interests

Authors declare no conflict of interests

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Author	**Study design**	**Number of patients**	**Treatment modality**	**Median follow up**	**Locoregional Failure**	**Survival**	**Toxicity**
Chou et al. (2010) [23]	Retrospective	29	*Surgery:* 15 (51.7%) *CRT:* 14 (48.3%)	NR	NR	**Mean survival:** *Surgery*: 36.2 months *CRT*: 34.4 months (p = 0.97)	Post treatment dysphagia score improvement: *Surgery:* 3.4 ± 0.5 to 0.6 ± 0.5, *CRT:* 3.5 ± 0.5 to 2.3 ± 0.7 (p < 0.001)
Tong et al. (2011) [20]	Retrospective	107	*Surgery:* 62 (57.9%) *CRT:* 21 (19.6%) *Palliative:* 24 (22.5%)	NR	*Surgery:* R0 resection—59.6%, *CRT:* Significant response—47.6%	**Median survival:** *Surgery*: 19.9 months *CRT*: 24.9 months (p = 0.39) **2-year**	*Surgery:* Hospital Mortality: 7.1%. Chest infection: 11.4% *CRT:* Significant mucositis: 9.5% Permanent

						OS: *Surgery:* 37.6% *CRT*: 46.9%	tracheostomy: 9.5% Stricture requiring repeated dilatation: 4.8% Carotid blowout 4.8%
Cao et al. (2014) [21]	Retrospective	224	*Surgery:* 63 (28.12%) *CRT*:161 (71.8%)	15 months	**2-year LFFS:** *Surgery:* 69.8 % *CRT*: 69.9% (p = 0.86) **2-year RFFS:** *Surgery*: 69.8% *CRT:* 79.5% (p = 0.15)	**2- year OS:** *Surgery:* 50.7% *CRT*: 49.3% (p = 0.31)	*Surgery:* Treatment related mortality: — 12.8% *CRT:* Treatment mortality: 3.5% (p = 0.03) *Surgery* ≥ Grade 3 dysphagia for anastomotic stenosis — 7.9% *CRT* ≥ Grade 3 toxicities Mucositis — 4.3%

							Dermatitis — 7.5% Leukopenia — 6.2% Dysphagia — 5.6%
Grass et al. (2014) [5]	Retrospective	362	*Surgery*: 5% *Radiation:* 71% *Surgery and Radiation:* 8% *No definitive treatment: 16%*	58 months	NR	**5-year disease specific survival:** Surgery alone: 26% RT alone: 28% Surgery + RT: 48% RT + surgery *vs.* RT alone: HR — 0.45 (p = 0.02)	NR
Takebayashi et al. (2017) [22]	Retrospective	49	*Surgery*: 13 (26.53%) *CRT*: 36 (73.46%)	43 months	**LRR:** *Surgery*: 53.8% *CRT:* 19.4%	**5-year OS:** *Surgery*: 60.6% *CRT*:	*Surgery*: Significant morbidity — 23.1% Anastomoti

					No significant difference among loco-regional *vs.* distant failures (p = 0.39)	51.4% (p = 0.89)	c leak — 15.4% Mortality rate — 0% *CRT:* Grade 3/4 leukopenia: 50% Grade 3/4 thrombocytopenia: 13.9% Grade 3/4 esophagitis: 8.3%
Chen et al. (2017) [27]	Retrospective	388	*Surgery alone:* 18 (4.64%), *CRT followed by Surgery:*8 (2.10%), NART followed by surgery: 2 (0.51%) *CRT*: 360 (92.78%)	NR	NR	**Median survival:** *Surgery ± CRT:* 19 months *CRT*: 25 months **5-year OS:** *Surgery ± CRT:* 41.9% *CRT*: 21% (p =	NR

