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Practice of radiation therapy for squamous cell esophageal cancer in Austria – a survey on behalf of the ÖGRO-GIT

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Abstract

Background To evaluate the patterns of care for chemoradiation for squamous cell carcinoma (SCC) of the esophagus in Austria.

Methods An anonymous questionnaire (57 items) was sent to all 14 public Austrian radiation oncology departments. Results were analyzed descriptively and compared to the latest versions of two major international guidelines.

Results The response rate was 93%. The median number of patients per center per year was 13 (5–30). All centers reported pretreatment multidisciplinary evaluation. Work-up generally included endoscopy and cross-sectional imaging of chest/abdomen (mainly CT). EUS was used by 61% and PET-CT by 54%. Functional lung testing was reported only by 46%. No center reported the prophylactic placement of feeding tubes or stents. All centers employed IMRT in conventional fractionation with (mostly daily) IGRT. Weekly Carboplatin/Paclitaxel was the preferred chemotherapy regimen in both neoadjuvant (85%) and definitive (69%) settings, although only SCC were included. Neoadjuvant treatment was generally preferred for locally advanced stages in suitable patients, except for those with cervical tumor locations. Median doses to the primary tumor were 41.4 Gy (41.4–50.4 Gy) in the neoadjuvant and 57.7 Gy (50.4–66 Gy) in the definitive setting. Target volumes varied considerably (roughly half of the centers preferred involved vs. elective nodal irradiation). Definition of main OARs was uniform, but dose constraints to OAR differed widely. Intensive follow-up was performed in 77% for at least 5 years.

Conclusion The use of advanced staging procedures, prescription of total (boost) doses in the definitive setting, the issue of involved vs. elective nodal irradiation, and dose constraints to OARs were identified as major areas of disagreement between Austrian centers and inconsistencies with major guidelines.

Keywords Esophageal cancer, Chemoradiation, Survey

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Background

Esophageal cancer is the sixth most common cause of cancer related mortality [1]. Histologically, two main subtypes are distinguished: squamous cell carcinoma (SCC) and adenocarcinoma (AC). These subtypes differ in terms of risk factors, main locations (upper vs. lower esophagus), and treatment strategies.

In small and localized tumors, endoscopic resection (ER) or surgery represents the standard of care. However, in locally advanced esophageal cancer (EC), the outcomes with surgery alone remain limited [2, 3]. Therefore, multidisciplinary treatment strategies including neoadjuvant chemoradiation (n-CRT) or chemotherapy have been implemented over the last decades and resulted in increased complete resection rates (R0) and improved overall survival (OS) [2–11]. While n-CRT is currently favored for SCC patients, neoadjuvant chemotherapy alone appears superior in adenocarcinoma based on the ESOPEC [11]. For patients with underlying comorbidities or locally inoperable tumors (especially cervical EC), definitive chemoradiation (d-CRT) is also a widely accepted curative-intent treatment option [12]. The introduction of immunotherapy further represents a promising new treatment that improves prognosis in several patient subgroups [13]. Regarding optimal treatment, most randomized or prospective trials have included both tumor subtypes, which must be considered when interpreting the results [2–4, 14, 15]. Moreover, not every question can be addressed easily by randomized trials. Therefore, several issues in radiation therapy for EC remain unsolved, likely contributing to differences in real-life patient care. Identifying these areas of disagreement and accordance with international guidelines may provide valuable insights for future study design, guideline development and adjustments in national health systems. A centralized care system like in Austria with only 14 radiation oncology institutions offers the possibility to analyze nationwide patterns of care more easily. We therefore conducted a survey regarding the patterns of care for patients with esophageal SCC treated with radiation therapy though the gastrointestinal working group of the national radiation oncology society (ÖGRO-GIT). The analysis was limited to SCC tumors because treatment paradigms for adenocarcinomas have shifted away from radiation therapy. The results were compared with recent versions of major international guidelines [16, 17] to identify potential areas of controversies and guide the development of future studies and harmonization of care across Austrian centers.

