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GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Cervical Esophageal Cancers: Challenges and Opportunities

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Abstract

Purpose of the Review Cervical esophageal cancers (CECs) are a rare subset of esophageal cancers that are distinct in their management and outcomes. This review explores current data on the optimal management of this disease.

Recent Findings While outcomes for CEC have been suboptimal, several strategies have been proven beneficial in recent years. These include selective surgical resection or salvage surgery, chemoradiation (CRT) vs. radiation (RT) alone, dose escalation, IMRT, and induction chemotherapy.

Summary The optimal management of CEC to achieve the best oncological outcomes and minimize morbidity appears to be definitive chemoradiation with surgery reserved for selective salvage. While the benefit of dose escalated vs. standard dosing for radiation is unclear, most appear to use doses in excess of 50.4 Gy, even in the United States. IMRT might provide a benefit independent of allowing for dose escalation. Induction chemotherapy might allow for "chemoselection", but the benefit is unclear.

Keywords Cervical esophagus cancer · Proximal esophagus · Squamous cell carcinoma · Radiation dose escalation · Chemoradiation · IMRT

Introduction

Cancers originating in the cervical esophagus are quite rare, representing ~5% of all esophageal cancers. These are predominantly squamous cell carcinomas (SCC), associated with significant tobacco and alcohol use. The highest prevalence of the disease is in Asia and Africa, with much lower rates in the United States [1, 2]. The majority of cervical esophageal cancers (CECs) present as locally advanced disease with invasion of adjacent structures and/or regional adenopathy (neck and mediastinal). Unlike thoracic esophageal cancers (TEC), surgery for CECs is limited by the complex anatomy at the junction of the neck and thorax and is associated with significant morbidity. Currently, chemoradiation (CRT) is the general recommendation for the definitive treatment of CEC. However, control rates remain poor, and CRT for CEC is also associated with significant functional morbidity. To improve the therapeutic ratio, optimizations in treatment schedule (dose and fractionation) and improved radiation technique are being investigated. There are also attempts to use induction chemotherapy. In this review, we detail the advances in management strategies for CEC and discuss possibilities for future endeavors to improve outcomes.

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Anatomy

The cervical esophagus is the most proximal part of the esophagus, starting at the cricopharyngeus (bottom of the hypopharynx), extending approximately 6–8 cm distally to the thoracic inlet at the level of the sternal notch [3]. The course of the cervical esophagus runs in close proximity to the larynx, thyroid gland, and trachea, as well as upper mediastinal structures. CECs often present with local invasion into these structures. Additionally, the rich lymphatic drainage of this area yields significant risk for supraclavicular, central neck, and/or mediastinal adenopathy.

Surgery

With publication of the CROSS trial, trimodality therapy consisting of chemoradiation followed by surgery is generally considered the most effective mode of treating esophageal cancers [4]. This advantage was recently shown to be true specifically in SCC of the esophagus in the NEOCRTEC5010 trial which randomized thoracic esophageal SCC (unresectable CEC was excluded) to neoadjuvant CRT followed by surgery vs. surgery alone and found an improvement in median survival of 100.1 vs. 66.5 months ($p = 0.025$) [5]. Of note, there are some older randomized data suggesting no overall survival (OS) advantage to CRT followed by surgery vs. CRT alone for SCC of the esophagus [6, 7]. Trimodality therapy is still recommended for operable esophageal cancers, even for SCC [8].

One of the challenging aspects of CEC, however, is that surgical resection typically involves either a total pharyngolaryngectomy or cervical esophagectomy which is associated with significant morbidity. Nevertheless, surgery might still be an option for some patients. In a series of 49 patients, well-matched in baseline characteristics, there was no difference in the overall survival between patients treated with primary surgery vs. chemoradiation [9]. Ten of 13 surgical patients in this series had total pharyngolarygectomy. Of note, even in this series, when given the option, 73.4% patients not surprisingly chose CRT over surgery. Another larger series looked at patients who received primary surgery (with a majority receiving adjuvant radiation ± chemotherapy) which had an impressive 55.2% five-year survival which was not statistically different from patients receiving primary surgery for thoracic/abdominal SCC [10]. Survival was even better in modern patients treated after the year 2000.

There appears to be no advantage to surgery with adjuvant radiation or, conversely, radiation with adjuvant surgery when compared to either modality alone based on a large series who received primary radiation with surgery ($n = 28$) or patients that received primary surgery ($n = 63$) with or without radiation [11•]. Even with matched-case analyses, there was no difference in local control, distant mets, and OS between surgery and radiation. The authors of this study concluded that radiation/CRT should be considered the definitive therapy for larynx preservation, and surgery should be used for salvage for an incomplete response.