						0.045)	
Valmasoni et al. (2018) [24]	Retrospective	148	*Surgery*: 56 (37.83%) *CRT*: 52 (35.13%) *CRT f/b surgery*: 40 (27.02%)	NR	**Proportion of local recurrence:** *Surgery :* 50% *CRT:* 84% *CRT f/b surgery* 50%(p = 0.024)	**5-year OS:** *Surgery*: 12.6% *CRT*: 26.7% *CRT f/b surgery:* 30.7% (p = 0.088)	*CRT:* Grade 3: 15.38% Grade 4: 19.23% *CRT f/b surgery:* Grade 3: 2.5% Grade 4: 10%
Chen et al. (2020) [19]	Retrospective	500	*Surgery:*171 (34.2%) *Non-surgical:* 322 (64.4%) (radiotherapy alone — 245, 49%; CRT: 66, 13.2%; chemotherapy: 11,2.2%; NR: 7; 1.4%)	NR	NR	**5-year OS:** 1973–1997 (n = 32) *Surgery:* 64.3% *Non-surgical :* 68.8% p = 0.912 1998-2007 (n = 266) *Surgery:* 48.1% *Non-surgical*	NR

						: 51.3% p = 0.922 2008–2018 (n = 195) *Surgery:* 48.5% *Non-surgical :* 34.4% p = 0.111	
Lu et al. (2021) (SEER database: 2004–2016) [26]	Retrospective	347	*RT alone*: 36 (10.37%), *CRT*: 227 (65.41%); *Surgery + CRT*: 15 (4.32%); Others : 69 (19.8%)	NR	NR	**Median survival :** *RT alone*: 7 months *CRT*: 14 months *Surgery + CRT*: 31 months *Surgery + CRT vs. RT*; p = 0.026 *CRT vs. RT*; p = 0.256	NR

						CRT vs. Surgery + CRT; p = 0.184	
Xu et al. (2022) [25] (SEER Database: 1977 to 2016)	Retrospective	1371	*Surgery alone*: 244 (17.79%) *RT*: 1107 (80.74%) *Chemotherapy*: 840 (61.26%)	NR	NR	**10-year OS:** Localized disease: *Surgery:* 20.7% *CRT*: 11.4% (p = 0.023) *Surgery based multimodality treatment*: 14.8% *CRT*: 11.1% (p = 0.084) Regional disease: *Surgery based multimodal*	NR

						therapy — 20.4% *CRT* — 9.0%, (p = 0.031)	

CRT — chemo-radiotherapy; OS — overall survival; LFFS — local failure free survival; RFFS — regional failure free survival; LRR — loco-regional recurrence; NR — not reported

Author (year)	**Study design**	**N**	**Treatment groups**	**Median follow up**	**Locoregional Failure**	**Survival**	**Toxicity**
Wang et al. (2006) [38] (*CEC — 62.9%*)	Retrospective	35	*< 50 Gy* *≥ 50 Gy*	39 months	**Complete response** *< 50 Gy*: 27.3% *≥ 50 Gy:* 79.2% (p = 0.003)	**5-year OS:** *< 50 Gy*: 0 % *≥ 50 Gy*: 29 % (p = 0.002) **5-year CSS:** *< 50 Gy*: 0% *≥ 50 Gy*: 44% (p = 0.0009)	NR
Huang et al. (2008) [40]	Retrospective	50	*54 Gy*: (42%) *70 Gy*: (38%)	32.1 years 29	**2 year LRRFS:** *54 Gy*:48% *70 Gy*: 46% (p = NS)	**2-year OS:** *54 Gy*: 52% *70 Gy:* 43% (p = 0.40)	Severe dysphagia: *54 Gy*: 50% *70 Gy*:30.76% (p = 0.13)
Ludmir et al. (2014) [42]	Retrospective	37	*< 40 Gy*: 3 (8%) *≥ 40 Gy to < 50*	129.4 months	**LRC:** *< 54 Gy*: 67.1% *≥ 54 Gy:*	**5-year OS:** *< 54 Gy:* 41.7%	NR

