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review

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Cervical esophageal cancer: a gap in cancer knowledge

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Background: The aim of this systematic review is to provide an overview of the diagnosis, treatment options and treatment-related complications of cervical esophageal carcinoma (CEC) and to subsequently provide recommendations to improve quality of care.

Design: Studies were identified in PubMed, EMBASE and Web of Science. A total of 107 publications fulfilled the inclusion criteria and were included.

Results: CEC is uncommon, accounting for 2%–10% of all esophageal carcinomas. These tumors are often locally advanced at presentation and have a poor prognosis, with a 5-year overall survival of 30%. Tobacco and alcohol consumption seem to be the major risk factors for developing CEC. Surgery is usually not possible due to the very close relationship to other organs such as the larynx, trachea and thyroid gland. Therefore, the current standard of care is definitive chemoradiation (dCRT) with curative intent. Treatment regimens used to treat CEC are adapted by established regimens in lower esophageal squamous cell carcinoma and head and neck squamous cell carcinoma. However, dCRT may be accompanied by severe side-effects and complications. Several diagnostic and predictive markers have been studied, but currently, there is no other biomarker than clinical stage to determine patient management. Suggestions to improve patient outcomes are to determine the exact radiation dose needed for adequate locoregional control and to combine radiotherapy with optimal systemic therapy backbone.

Conclusion: CEC remains unchartered territory for many practising physicians and patients with CEC have a poor prognosis. To improve the outcome for CEC patients, future studies should focus on the identification of new diagnostic biomarkers or targets for radiosensitizers, amelioration of radiation schedules, optimal combination of chemotherapeutic agents and/or new therapeutic targets.

Key words: cervical esophageal cancer, chemoradiation, targeted therapy, toxicity, survival, review

introduction

The cervical esophagus is the short part of the esophagus between the lower border of the cricoid cartilage and the thoracic inlet (suprasternal notch), ~18 cm from the incisor teeth [1]. Carcinoma of the cervical esophagus (CEC), usually squamous cell carcinoma (SCC), is uncommon, with 5 new cases per 1 million person years in the United States [2] and accounts for 2%–10% of all esophageal carcinomas [3]. The highest rates of SCC are found in Eastern Asia and Southern Africa, and the lowest rates in Western Africa and Central America [4]. The management of CEC differs from that of cancers of the lower two-thirds of the esophagus because CECs are often locally advanced at the time of diagnosis infiltrating nearby anatomical structures including, for example, the cricoid, thyroid cartilage or thyroid gland. Moreover, patients with CEC often present with lymph node metastases [1]. Most CECs are not treatable by surgery, as this would involve mutilating resections including pharyngo-laryngo-esophagectomy (PLE). Therefore, definitive chemoradiation (dCRT) is the standard treatment modality recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines [5, 6]. dCRT usually consists of 50.4 Gy in 1.8 Gy per fraction per day. Higher doses up to 60–66 Gy may be appropriate if no surgery is planned. Concurrent chemotherapy generally consists of cisplatin and 5-fluorouracil (5-FU), oxaliplatin and 5-FU or carboplatin and paclitaxel [5]. As CECs behave very aggressively, as they grow in an area of abundant lymphatic drainage and fail to produce early symptoms, and easily and frequently extend toward the hypopharynx, these tumors are sometimes treated with schedules for locally advanced head and neck squamous cell carcinoma (LAHNSCC), which consists of 70 Gy in 35 fractions and cisplatin 100 mg/m^2 on day 1, 22 and 43 of radiotherapy (RT) (NCCN guidelines for head and neck

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cancers [7]). dCRT is related to life-threatening adverse events in 5%–10% of patients [8, 9]; thus, further research is needed to define the optimal treatment schedule with adequate survival and acceptable toxicity. In this literature review, we will provide an overview of the current knowledge and controversies surrounding CEC with respect to histopathology, genetic factors, etiology, diagnosis, treatment, toxicity and local disease control rate and survival and we will provide recommendations for future studies regarding potential curative treatment options, based on the current literature.

methods

literature search strategy

In May 2015, the PubMed, Web of Science and EMBASE databases were searched for relevant evidence. The literature search strategy is detailed in supplementary Section 1, available at *Annals of Oncology* online. The reference lists from included articles were also searched for additional relevant studies.

study inclusion and exclusion criteria

Language was restricted to English. Articles published during the last three decades were selected. Studies were included if they comprised a minimum of five patients diagnosed with cancer in the cervical esophagus and treated with curative intent. Studies were excluded if patients had distant metastasis and were treated with palliative intent. Only studies published as abstracts were excluded.