The role of surgery as a salvage to radiation has been supported by other studies as well. One series of patients who had all had a local recurrence after definitive chemoradiation for hypopharyngeal cancer ($n = 26$) or CEC ($n = 11$) found 3-year relapse-free survival and OS of 49.9% and 70.1%, respectively, which was statistically similar to salvage surgery for recurrent hypopharynx SCC after definitive CRT [12]. Operating in a previously irradiated field was associated with worse morbidity and tracheal-related complications when compared with similar salvage surgery for hypopharynx SCC. Conversely, a small series of 12 patients from the Mayo Clinic found a 3-year survival of only 33% with a 42% perioperative complication rate [13]. Since local failure rates after chemoradiation can be as high as 40–75%, salvage surgery can be considered an option for local control, and even cure, in well-selected patients, but it must be carefully balanced against the risk of complication and overall poor survival rate.

Radiation and Chemoradiation

Because of the high morbidity of surgical resection for CEC, radiation has been the mainstay of treatment for decades. While concurrent CRT is now considered standard, it is important to appreciate control rates with radiation alone for perspective and also to predict outcomes for patients that are not candidates for concurrent chemotherapy. Older series suggest local control rates with radiation alone at 5 years of 24.8% [14]. Even some more modern series with improvement in radiation technique and dose escalation also find a 2-year local control of 25% without chemotherapy [15]. Other series have seen better control rates, and this improvement might reflect the advantage of dose escalation. A large series with 80 CEC treated to a median dose of 68 Gy with radiation alone found a 68% local failure-free survival at 2 years [16].

CRT has become the preferred treatment for CEC with multiple series showing the consistently best rates of local control and overall survival when compared to radiation alone. While multiple chemotherapy regimens have been used, cisplatin-based regimens seem to be optimal. One series of 55 patients saw 3- and 5-year local control rates of 55 and 47%, respectively, which translated into 3- and 5-year OS rates of 29% and 25%, respectively [17]. A large series of 102 patients found a 3-year OS of 39.3% and a local-regional failure-free survival (LRFFS) of 35.3% with platinum-based chemoradiation [18]. Another series of 92 patients using platinum doublets concurrent with radiation and for 2–3 cycles post-radiation found a 3-year OS of 49.8% with progression-free survival (PFS) of 42.1% [19]. There are insufficient data to compare chemotherapy regimens since all of the series are retrospective with small numbers. The oncologic control of CRT has to be balanced against increased toxicity. There is an increased incidence of acute grade 3 mucositis (including pharyngitis), leukopenia, and gastrointestinal toxicity (22.5%, 14.7%, and 24.5%, respectively) [18].

The only prospective study looking at concurrent chemoradiation for CEC is a multi-institutional Japanese study conducted from 2009 to 2012 which treated 30 patients to 60 Gy in 30 fractions with a 3D technique with concurrent 5FU and cisplatin [20••]. Given the rarity of this disease, the investigators deserve credit for conducting such a trial. The protocol allowed additional chemotherapy for incomplete responders.

Since it is prospective in the modern era with a standardized protocol, this study provides some of the best data on outcomes and toxicity. With acceptable toxicities (20% grade 3 and 4 hematological toxity and two grade 4 fistulas), outcomes were excellent with a complete response rate of 73.3%. With a median follow-up of 40.8 months, 3-year OS was 66.5%, PFS was 36.6%, and laryngectomy-free survival was 52.5%. Complete responders had improved 3-year survival (74.6%) compared with non-responders (25.0%).

Overall, while CRT appears to offer optimal control for CEC with the most acceptable morbidity, there is still a significant need for improvement both with regard to local control where 5-year failure rates still range from 50 to 70% and distant metastases which occur in approximately 40% of patients. For comparison, these numbers are far worse than SCC patients of the thoracic esophagus in the NEOCRTEC5010 where OS and disease-free survival (DFS) are at 69.1% and > 70%, respectively [5]. Selected papers are summarized in Table 1.