			Gy: 7 (19%) *≥ 50 Gy to < 60 Gy*: 12 (32%) *≥ 60 Gy* to < *70 Gy*: 11 (30%) *≥ 70 Gy*: 4 (11%)		62.1% (p = 0.809)	*≥ 54 Gy:* 33.6% (p = 0.982)	
Gkika et al. (2014) [43]	Retrospective	55	*≤ 60 Gy*: 29 (52.73%) *> 60 Gy*: 26 (49.06%)	146 months	NR (1)	**5-year OS:** *≤ 60 Gy*: 26% *> 60 Gy*: 24% (p = 0.78)	NR
De et al. (2017) [39]	Retrospective	789	*50–50.4 Gy* — 215 (27.25%) *> 50.4 to < 66 Gy* — 375 (47.52%) *66–74 Gy* — 199 (25.22%)	19 months	NR	**5-year OS:** *50–50.4 Gy*: 28% *> 50.4 to < 66 Gy*: 24% *66–74 Gy*: 33% *50–50.4 Gy vs. > 50.4 to < 66 Gy:* p = 0.15 *50–50.4 Gy vs.*	NR

						66–74 Gy p = 0.39	
Herrmann et al. (2017) [37]	Retrospective	55	*< 56 Gy*: 26 *≥ 56 Gy*: 29	34 months	**3 year LRC:** *< 56 Gy*: 50% *≥ 56 Gy*: 56% (p = 0.76)	**3-year OS:** *< 56 Gy*: 49% *≥ 56 Gy*: 56% (p < 0.006)	Dysphagia: Grade 1 — 13% Grade 2 — 11% Grade 3 — 9%
Zhao et al. (2017) [35]	Retrospective	86	GTV dose *< 66 Gy:* 66 (76.7%) *≥ 66 Gy:* 20 (23.3%)	19.4 months	**3 year LRFFS** ≥ 66 Gy: 96% < 66 Gy: 40% (p = 0.009)	Non-significant difference	Acute grade 3 toxicity Mucositis: 2.3% Leucopenia: 16.3% Thrombocytopenia: 3.5%
Kim et al. (2018) [34]	Retrospective	79	*< 59.4 Gy*: 35 *≥ 59.4 Gy:* 44	18 months	**3-years LC:** *< 59.4 Gy*: 60.4% *≥ 59.4 Gy*: 90.0% (p = 0.001) **LRC:** *< 59.4 Gy*: 45.3% *≥ 59.4*	**3-year OS:** *< 59.4 Gy:* 49.1% *≥ 59.4 Gy:* 58.4% (p = 0.69)	Esophageal stenosis requiring dilatation *< 59.4 Gy*: 9% *≥ 59.4 Gy*: 14% (p = 0.72) Tracheoesophageal fistula requiring intervention *< 59.4 Gy*: 6% *≥ 59.4 Gy*:

					Gy: 70.4% (p= 0.04)		5% (p > 0.99)
De Vos-Geelen et. al. (2020) [41] (*CEC — 33.5%*)	Retrospective	200	*Cis, ≤ 50.4 Gy:* 44 (26%) *Cis, > 50.4 Gy*: 39 (19.5%) *CP, < 50.4Gy*: 95 (47.5%) *CP, > 50.4 Gy:* 12 (6%)	62.6 months	**Complete response rates** *Cis, ≤ 50.4 Gy*: 57% *Cis, > 50.4 Gy*: 69% *CP, ≤ 50.4 Gy*: 68% *CP, > 50.4Gy*: 75% (p = 0.72)	**3-year OS:** *Cis, ≤ 50.4 Gy* 35% *Cis, > 50.4 Gy*: 46% *CP, ≤ 50.4 Gy* 40% *CP, > 50.4 Gy*: 33% (p = 0.76)	Grade 3–5 acute events: *Cis, ≤ 50.4 Gy*: 41% *Cis, > 50.4 Gy*: 49% *CP, ≤ 50.4 Gy*: 22% *CP, > 50.4 Gy*: 42% (p = 0.01)
Li et al. (2021) [36]	Propensity score matched retrospective analysis	141	*50-50.4 Gy:* 27 (19.15%) *60–70 Gy*: 114 (80.85%)	19 months	NR	**4-years OS**: *50-50.4 Gy*: 7% *60–70 Gy* 32 % (p = 0.07)	NR

*Cis — cisplatin; **CP — carboplatin, paclitaxel; LRRFS — loco-regional recurrence free survival; NS — not significant; CSS — cause specific survival; LRC — loco-regional control; LC — local control; OS — overall survival