Methods

All 14 Austrian radiation oncology institutions were invited to participate in the survey (clinical trial number is not applicable), which focused exclusively on the treatment of non–metastatic SCC. The survey included a total of 57 questions, with either predefined choices of answers or the option for the centers to provide a written description of their approach (see supplementary material). Four questions addressed general issues of the radiation oncology department, 15 covered indications and work-up, 23 questions focused on radiation treatment planning, target volume definition, dose and fractionation, dose constraints and radiation delivery and 11 questions pertained to concomitant chemotherapy regimens. The remaining 4 questions focused on the follow-up care. The survey was hosted on an online platform allowing for anonymous participation. Numerical variables were analyzed descriptively using IBM SPSS statistics Version 24 and results were presented as median and range. Free-text responses were analyzed separately. Results were descriptively compared to the actual versions of multidisciplinary guidelines from the US [17] and Europe [16] in the absence of a multidisciplinary Austrian guideline.

Results

Response rate/general information

Thirteen out of 14 centers responded, resulting in a response rate of 93%. Five of them are affiliated with university hospitals. The median number of patients treated with curative intent using neoadjuvant or definitive CRT per year per institution was 13 (5–30). Written standard operating procedures (SOP) are available in 61%. Clinical trials currently recruiting patients were reported by two centers (both participating in the SKYSCRAPER 07 trial, NCT 04543617).

Work-up and treatment algorithm

Esophagoduodenoscopy (EGD) with biopsy is performed in all centers to confirm the diagnosis, while endoscopic ultrasound (EUS) is used in 61%. For staging, all centers conduct cross-sectional imaging, either thoracic and abdominal computed tomography (CT) or as part of PET-CT (54%). Head and neck examination (ENT examination) and/or panendoscopy is performed in 85% of the centers in case of cervical cancer, 69% conduct bronchoscopy (always or when suspected infiltration is present) in patients with suprabifurcal tumor localization. Only 46% request pretherapeutic pulmonary function testing.

No center reported the routine prophylactic use of percutaneous feeding tubes (PEG), stents or fiducials, though some centers indicated their use on an individual basis. PEG tubes are inserted before treatment if food intake is significantly restricted (54%) or if there is a risk of aspiration (31%). Stents are inserted on an individual basis in two centers, while three centers consider it a contraindication for curative CRT. Fiducials are inserted endoscopically in 46% as an individual decision, usually

Table 1 Examinations for work-up and follow-up

	Examination for work -up		Examination for follow up	
	n	%	*n*	%
Esophagoduodenoscopy	13	100	12	92
Endoscopic ultrasound	8	61	2	15
EBUS + biopsy of LN	4	31		
Bronchoscopy (in suprabif. C.)	9	69		
Pulmonary function test	6	46		
ENT examination (in cervical c.)	11	85		
Panendoscopy (in cervical c.)	4	31		
Abdominal CT	12	92	10	77
Chest CT	11	85	12	92
PET-CT	7	54	2	15
Prophylactic PEG tube	0	0		
Swallow examination	0	0		
Tumor marker (SCC)	1	8		
Quality of life survey	0	0	2	15

n: number of centers, %: percentage, EBUS: endobronchial-ultrasound, LN: lymph nodes; ENT: ear-nose-throat, CT: computed tomography, PET-CT: positron-emission tomography computed tomography, PEG: percutaneous feeding tube, SCC: squamous cell carcinoma antigen