literature search results

The initial search in the three databases yielded 639 articles. Based on reading the titles and abstracts, 488 articles were excluded. Using Endnote (Version X6, Thomson Reuters) and manual screening, 63 duplicate articles were excluded. Eighty-eight original articles and reviews were further screened. Thirty articles were excluded based on our predefined exclusion criteria leaving 58 full publications for inclusion in this review. During the manual search of the reference lists of the included articles, a further 49 relevant publications were identified, resulting in 107 articles that formed the basis of this review (for details, see flowchart in supplementary Figure S1, available at *Annals of Oncology* online).

histopathology and genetic factors

SCC accounts for 95% of cervical esophageal malignancies [10]. Very little is known about SCC precursor lesions and genetic factors predisposing for CEC in particular. The malignant transformation to SCC involves basal cell hyperplasia, low- and high-grade dysplasia and invasive carcinoma. Squamous dysplasia is a well-described histological precursor lesion of esophageal SCC [11–14]. Dysplasia is thought to be caused by molecular alterations [15]. Early detection of molecular alterations, endoscopic and histological features of squamous dysplasia is necessary to identify SCC at an early stage [16–19]. Modern endoscopy techniques, like micro-endoscopy, lugol staining and the use of biomarkers, have the potential to increase early detection [17–19].

Genetic alterations in CEC are currently poorly understood and to the best of our knowledge, there are no studies investigating only genetic alterations in carcinomas located in the cervical esophagus. Several genes have been shown to be down- or upregulated in (pre)malignant lesions of esophageal SCC [11, 20–29]. The most common genetic alterations consist of allelic losses at chromosomes 3p, 5q, 9p, 9q, 3q, 17p, 17q, 18q and mutations of *p53*, *RB1* (retinoblastoma protein), *ALDH2* (aldehyde dehydrogenase-2 gene), *MTHFR* (methylene tetrahydrofolate reductase gene), *EGR1* (early growth response gene-1), *CCND1* (cyclin D1) and *cMYC* [30–34]. A recent work by the Cancer Genome Atlas Initiative provides comprehensive molecular profiling data of squamous cancers of the esophagus that may also facilitate future research for diagnostic and therapeutic molecular targets in CEC [35]. There is an urgent clinical need for further research to investigate the potential usefulness of genetic and protein alterations for early diagnosis of CEC.

etiology and risk factors

Tobacco and alcohol consumption are well-known risk factors for CEC [10, 15, 34, 36]. Mutations in *ADH* (alcohol-dehydrogenase) 1B and *ALDH-2*, both enzymes involved in alcohol metabolism, have been related to the occurrence of neoplasia in the upper aerodigestive tract [10].

The variable geographic incidence of CEC with high-risk regions in Iran, Central Asia, Mongolia, Northern China and Eastern Cape South Africa suggests a potential influence of nutritional and environmental factors. The role of family history has not been clarified yet [34, 37]. Occupational factors have been difficult to evaluate independently because esophageal carcinomas often occur in unqualified workers in industry and agriculture, who are often also frequent tobacco and/or alcohol consumers. High exposure to polycyclic aromatic hydrocarbons (PAHs) has also been associated with a high risk of esophageal cancer [38].

Studies investigating the potential association between human papilloma virus (HPV) infection and CEC incidence have conflicting results. Geographical locations with a high incidence of esophageal SCC tend to also have a higher incidence of HPV infection in patients with esophageal SCC (more than 10% of esophageal SCC cases are related to HPV infection) [39–41]. The main strains involved in esophageal cancer appear to be HPV 16 and 18 [40].

diagnosis and staging

Endoscopy and biopsy are the first choice of examination if a CEC is suspected. Recommendations regarding the minimum number of biopsies vary between countries, ranging from 1 up to 8 [42]. Endoscopic ultrasonography (EUS) is considered to be the best technique to assess the depth of tumor infiltration and lymph node status and can be combined with fine needle aspiration cytology [3, 43, 44]. ^{18}-Fluorodeoxyglucose-positron-emission-tomography-computed-tomography (^{18}F-FDG-PET CT) is highly recommended to detect potential tumor invasion into adjacent structures and lymph node or distant metastases [44]. Bronchoscopy, with endobronchial ultrasound and biopsy, can be used to assess infiltration in adjacent structures, e.g. trachea [45].

Most CECs are locally advanced at the time of diagnosis, with ~55% being TNM stage III or IV tumors and 27% stage II tumors [1, 46–49]. An overview of the current TNM staging can be found in supplementary table 2, available at *Annals of Oncology* online.

treatment

Historically, surgery has been the standard treatment for CEC. Mostly, a PLE was carried out, a procedure that includes the resection of the larynx and has a huge impact on quality of life [50]. Nonetheless, during the last decades, the outcome for patients who underwent surgery for CEC has improved due to the newly developed surgical strategies, such as minimally invasive surgery and neoadjuvant (chemo)radiotherapy [51]. Furthermore, reconstruction methods like free jejunal graft, gastric pull-up or deltopectoral or pectoralis major myocutaneus flap have been introduced [50, 52–62]. Despite these efforts, surgical treatment still has a great risk of major complications and a high morbidity and mortality rate [57, 63–68].