Dose Escalation

If local failure remains a major pattern of failure, radiation dose escalation is an obvious strategy to enhance local control and potentially improve outcomes. While intergroup 0123/RTOG 94-05 showed no benefit to radiation dose escalation beyond 50.4 Gy for esophageal cancers, CEC is thought to represent a different disease, perhaps more similar to head and neck cancers where doses are consistently taken to 60–70 Gy [24]. Multiple smaller, retrospective series have shown improved outcomes with dose escalation. A multicenter retrospective study from Switzerland found on multivariate analysis (MVA) that doses > 56 Gy were associated with improved disease-free survival (DFS) and OS [25]. Using 3D technique and concurrent 5FU/cisplatin chemotherapy, Kim et al. compared high dose (> 59.4 Gy) vs. standard dose and found no differences in 3-year OS and PFS rates. However, there was an improvement in local control (LC) from 60.4 to 90.0% with dose escalation [21]. In contrast, multiple other series have not shown improvement with dose escalation [17–19, 26]. It is important to note that many groups, like the prospective trial from Japan, use 60 Gy as a standard dose, despite no clear evidence of superiority, and this has become widely accepted across the globe [20••].

It is important to emphasize that all of these series are small and retrospective so there is a strong clinical bias in selecting better performing patients for dose escalation. It is also very difficult to tease out the effects of dose escalation from the use of chemotherapy in many of the above series. In order to address these limitations, a review of dose escalation from the National Cancer Database (NCDB) was conducted which identified 789 cases of CEC [27•]. Dividing dose levels into standard (50–50.4 Gy), medium (> 50.4–66 Gy), and high (> 66–74 Gy) dose groups, this study found no difference in OS between the dose levels when controlling for confounding variables. There are many limitations to the NCDB analysis, not the least of which is lack of data on local control and progression-free survival. Nevertheless, this the largest study looking at CEC. As an interesting aside, this study found that 73% of CEC treated in the US from 2004 to 2013 was treated with doses greater than 50.4 Gy, despite the results of RTOG 94-05, possibly reflecting a strong bias among oncologists to treat CEC more like a head and neck cancer.

IMRT

In conjunction with dose escalation, some have hypothesized that using intensity-modulated radiation therapy (IMRT) might produce superior outcomes for CEC compared with 2D or 3D techniques. IMRT delivers more conformal doses with better sparing of normal tissue. A well-performed retrospective analysis from the Princess Margaret Hospital compared patients with CEC, treated with 3 consecutive protocols in their institution from the years 1997–2013: 54 Gy in 20 fractions with 2D RT with 5FU and MMC or cisplatin vs. ≥ 60 Gy in 30 fractions with 3D RT with elective nodal RT with cisplatin vs. ≥ 60 Gy with IMRT with elective nodal RT with cisplatin [22•]. Using multivariate analyses to attempt to control baseline differences in the cohorts, this study found no difference between the groups in terms of 2-year local control (although a trend favored IMRT). However, there was a significant improvement in 2-year OS from 33% to 43% to 53%, respectively, between the regimens. On MVA, IMRT treatments were superior to non-IMRT for OS. The authors hypothesized that perhaps improved late toxicity with IMRT could explain the apparent contradiction between no improvement in LC and improvement in OS. Specifically, the authors noted lower swallowing dysfunction (when looking at PEG dependence and/or esophageal dilation) in their IMRT arm, despite dose escalation. These data were reproduced by a Japanese group who compared 32 patients treated with IMRT vs. 48 patients treated with 3D RT, all with concurrent chemotherapy and all prescribed 60 Gy in 30 fractions with prophylactic nodal radiation [23]. While there was no improvement in local control or PFS, 3-year OS was improved from 57.2% to 81.6% with IMRT. This remained significant on MVA. While selection biases and improvement in supportive care in more recent years might explain the improvement in outcomes with IMRT, there is perhaps a signal of efficacy that should be further explored. Presumably, the improved outcomes come from sparing critical structures like the pharyngeal constrictors, pharynx, and/or larynx, but there is not enough data available to inform which structures and what dose levels are acceptable.