Table 2 Treatment algorithm in Austrian centers TNM Stage n/% Treatment

TNM Stage	n/%	Treatment
T1b N0 (12/13)	*n* = 4 (31)	1. Endoscopic en bloc resection
	n = 6 (46)	2. Esophagectomy
	n = 2 (16)	3. Individualized (1 or 2)
T2 N0 (12/13)	*n* = 6 (46)	1. Esophagectomy
	n = 2 (16)	2. Neoadj. CRT + Esophagectomy
	n = 4 (31)	3. Individualized (1 or 2 or def. CRT)
T3 N0 (12/13)	*n* = 9 (69)	1. Neoadj. CRT + Esophagectomy
	n = 1 (7)	2. Definitive CRT
	n = 2 (16)	3. Individualized (1 or 2)
T1b-2 N+ (12/13)	*n* = 9 (69)	1. Neoadj. CRT + Esophagectomy
	n = 1 (8)	2. Definitive CRT
	n = 2 (16)	3. Individualized (1 or 2)
T3 N+ (13/13)	*n* = 9 (69)	1. Neoadj. CRT + Esophagectomy
	n = 1 (8)	2. Definitive CRT
	n = 3 (24)	3. Individualized (1 or 2)
T4a N0/N+ (13/13)	*n* = 6 (46)	1. Neoadj. CRT + Esophagectomy
	n = 3 (24)	2. Definitive CRT
	n = 4 (31)	3. Individualized (1 or 2)
T4b N0/N+ (13/13)	*n* = 2 (16)	1. Neoadj. CRT + Esophagectomy
	n = 6 (46)	2. Definitive CRT
	n = 3 (24)	3. Individualized (neoadj CRT + S or def. CRT)
	n = 1 (8)	4. Upfront Chemotherapy
	n = 1 (8)	5. Chemotherapy or def. CRT

n: number of centers, %: percentage, CRT: chemoradiotherapy, S: surgery, neoad.: neoadjuvant, def.: definitive

if the tumor is not visible on cross-sectional imaging. Detailed pretreatment procedures used for diagnostic work-up are listed in Table 1.

Treatment recommendations are routinely made by a multidisciplinary tumor board in all centers. Depending on tumor stage and localization, preferred treatments are summarized in Table 2. Definitive CRT is usually recommended for cervical tumor sites ($n = 10$, 77%) and/or aged ≥ 70 years ($n = 2$, 16%).

For patients undergoing n-CRT, restaging to assess tumor response is performed in all centers. Half of the centers organize restaging at the end of n-CRT, while the other half perform restaging 2–12 weeks following n-CRT. Restaging procedures always include a CT scan (CT scan only 46%, CT as part of a PET-CT scan 54%), and 61% additionally perform an endoscopy. Routine use of EUS or biopsies was reported only by one center each.

After restaging, 85% of centers discuss the next steps in a multidisciplinary tumor board again. Patients with clinical and/or radiological complete response (CR) will proceed to surgery in 69%. Only one center would immediately switch to a "watch and wait" strategy, while three centers (23%) would continue CRT up to an increased total dose. The median time to scheduled surgery is usually 6 weeks (range 4–12 weeks) from the last day of CRT. If patients are judged unsuitable for resection after restaging, 69% of the centers would continue with CRT to an increased total dose while 31% would proceed with systemic therapy only.

Simulation/treatment planning

Motion management strategies, such as 4D-CT scanning ($n = 4$) or deep-inspiration breath hold ($n = 1$), are employed in 5 centers in addition to the free-breathing treatment-planning CT. These strategies are used either for all patients ($n = 1$) or only for those with infrabifurcal tumor localization ($n = 4$). Oral or intravenous contrast agents are used in 31% and 38% of the centers, respectively. Patients are required to fast in 54% of centers, either for all patients or only for those with distal localization.

Target volume definition/dose prescription

Since target volumes may depend on clinical (in particular nodal) stage, we asked participants to indicate their choice of lymph node regions for the CTV in cN0 and cN+ situations based on the tumor localization (cervical, thoracic supra -/ infrabifurcal and abdominal) and treatment intention (neoadjuvant vs. definitive). Additionally, we requested information on the general target volume concept used, defined as follows:

- Strict INI (strict involved nodal irradiation): Tumor with positive nodes plus a safety margin in separate volumes.
- INI (involved nodal irradiation): Tumor with positive nodes plus safety margin in a single volume.
- ENI (elective nodal irradiation): Tumor, positive nodes and elective nodal regions in one volume, see Fig. 1.