To improve survival and quality of life, non-invasive treatment options like RT and dCRT have been explored. The Radiation Therapy Oncology Group (RTOG) compared dCRT versus RT alone for the treatment of patients with thoracic esophageal cancer and found that dCRT significantly increased 5-year overall survival (OS) compared with RT alone, 26% versus 0% [8]. Although this study included only patients with thoracic esophageal cancer, the study results form the basis of the current non-surgical treatment of patients with esophageal cancer, including CEC. An update of the original RTOG 85-01 trial by al-Sarraf et al. [69] reports higher survival rates of patients treated with dCRT compared with RT alone in the treatment of locally advanced esophageal cancer. Another study carried out in patients with cervical and upper thoracic esophageal cancer showed less favorable results than the RTOG study, reporting 5-year OS of 18.6% in patients treated with dCRT [70]. Other studies reported a 5-year OS of ~30% for CEC patients treated with dCRT [46, 71] which is comparable with OS after surgery alone (24%–47%) [56, 58, 63, 66, 72–74]. In comparison with other SCCs in the head and neck region, 5-year OS of patients with CEC is relatively low [10], while it is comparable with 5-year OS in patients with SCC located in other parts of the esophagus, which is ~26% [8]. dCRT may cause high rates of toxicity in CEC patients. Common toxic effects include dysphagia, dehydration, mucositis, esophagitis, dermatitis and fatigue. An additional side-effect of chemotherapy is bone marrow suppression [8, 9, 47–49, 71, 75, 76]. Moreover, late toxic effects like strictures and fistulas may occur [48, 71, 77].

In the following, we will describe the currently available organ-sparing treatment options for locally advanced CEC, which combine RT with chemotherapy.

systemic therapy used within concurrent treatment regimens for CEC

Several chemotherapeutic regimens are used, adapted by established regimens in lower esophageal SCC and head and neck squamous cell carcinoma (HNSCC). High-dose cisplatin-based chemotherapy, consisting of 100 mg/m^2 on day 1, 22 and 43 of RT, is currently considered one of the treatment options for patients with CEC based on increased cure rates that were observed with high-dose cisplatin in patients with head and neck cancer [7, 46]. However, no difference was seen in OS, disease-free survival (DFS) or locoregional recurrence-free survival (LRFS) comparing CEC patients treated with high-dose cisplatin with a concurrent RT dose of 70 Gy versus low-dose cisplatin combined with 5-FU or mitomycin C, concurrently administered with an RT schedule of 54 Gy (Table 1) [46].

SCC of the lower esophagus is often treated with a combination of cisplatin and 5-FU [82], a key factor in the treatment of gastroesophageal cancer [84]. In CEC, the combination of cisplatin and 5-FU has shown acceptable cure and survival rates [9, 46–48, 71] (Table 1), but combination therapy can lead to higher toxicity rates when compared with cisplatin alone. Bleiberg et al. [80] randomized patients with advanced esophageal SCC to either receive cisplatin (100 mg/m^2) and continuous 5-FU (1000 mg/m^2/day) from day 1 to 5 or cisplatin alone (100 mg/m^2) and found higher 2-year OS rates (18% and 9%, respectively), but also higher toxicity rates in the cisplatin/5-FU group (16% treatment-related deaths in the cisplatin/5-FU group versus 0% in the cisplatin alone group).

Other chemotherapeutic regimens have been studied with comparable results [78, 81]. Conroy et al. [78] studied the role of FOLFOX regimen: 5-FU (bolus 400 mg/m^2, followed by infusional 5-FU 1600 mg/m^2 over 46 h) plus leucovorin (200 mg/m^2) and oxaliplatin (85 mg/m^2) in patients with adeno-, squamous cell or adenosquamous carcinoma. They compared the FOLFOX regimen with standard cisplatin/5-FU and found more treatment-related deaths in the cisplatin/5-FU group (4.5% in the cisplatin/5-FU group versus 0.7% in the FOLFOX group). Three-year OS was 19.9% [95% confidence interval (CI) 10.8–31.0] in the FOLFOX group and 26.9% (95% CI 16.9–37.8) in the cisplatin/5-FU group. Ruppert et al. [81] identified carboplatin-/paclitaxel-based chemotherapy, a regimen already used in SCC of the lower esophagus, as a useful alternative to the cisplatin-based regimen. Van Hagen et al. [85] studied the role of neoadjuvant carboplatin AUC 2 and paclitaxel 50 mg/m^2 for 5 weeks and concurrent RT (41.4 Gy in 23 fractions), followed by surgery in esophageal and esophagogastric junction SCC, adenocarcinoma and large-cell undifferentiated carcinoma and found a pathological complete response (pCR) in 49% of patients with SCC. There was only one treatment-related death among the patients (n = 171) that were treated with neoadjuvant chemoradiation, which indicates the great tolerance of this regimen. Three-year OS in this group was 58%, compared with 44% in the group that received surgery alone. Moreover, Blom et al. [86] found in patients treated with chemoradiation before surgery, that the combination of carboplatin/paclitaxel/41.4 Gy had a lower percentage of treatment-related deaths (1.1% versus 4.1%) and a comparable 3-year OS rate (57% versus 61%) compared with the cisplatin/5-FU/50.4 Gy regimen. Hence, low-dose cisplatin, FOLFOX and carboplatin/paclitaxel (especially in combination with a low RT dose of 41.4 Gy) are useful alternatives to a high-dose cisplatin-based chemotherapy.