Author (year)	**Study design**	**N**	**Treatment groups**	**Median follow up**	**Locoregional Failure**	**Survival Outcomes**	**Toxicities**
Liu et al. (2014) [48] (*CEC: 10.6%*)	Retrospective	169	*ENI*: 70 (41%) *IFI*: 99 (59%)	30 months	*ENI*: 10% *IFI*: 8% (p = 0.741)	**3-year OS:** *ENI*: 47% *IFI*: 49% (p = 0.741)	Acute and late: ≥ Grade 3 esophagitis *ENI*: 6% *IFI*: 6% (p > 0.05) ≥ Grade 3 pneumonitis *ENI*: 4% *IFI*: 2% (p > 0.05)
Zhao et al. (2017) [35]	Retrospective	86	*ENI:* 46 (53.5%) *IFI:* 40 (46.5%)	19.4 months	**RFFS:** *ENI:* 96% *IFI:* 80% (p = 0.025)	NR	Acute grade 3 toxicity Mucositis: 2.3% Leucopenia: 16.3% Thrombocytopenia: 3.5%
Wang et al. (2022) [49]	Propensity score matched retrospective analysis	131	*ENI*: 60 (45.8%) *IFI*: 71 (54.2%)	91.1 months	**Local failure** *ENI:* 22.4% *IFI:* 26.5% (p = 0.815) **Regional failure** *ENI*: 4.3% *IFI:* 4.1% (p = 0.159)	**3-year OS:** *ENI:* 31.1 % *IFI:* 26.1 % (p = 0.966)	Acute ≥ Grade 3 Esophagitis: *ENI*: 4 % *IFI*: 0% Pneumonitis *ENI*: 2% *IFI*: 0% Upper GI reaction

							ENI: 5.1% *IFI*: 0% Leukocytopenia *ENI:* 59.2% *IFI:* 38.8% (p = 0.068) Neutropenia *ENI*: 30.6% *IFI:* 14.3% (p = 0.089)
Zhang et al. (2022) [47]	Retrospective	156 IFI	NR	35 months	Local: 30.13% In-field nodal failures: 10.26% Out of field nodal failures — 1.28%	5-year OS: 33.33%	NR

CEC — cervical oesophageal cancer; ENI — elective nodal irradiation; IFI — involved field irradiation; OS — overall survival; RFFS — regional failure free survival; NR — not reported; GI — gastrointestinal

Author (year)	**Study design**	**N**	**Treatment groups**	**Median follow up**	**Locoregional failure**	**Survival outcomes**	**Toxicity**
Chen et al. (2020) [57]	Propensity score matched retrospective analysis	112	*3DCRT:* (50%) *IMRT*: (50%)	34.9 months 56	NR	**5-year OS:** *3DCRT*: 45.6% *IMRT*:	Tracheostomy: *3DCRT*: 1.8% *IMRT*: 14.3% (p = 0.032) Stricture:

						43.8% (p = 0.927)	*3DCRT*: 21.4% *IMRT*: 12.5% (p = 0.314)
Yang et al. (2017) [58]	Retrospective	78	*3DCRT*: 26 (30.23%) *IMRT*: (34.88%) *VMAT*: (25.58%)	28 months 30 22	NR	**2-year OS:** *3DCRT*: 53.6% *IMRT*: 55.6% *VMAT*: 60.6%, (p = 0.965)	Radiation pneumonitis *3DCRT*: 61.5% *IMRT*: 30% *VMAT*: 22.7% (p = 0.011) Total toxicities *3DCRT*: 20% *IMRT*: 14% *VMAT*: 12.7% (p = 0.236)
Chen et al. (2019) [59] *CEC 10%*	Retrospective —	120	*3DCRT*: (50%) *IMRT*: (50%)	NR 60 60	**Complete response:** *3DCRT*: 6.67% *IMRT*: 8.33% (p = 0.529)	NR	≥ Grade 3 toxicities: Esophagitis: *3DCRT*: 65% *IMRT*: 28.33% (p < 0.001) Pneumonitis: *3DCRT*: 40% *IMRT*: 20% (p = 0.028)

CEC — cervical oesophageal cancer; OS — overall survival; NR — not reported; IMRT — intensity-modulated radiotherapy/volumetric arc therapy; VMAT — volumetric arc therapy; 3DCRT — three-dimensional conformal radiotherapy