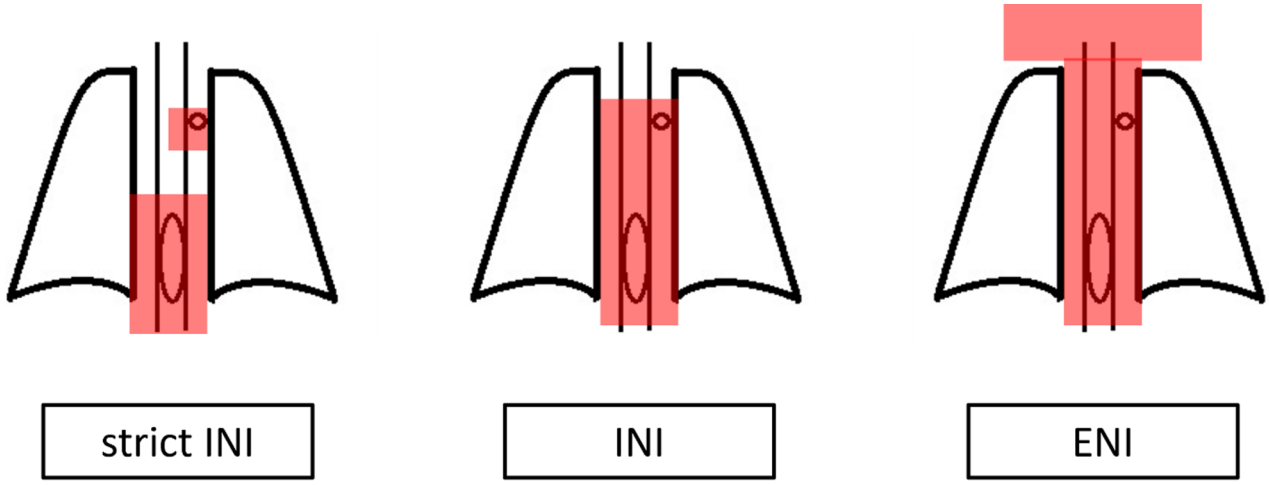

Fig. 1 Strict INI: tumor with positive nodes plus safety margin in separate volumes, INI: tumor with positive nodes plus safety margin in a single volume, ENI: tumor, positive nodes and elective nodal regions in one volume

Table 3 Distribution of target volume concepts

	Neoadjuvant CRT	Definitive CRT
cN0	*n* = 7 PT + SM	*n* = 6 PT + SM
	n = 6 ENI	*n* = 7 ENI
cN+	*n* = 1 strict INI	*n* = 4 strict INI
	n = 6 INI	*n* = 9 INI
	n = 6 ENI	*n* = 0 ENI

cN0: clinically node-negative disease, cN+: clinically node-positive disease, n: number of centers including the respective region, CRT: chemoradiation, PT + SM: primary tumor plus safety margin, strict INI: tumor with positive nodes plus safety margin in separate volumes, INI: tumor with positive nodes plus safety margin in a single volume, ENI: tumor, positive nodes and elective nodal regions in one volume

Table 4 Elective nodal volumes in cN0/cN+ patients for neoadjuvant treatment setting

Elective nodal region	Tumor localization			
	Cervical *n* (%)	Thoracal suprabif. *n* (%)	Thoracal Infrabif. *n* (%)	Abdominal *n* (%)
Bilateral cervical nodes	6 (100)	6 (100)	0	0
Bilateral supraclavicular nodes	6 (100)	6 (100)	1 (17)	0
Paraesophageal suprabif. nodes	5 (83)	5 (83)	6 (100)	0
Paraesophageal infrabif. nodes	1 (17)	1 (17)	6 (100)	6 (100)
Perigastric nodes	0	0	3 (50)	5 (83)
Coeliac nodes	0	0	3 (50)	6 (100)

cN0: clinically node-negative disease, cN+: clinically node-positive disease, n: number of centers including the respective region, %: percentage, ENI: tumor, positive nodes and elective nodal regions in one volume, infrabif.: infrabifurcal, suprabif.: suprabifurcal

In node-negative cases, about half of the centers treated only the primary tumor with a safety margin (neoadjuvant 54%, definitive 46%), while the others included elective nodal volumes as well (neoadjuvant 46%, definitive 54%).