The role of epidermal growth factor receptor (EGFR), targeting therapy using cetuximab, an established radiosensitizer in HNSCC [7], seems to be not that prominent in CEC. On the basis of the results of the SCOPE1 trial, a multicenter phase II/III trial, randomizing 258 patients between standard dCRT and dCRT combined with cetuximab, the use of cetuximab cannot be

Table 1. Included studies using definitive chemoradiation (dCRT) or chemotherapy in patients with esophageal cancer

Author(s)/reference number	Study design	Patients	Treatment	Response rates (%)	Survival (%)
Tepper et al. [51]	RCT phase III	56 (SCC, AC)	(1) CDDP/5-FU/50.4 Gy + SX ($n = 30$)	(1) CR 33.3 PR 26.7 SD 6.7 PD 6.7	5-year OS: (1) 39 (95% CI 21–57)
			(2) SX ($n = 26$)	(2) No data	(2) 16 (95% CI 5–33)
Cooper et al. [8]	RCT phase III	123 (SCC, AC)	(1) CDDP/5-FU/50 Gy ($n = 61$)(2) 64 Gy	(1) PD 26 (2) PD 37	5-year OS: (1) 26 (95% CI 15–37) (2) 0
al-Sarraf et al. [69]	RCT phase III (update of RTOG 85-01 trial)	123 (SCC)	(1) CDDP/5-FU/50 Gy ($n = 61$) (2) 64 Gy ($n = 62$)		5-year OS: (1) 27 (2) 0
Wang et al. [70]	RS	35 (SCC, AC)	(1) 5-FU/50.4 Gy ($n = 35$)	CR >50 Gy: 79.2, <50 Gy: 27.3 PR 8.6 SD 5.7 PD 5.7	5-year OS: 18.6 5-year DFS: 22.4
Uno et al. [49]	RS	21 (SCC)	(1) CDDP/5-FU/64 Gy ($n = 14$) (2) CDDP/5-FU/40 Gy + SX ($n = 5$) (3) 64 Gy ($n = 2$)	Initial LCR: 57.9 (including 5 SX patients)	(1) + (2) + (3) 2-year OS: 41 5-year OS: 27
Yamada et al. [47]	RS	27 (SCC)	(1) CDDP/5-FU/66 Gy ($n = 23$) (2) 66 Gy ($n = 4$)	CR 48.1 PR 40.7 SD 11.1 PD 0	(1) + (2) 5-year OS: 37.9
Gkika et al. [71]	RS	55 (SCC, AC, undifferentiated carcinoma)	(1) 56–70 Gy/CDDP/5-FU (RTOG 85-01)[a] NAT: LV/5-FU/CDDP ($n = 25$) (2) 56–70 Gy/CDDP/VP-16 (FLEP)[b] NAT: 5-FU/LV/CDDP/VP-16 ($n = 22$) (3) 56–70 Gy/CDDP-based/irinotecan or taxanes (exact dose is not mentioned) ($n = 8$)	CR 64 RD 26 PD 14.5 PR 10.9	3-year OS: (1) 18 (2) 37 (3) 31
Stuschke et al. [9]	RS	17 (SCC)	(1) 60–66 Gy NAT: 5-FU/LV/VP-16 (FLEP)[c] CRT: CDDP/VP-16 (FLEP)[c] ($n = 11$) (2) 60–66 Gy NAT: LV/5-FU/CDDP CRT: CDDP/VP-16 (FLEP)[c] ($n = 6$)	2-, 3-year LRR 67 ± 14	(1) + (2) 2- and 3-year OS: 24
Burmeister et al. [48]	PCS	34 (SCC, AC)	(1) CDDP 80/5-FU/61.2 Gy ($n = 24$) (2) CDDP 20/5-FU/61.2 Gy ($n = 8$) (3) 5-FU/61.2 Gy ($n = 2$)	CR 91.1 PR 5.9 SD 0 PD 2.9	(1) + (2) + (3) 5-year OS 55 (95% CI 38–74)[d]