Table 1 Selected studies in cervical esophageal cancer

Authors (Year)	Study Design	Patients	Question(s) Study Addresses	Treatment	Selected outcomes
Saeki et al. (2017) [10]	RS	63 CEC, 977 TAEC (1980–2013) 54% stage III/IV (CEC) 42% stage III/IV (TAEC)	Surgery feasibility	75% received neo adj RT ± cis/5FU 88% TPLE or PLCE 70% curative resection RT = 30–45Gy	5-year OS (all patients) 55% CEC, 38% TAEC; NS 5-year OS (if curative resection) 77% CEC, 47% TAEC; $p = 0.0067$
Cao et al. (2014) [11•]	RS	224 (63 surgery, 161 RT) (2001–2012) 57% stage III (primary surgery) 90% stage III (primary RT)	Surgery vs. RT	Primary surgery = 43% surgery alone, 67% surgery + RT primary RT = 82% RT ± CC, 18% RT + surgery RT = mostly IMRT, median 68 Gy CC = mostly cis surgery = mostly PLE	2-year OS 51%(surg) vs. 49 (RT); NS 2-year LFFS 69% vs. 70%; NS 2-year RFFS 70% vs. 80%; NS 2-year DFFS 63% vs. 74%; NS No difference in cancer outcomes with primary surgery vs. RT
Takebayashi et al. (2017) [12]	RS	49 (2003–2013) 70% stage III/IVa	Surgery vs. CRT	IC then surgery vs. CRT (13 surgery, 36 CRT) IC = cis/5FUCRT = 60 Gy + cis/5FU	5-year OS 61% (surgery) vs. 54% (CRT); NS median DFS 6 vs. 8 m; NS No difference in survival with surgery vs. CRT
Cao et al. (2015) [17]	RS	115 (2001–2012) 70% stage III	RT vs. CRT RT Dose escalation > 66 Gy	RT ± CC (30% CRT) RT = 55% IMRT, median dose 66Gy CC = weekly cis or q3 weekly high-dose cis	2-year OS 48%2-year DFFS 76% No difference in survival between RT vs. CRT ≥ 66 Gy vs. < 66 Gy 2-year OS 55.6% vs. 37.5%; $p = .018$ Dose escalation associated with improved survival
Herrman et al. (2017) [21]	RS	55 (2004–2013) 34% stage III	RT Dose escalation > 56 Gy Induction chemotherapy	CRT ± IC (58% had IC) RT = median 56Gy, conformal techniques IC = platin-based, median 2 cycles CC = mostly cis/5FU	No difference in 3-year DFS and OS with > 56 Gy On MVA, improved DFS and OS with > 56 Gy No difference in 3-year DFS and OS with induction chemoOn MVA, improved DFS and OS with induction chemo
De at al (2017) [22•]	RS	789 (NCDB) (2004–2013) 49% stage III	Dose escalation	RT ± CC (90% had CC) (44% IMRT) 27% "standard" (50 Gy) 48% "medium" (> 50.4–< 66 Gy) 25% "high" (66–74 Gy)	No difference in OS with dose escalation at any level
McDowell et al. (2017) [23]	RS	81 (1997–2013) 15% stage III (1983 staging) (30% 3DCRT era, 10% in 2D or IMRT eras)	2D vs. 3D vs. IMRT	CRT 26% 2D (1997–2000) = 54 Gy +5FU/MMC or cis 28% 3DCRT (2001–2005) = 70 Gy + cis 46% IMRT (2006–2013) = 70Gy + cis	No difference in LC but improved OS with high-dose IMRT
Gkika et al. (2014) [18]	RS	55 (1992–2010) 65% stage III	Induction chemotherapy	IC + CRT RT = 3DCRT, 50 Gy + boost, brachy allowed, median dose 60 Gy chemo regimens = FLEP then cis/etoposide + RT, 5FU/LV/cis then cis/5FU + RT, and cis doublets	Median surv 16 m3-year OS 29% (5-year 25%)3-year LRC 55% (5-year 47%)3-year PFS 25% (5-year 20%) No difference in survival between chemo or RT regimens 64% with CR (3-year OS 45% vs. 0% with non-CR) Improved survival if patients achieved CR

Table 1 (continued)

Authors (Year)	Study Design	Patients	Question(s) Study Addresses	Treatment	Selected outcomes
Zhang et al. (2015) [19]	RS	102(2002–2013) 70% stage III	CRT	CRT (15% had IC) RT = 55% 3DCRT, 45% IMRT, 90% $\geq$60 Gy CC = cis/5FU or cis/docetaxel	3-year OS 39% median surv 27 m 3-year LRFFS 35% 3-year PFS 34% worse OS, LRFFS and PFS for pts. with hoarseness
Zenda et al. (2016) [24]	PS	30 (2009–2012) 60% stage III+	CRT	CRT RT = 3DCRT, 60 Gy in 30 fractions CC = cis/5FU	3-year OS 67% 3-year LFFS 47% 3-year PFS 37% Only prospective trial