Huang et al. [46]	RS	50 (CEC)	(1) 5-FU/mitomycin C or CDDP/54 Gy ($n = 13$) + SX ($n = 6$) (2) CDDP/70 Gy ($n = 22$) (3) RT alone ($n = 9$) (dose unknown)	(1) CR (1-year) 71 CR (2-year) 48 (2) CR (1-year) 64 CR (2-year) 46	(1) 1-year OS: 86 (95% CI 62–95) 2-year OS: 52 (95% CI 30–71) (2) 1-year OS: 69 (95% CI 49–82) 2-year OS: 43 (95% CI 24–60)
Conroy et al. [78]	RCT phase II/III	267 (SCC, AC, ASCC)	(1) Oxaliplatin/LV/5-FU (FOLFOX)/50 Gy ($n = 134$) (2) CDDP/5-FU/50 Gy ($n = 133$)	(1)CR 44 PR 22 SD 11 PD 9 (2)CR 43 PR 22 SD 8 PD 9	3-YR OS: (1) 19.9 (95% CI 10.8–31.0) (2) 26.9 (95% CI 16.9–37.8)
Crosby et al. (2013) [79]	RCT phase II/III	258 (SCC, AC)	(1) CDDP/capecitabine/50 Gy (2 cycles CDDP/capecitabine NAT) ($n = 129$) (2) CDDP/capecitabine/50 Gy + cetuximab (2 cycles CDDP/capecitabine NAT) ($n = 129$)	TFF at 24 weeks: (1) 66.4 (90% CI 58.6–73.6) (2) 76.9 (90% CI 69.7–83.0)	mOS[c]: (1) 25.4 months (95% CI 20.5–37.9) (2) 22.1 months (95% CI 15.1–24.5)
Ma et al. [76]	RCT	102 (SCC)	(1) Paclitaxel/CDDP/59.4 Gy + IFI ($n = 51$) (2) Paclitaxel/CDDP/59.4 Gy + ENI ($n = 51$)	(1) CR (1-year) 90.0 CR (2-year) 80.1 CR (3-year) 80.1 (2) CR (1-year) 92.8 CR (2-year) 92.8 CR (3-year) 85.7	(1) 1-year OS: 100 2-year OS: 87.5 3-year OS: 32.0 (2) 1-year OS: 100 2-year OS: 84.0 3-year OS: 41.3
Tu et al. [75]	RS	36 (SCC)	(1) Paclitaxel/CDDP/60 Gy (IMRT) ($n = 36$)	CR 16.7 PR 33.3 SD 41.7	1-year OS: 83.3 2-year OS: 42.8
Bleiberg et al. [80]	RCT phase II	88 (SCC)	(1) CTx: CDDP/5-FU ($n = 44$) Prior SX ($n = 5$) Prior radiotherapy ($n = 4$) (2) CTx: CDDP ($n = 44$) prior SX ($n = 8$) prior radiotherapy ($n = 6$)	(1) CR 3 PR 32 SD 29 PD 18 Early death 15 Not assessable 3 (2) CR 3 PR 16 SD 38 PD 43 Early death 0 Not assessable 0	(1) 1-year OS: 34 (95% CI 20–48) 2-year OS: 18 (95% CI 7–29) (2) 1-year OS: 27 (95% CI 14–40) 2-year OS: 9 (95% CI 1–17)
Ruppert et al. [81]	RS	57 (SCC, AC)	(1) CDDP/irinotecan/50.4–61.2 Gy (2 cycles CDDP/irinotecan NAT) ($n = 38$) (2) Carboplatin/paclitaxel/50.4–61.2 Gy ($n = 19$)	(1) CR 21.1 (2) CR 31.6	(1)[e] 2-year OS: 40.6 (95% CI 26.9–61.3) (2) 2-year OS: 63.2 (95% CI 44.8–89.0)

Continued

Table 1. *Continued*

Author(s)/reference number	Study design	Patients	Treatment	Response rates (%)	Survival (%)
Ludmir et al. [40]	RS	37 (CEC)	CRT ($n = 37$) RT: 54 Gy (14.4–71) CTx: CDDP/5-FU ($n = 16$), CDDP ($n = 4$), CDDP/VP-16 ($n = 6$), CDDP/paclitaxel ($n = 6$), other ($n = 7$)	CR 5.6	5-year OS: 34.1
Minsky et al. [82]	RCT phase III	236 (SCC, AC)	(1) CDDP/5-FU/64.8 Gy ($n = 109$) (2) CDDP/5-FU/50.4 Gy ($n = 109$)		2-year OS: (1) 31 (2) 40
Zhang et al. [83]	RS	102 (CEC)	CRT ($n = 102$) RT: 60 Gy (50–70) CTx: NAT: CDDP-based ($n = 18$) CRT: 1) docetaxel/CDDP($n = 13$) 2) CDDP/docetaxel ($n = 26$) 3) CDDP/5-FU ($n = 63$)		3-year OS: 39.3

RCT, randomized, controlled trial; SCC, squamous cell carcinoma; AC, adenocarcinoma; CDDP, cisplatin; 5-FU, 5-fluorouracil; SX, surgery; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; CI, confidence interval;TFF, treatment failure free; RS, retrospective study; DFS, disease-free survival; LCR, local control rate; CRT, chemoradiation; NAT, neoadjuvant; LV, leucovorin; VP-16, etoposide; LRR, locoregional recurrence rate; PCS, prospective cohort study; CEC, cervical esophageal cancer; ASCC, adenosquamous carcinoma; MOS, median overall survival; HR, hazard ratio; IFI, involved field irradiation; ENI, elective nodal irradiation; IMRT, intensity-modulated radiation therapy; CTx, chemotherapy; LRC, locoregional control.

[a]RTOG 85-01: CRT: CDDP 75 mg/m^2 (first day of week 1, 5, 8 and 11)/5-FU 1 g/m^2 (first 4 days of week 1, 5, 8 and 11) [7].

[b]FLEP: NAT: LV 300 mg/m^2, VP-16 100 mg/m^2, 5-FU 500 mg/m^2, CDDP 30 mg/m^2 on days 1–3. Second and third course were started at day 22 of the last course. CRT started between days 22 and 28 of last NAT course. CRT: CDDP 50 mg/m^2 days 2 and 8, VP-16 100 mg/m^2 on days 4, 5 and 6 (60 h infusion) [8].

[c]HR: 1.53 (95% CI 1.03–2.27) ($P = 0.035$).

[d]No significant difference between the two regimens in terms of overall and disease-free survival.

[e]HR: 2.42 ($P = 0.022$).

recommended due to treatment-limiting toxicity [79]. Likewise, the randomized phase III RTOG 0436 trial that compared OS between patients treated with dCRT with or without cetuximab [87], and the COG trial, in which esophageal cancer patients who had progressed under chemotherapy were randomly assigned to either gefitinib or placebo [88], did not find an improvement in OS when an anti-EGFR target was added. This is in contrast to the study by Lorenzen et al. [89], which was published before the SCOPE1 trial, but included only 62 patients. They reported a 75% disease control rate in the group randomized to standard chemotherapy combined with cetuximab (CET-CF), compared with 57% in the group randomized to standard chemotherapy alone (CF). This study also found a difference in survival rates, with a median OS of 9.5 and 5.5 months for CET-CF and CF, respectively, and therefore concluded that the addition of cetuximab to standard chemotherapy might be a useful therapeutic approach in patients with advanced (metastatic) esophageal SCC. Recently, the subsequent phase III REAL3 trial had to be closed early due to a lack of efficacy [90]. These findings seem to indicate that the use of cetuximab is not recommended in patients with CEC.

RT used within concurrent treatment regimens for CEC

The standard of care regarding dCRT for patients with esophageal cancer is 50.4 Gy with concurrent chemotherapy. In the case of CEC, there exists some tendency to increase the radiation dose of 60–70 Gy to the primary tumor and ~40–45 Gy to elective lymph node regions, analogous to the treatment of LAHNSCC [91]. The randomized phase III INT-0123/RTOG 94-05 trial investigated the effect of dose escalation from 50.4 to 64.8 Gy of RT combined with chemotherapy in esophageal cancer from all anatomical locations [82]. There was no increase in survival or local/regional control for the high-dose arm. In CEC, there has been a tendency to use higher doses of radiation than the standard dose of 50.4 Gy, up to 66–70 Gy [9, 47, 48, 55, 83, 92]. In retrospective studies, there are some indications that higher dose of radiation might be associated with improved outcome in esophageal cancer; Zhang et al. [93] investigated local disease control and survival rates in patients with stage II–III esophageal cancer treated either with high-dose RT (>51 Gy) or with low-dose RT (≤51 Gy) and found a positive correlation between radiation dose and locoregional control rate and survival. Comparable results regarding the association between a higher radiation dose and survival were published by Sun [94]. On the other hand, Huang et al. [46] concluded that when using conventionally fractionated RT (70 Gy) rather than hypofractionated RT (54 Gy), the addition of prophylactic nodal RT and a change to high-dose cisplatin chemotherapy did not result in improved outcome in CEC patients. Currently, the ARTDECO study, in which differences in local tumor control, survival and grade 3 and 4 toxicity are measured between patients with inoperable esophageal cancer treated with a total RT dose of 61.6 Gy in combination with carboplatin/paclitaxel and in patients with similar tumor characteristics treated with a total RT dose of 50.4 Gy with the same concurrent chemotherapy regimen, is ongoing [95].