CC, concurrent chemotherapy; *CEC*, cervical esophageal cancer; *cis*, cisplatin; *CR*, complete response; *CRT*, chemoradiation; *DFFS*, distant failure-free survival; *DFS*, disease-free survival; *5FU*, 5-fluorouracil; *IC*, induction chemotherapy; *IMRT*, intensity-modulated radiation therapy; *LC*, local control; *LFFS*, local failure-free survival; *LRFFS*, local recurrence-free survival; *LV*, leucovorin; *MMC*, mitomycin C; *MVA*, multivariate analysis; *NS*, non-significant; *OS*, overall survival; *PFS*, progression-free survival; *PLCE*, pharyngo-laryngo-cervical esophagectomy; *PLE*, pharyngo-laryngo esophagectomy; *RFFS*, regional failure-free survival; *RT*, radiation therapy; *TAEC*, thoracic and abdominal esophageal cancers; *TPLE*, total pharyngo-laryngo-esophagectomy; *3DCRT*, 3D-conformal radiation therapy

Induction Chemotherapy

Another strategy to improve outcomes is induction chemotherapy. Like head and neck cancers, induction chemotherapy might decrease the risk of metastases and make for smaller treatment volumes. There are some older reports with promising outcomes using this strategy [28]. Using two induction regimens, a group from the University of Essen conducted a retrospective review of their CEC patients [17]. While they found that an impressive 64% of patients had a complete clinical response to therapy, there was no association with response to induction therapy and OS which was 29% for the cohort. Using selective induction chemotherapy or "chemoselection", another retrospective study reported on a strategy of referring chemotherapy responders to definitive chemoradiation vs. primary chemoradiation for everyone [15]. Recognizing that this is an intrinsically biased study, 2-year OS was significantly improved in the induction arm (65.1%) vs. standard chemoradiation arm (40%). There was also an improved LC from 25.0 to 68.0% at 2 years which translated into better larynx preservation rates. Since these data are retrospective, it is very difficult to determine if induction therapy should be a standard of care. There is growing data that responders vs. non-responders to therapy have very different outcomes suggesting that an induction or "chemoselection" approach might be a good strategy for intensifying therapy for worse players [19, 20••]. This approach has been piloted in resectable esophageal adenocarcinomas with CALGB 80803 which showed that there might be a benefit to early changes in chemotherapy for non-responders [29]. There is also evidence in head and neck cancers that intensified induction chemotherapy with docetaxel, cisplatin, and fluorouracil has better overall survival than cisplatin and fluorouracil alone [30]. However, more recent data in head and neck cancers have not found a clear benefit to induction chemotherapy before chemoradiation versus chemoradiation alone (albeit in two trials that did not meet accrual goals) [31, 32]. More data are needed before applying this to CEC.

Areas for Improvement

While the data for management of CEC is largely from smaller, almost exclusively retrospective series, several clear areas emerge as areas with need for further investigation and intensification of care. The first such category is locally advanced disease such as hypopharyngeal invasion. The distribution of nodal metastases can change with hypopharyngeal invasion and outcomes can be worse [11•, 33, 34]. Similarly, the role, dosing, and distribution for elective nodal radiation for CEC are not well characterized, as is true for all esophageal cancers.

Another area of concern is the aforementioned "poor responders" to either definitive therapy or induction therapy. These individuals need to receive more aggressive therapy earlier, perhaps even surgery after the failure of induction, to preempt universally poor outcomes in every series where this has been explored. There is also a paucity of genetic data and biomarkers to predict responses in this disease. For instance, one group looked at HPV status of CEC in a very small series found HPV infection only 5.3% of cases [26]. On a similar line, the overwhelming majority of data about CEC comes from East Asia, and there is growing data that there are differences between Asian and non-Asian populations in terms of epidemiology and outcomes [35].

Conclusions

Cervical esophageal cancers are a rare entity. Management is challenging due to the complex surrounding anatomy and natural history of disease, with most CECs presenting with locally advanced disease. Currently, definitive CRT is favored for most curable CECs, with surgery reserved for selective salvage of incomplete responders. Dose-escalated radiation, with doses approaching those used for head and neck SCCs, seems to improve local control but the absolute benefit is unclear. More conformal radiation techniques such as IMRT may improve survival for patients with CEC by decreasing morbidity and late toxicities. There might be a role for induction chemotherapy or selective intensification of therapy if clinical and biological correlates can be developed to help direct therapy. Further research into these topics can improve outcomes. While the authors were unable to identify any trials in western countries specifically addressing CEC, there are some trials that allow for CEC in their inclusion criteria. For instance, several institutions such as the Washington University in St. Louis and MD Anderson Cancer Center are conducting trials exploring protons for esophageal cancer and allow for CEC. Likewise, there are multiple trials opening looking at early incorporation of immunotherapy into treatment of esophageal cancers and allow for CEC. However, given its rarity, it is unlikely that a trial will be developed to specifically address the clinical needs of this challenging disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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