Administering an adequate RT dose to the tumor is often challenging because of the close proximity of the cervical esophagus to vital structures such as the spinal cord and lungs. Modern RT techniques, such as intensity-modulated radiation therapy (IMRT) and simultaneous integrated boost (SIB), in which the intensity of the radiation can be changed during treatment, enable a higher dose to the tumor and a reduced dose to adjacent structures. Studies suggest that these techniques may be useful in the treatment of CEC [75, 91, 96, 97]. Volume-modulated arc RT, a rotational radiation treatment technique, allows to deliver a more conformal dose to the tumor and improved sparing of nearby organs at risk, providing an alternative CEC treatment option [98, 99].

No consensus has been reached so far regarding elective lymph node irradiation (ENI). According to some authors, the omission of ENI did not have a significant effect on the failure rate of non-irradiated lymph nodes and OS, but would delay cervical nodal progression [76, 100, 101], while others do recommend elective irradiation of neck and upper mediastinal lymph node stations [102–104]. Patients who have not been treated with ENI might need salvage treatment more frequently than those treated with ENI. However, the latter group of patients might experience more frequently and more severe treatment-related toxicity, because of the larger radiation field [76, 105]. There are no guidelines recommending the treatment of paratracheal lymph nodes, despite the fact that the lymphatic drainage of the cervical esophagus is primarily to the paratracheal nodes and 43% of CEC patients have paratracheal lymph node metastases [106, 107].

local disease control rate and survival

The local disease control rate depends mainly on the depth of tumor invasion, lymph node status and type of treatment [8, 46, 47, 49, 76, 81]. Locoregional recurrence rates in CEC patients treated with dCRT, range from 13.7% to 42% within 0–8.7 years [46, 76, 101] compared with 51%–74.1% within 0–4 years in patients treated with RT alone [47, 100] and 15.6%–48.6% within 0–15 years in surgically treated patients [53, 56, 63, 66].

Local failure is an important prognostic factor for survival. Uno et al. [49] found that after dCRT, none of the patients with initial local failure as determined by endoscopic examination, survived more than 20 months compared with 2- and 5-year survival rates of 60% and 40%, respectively, in patients with initial local control. Local recurrences can be treated by salvage surgery, which potentially has a high morbidity rate, but is the only chance for relatively long-term survival [108]. Otherwise, palliative treatment options have to be considered.

Survival rates of patients with CEC remain poor, due to a delayed diagnosis, poor performance status of many patients, particularly anatomic characteristics of the viscera associated with high malignancy potential, frequent occurrence of locoregional and distant metastases and 12%–30% increased risk of synchronous or metachronous lesions [9, 46, 109]. Yamada et al. [47] found that performance status and tumor length (≤6 or >6 cm) were factors that were significantly related to survival.

discussion and recommendations

CEC is a very rare disease and often locally advanced at the time of diagnosis resulting in limited locoregional disease control and poor survival. Dysplasia is a known precursor lesion of SCC [11–14] and can be diagnosed by endoscopic biopsy improving the detection

of patients at high risk of malignant transformation. Detection of genetic changes could also be an effective manner of diagnosing early tumors, but unfortunately the molecular changes in CEC and its precursor lesions remain to be clarified.

Owing to the presence of locally advanced disease at the time of diagnosis and the cancer being close to vital structures such as the larynx, upper airway and spinal cord, non-surgical management seems to be the current preferred therapeutic option. Our review suggests that the best results with respect to locoregional disease control and survival can be achieved with dCRT, however, at the costs of higher incidence of toxicity compared with RT alone. Despite the introduction of dCRT, survival rates remain relatively low and patients require optimal clinical support to retain food intake and exercise to maintain good quality of life and to achieve best patient outcome [110].

Several different chemoradiation schedules and techniques have been investigated in the past, but no consensus has been reached regarding the optimal treatment for CEC patients. High-dose RT (60–70 Gy) and concurrent cisplatin, similar to the established treatment regimen in locally advanced head and neck SCC (HNSCC), could be an option; however, there is no level I evidence to support this approach. Although thoracic esophageal SCCs, defined by being localized caudal of the suprasternal notch, develop only few centimeters distal from cervical SCC, the commonly used dCRT schedule for thoracic esophageal SCCs consists of a lower radiation dose (50.4 Gy) combined with cisplatin/5-fluorouracil (5-FU), oxaliplatin/5-FU or carboplatin/paclitaxel regimen [6]. A possible rationale for the use of a lower radiation dose is the very close proximity of vital structures in the mediastinum and the lungs. In the CROSS study on preoperative chemoradiation, Van Hagen et al. [85] found a pCR of 49% after neoadjuvant chemoradiation (41.4 Gy and concurrent carboplatin/paclitaxel) in esophageal SCC of which 2% were located in the proximal third of the esophagus. The study by Blom et al. [86] suggests this regimen is as effective as dCRT consisting of an RT dose of 50.4 Gy and cisplatin/5-FU, and has a more favorable toxicity profile [86]. Therefore, we could hypothesize that the currently used high radiation dose in CEC is potentially unnecessary as it does not seem to result in higher complete response (CR) rates and outcome in SCC of the lower esophagus [82]. While the use of a high RT dose of 61.6 Gy concurrently with chemotherapy in patients with inoperable/irresectable esophageal cancer is currently studied in the ARTDECO study [95], it could also be of potential interest to study the effect of lower dose RT in CEC alone, which may be accompanied by lower toxicity rates.

However, high toxicity rates in CEC patients [8, 9] might not only be a result of a high radiation dose, but could also be an effect of a relatively large radiation field [105], especially when combined with concurrent chemotherapy. A reduction in toxicity rates may be expected by applying modern state-of-the-art radiation techniques like IMRT, lowering the dose to normal structures. However, the current literature is inconclusive; some studies propose that only an irradiation volume covering the gross volume is appropriate and accompanied with lower toxicity rates [76, 100], while others recommend consideration of ENI, especially in the case of nodal stage N1 and higher [5, 101]. Given the reported incidence of metastases in surrounding lymph nodes (~50% of all CECs), especially in the neck (levels II, III and the supraclavicular lymph nodes) and upper mediastinum [103, 106], we recommend that ENI of cervical, supraclavicular and paratracheal lymph nodes should be considered in CEC invading the hypopharynx. In more distally located CEC, which are located close to the suprasternal notch, ENI of mediastinal and paratracheal lymph nodes should be considered [104]. We anticipate that radiation techniques will improve in the near future enabling the discovery and use of newer techniques (e.g. dose painting, in which a non-uniform radiation dose distribution is applied to the target volume based on functional or molecular imaging), where only the radiation dose needed for adequate locoregional disease control is applied, hopefully minimizing the rate of adverse events.

With respect to systemic therapy, a cisplatin-based schedule is currently often used, since this has shown to be effective in the treatment of HNSCC. Current guidelines are inconclusive regarding the most adequate chemotherapy treatment regimen and cisplatin/5-FU, oxaliplatin/5-FU or carboplatin/paclitaxel are equally recommended [5]. Since the combination of carboplatin and paclitaxel is proven to be effective with acceptable adverse event rates in the (neoadjuvant) treatment of lower esophageal SCC [81, 85], future studies might want to compare the combination of carboplatin/paclitaxel with current cisplatin-based schedules. When molecular profiles of CEC including driver oncogenes and potential therapeutic targets will become apparent, the use of targeted agents, e.g. as radiosensitizers, might become worthwhile to investigate in future clinical trials. Furthermore, future research should focus on identifying a dCRT design with adequate survival and acceptable toxicity rates. It is of clinical interest to establish whether CECs are best treated with head and neck cancer protocols or regimens established in lower esophageal SCC. As patients with CECs treated according to the head and neck cancer protocol have a worse prognosis compared with patients with HNSCC [72, 74, 107], it could be interesting to study the potential underlying molecular differences between these two types of SCCs.

Recommendations

Future studies that focus on early detection of CEC precancerous conditions, molecular changes and on identification of biomarkers for detection of early disease or as targets for radiosensitizers would be desirable for the future. However, since CEC is rare in Western countries, it is improbable that screening will impact on this disease outside high-risk areas

Taking the survival data and toxicity profiles of the different dCRT regimens in consideration, the optimal treatment regimen for CEC patients is not yet defined

Future studies should focus on whether CEC is best treated according to a head and neck cancer or esophageal cancer protocol

We recommend that ENI of cervical, supraclavicular and paratracheal lymph nodes should be considered

Finally, one should be aware that patients will need optimal clinical support to retain food intake and exercise to optimize patient outcome and quality of life

conclusion

CEC remains unchartered territory for many practising physicians. Treatment of cancers at this site is often difficult because of the cervical location and most tumors are locally advanced

with invasion of surrounding vital structures. To improve survival outcome and reduce morbidity and mortality rates, future studies should focus on earlier detection of these cancers and improving treatment design by investigating innovative radiation schedules and identifying the optimal backbone of systemic therapy.

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