In node positive cases, one center indicated to use strict INI, 46% used INI and 46% used ENI for neoadjuvant treatment, while no center indicated the inclusion of elective nodal regions in definitive treatment. For further details see Tables 3, 4 and 5.

We also asked participants to specify the total and single doses for each treated region (elective nodal areas if any, suspicious nodes, and primary tumor) in neoadjuvant and definitive treatment setting.

Neoadjuvant setting (cN0/cN+): Elective lymph node (LN) regions are irradiated in 6 centers in both cN0 and cN+, situations, with total doses ranging from 41.4 to 50 Gy (median 45 Gy) delivered in conventional fractionation (single dose 1.8–2.0 Gy). Only 1 center applies a simultaneous integrated boost (SIB) to macroscopic tumor sites, resulting in a local dose escalation to 49.92 Gy while treating all other regions to 41.4 Gy. One additional center reported a broad dose range of 41.4–60 Gy.

Definitive setting (cN0/cN+): Only 7 centers (54%) reported the use of ENI in cN0 situations, while none plied ENI in cN+ cases. Total doses to elective regions ranged from 45 to 50.4 Gy (median 50 Gy) using conventional fractionation (single dose 1.6–2.0 Gy, median 1.8 Gy). Dose escalation to the primary tumor is generally performed by 85% ($n = 11$), either via a sequential (61.5%) or simultaneous integrated (SIB) (23%) external beam photon boost. Dose escalation to suspicious LNs is also performed in 69% ($n = 9$), with 3 centers using SIBs and the remaining 6 applying sequential boosts. These approaches result in higher absolute tumor and LN doses compared with neoadjuvant irradiation (tumor: 50–66 Gy, median 57.7 Gy, LN: 50–66 Gy, median 54 Gy). All institutions use conventional or slightly accelerated fractionation for tumor and LN boosts (single doses 1.8–2.2 Gy).

Table 5 Elective nodal volumes in cN0 patients for definitive treatment setting

Elective nodal region	Tumor localization			
	Cervical *n* (%)	Thoracal suprabif. *n* (%)	Thoracal Infrabif. *n* (%)	Abdominal *n* (%)
Bilateral cervical nodes	7 (100)	1 (14)	0	0
Bilateral supraclavicular nodes	7 (100)	6 (85)	1 (14)	0
Paraesophageal suprabif. nodes	6 (85)	7 (100)	6 (85)	0
Paraesophageal infrabif. nodes	2 (28)	6 (85)	6 (100)	7 (100)
Perigastric nodes	0	1 (14)	3 (43)	6 (85)
Coeliac nodes	0	0	1 (14)	7 (100)

cN0: clinically node-negative disease, cN+: clinically node-positive disease, n: number of centers including the respective region, %: percentage, ENI: tumor, positive nodes and elective nodal regions in one volume, infrabif.: infrabifurcal, suprabif.: suprabifurcal

Table 6 Outlined organs at risk (OAR) and specific dose constraints in Austria and in NCCN guidelines

Organ at risk	Outlined (Austria)		Specific Constraints (Austria)		NCCN [2]
	n	%		*n*	
Heart	13	100	Mean V20–40	6 8	Mean < 30 Gy (26 Gy) V30 < 30%
Lung bilateral	13	100	Mean (12–20 Gy) V20 (20–40%)	8 9	Mean < 20 Gy V5 < 50% V10 < 40% V20 < 20% V30 < 15% V40 < 10%
Spinal cord	13	100	Dmax (40–50 Gy)	13	Dmax < 45 Gy
Larynx	8	61	D max (40–66 Gy) Mean (40–50 Gy)	3 4	Not defined
Stomach	12	92	D max (40–60 Gy) Mean (30–45 Gy)	10 5	D max < 54 Gy Mean < 45 Gy
Liver	12	92	Mean (18–30 Gy)	10	V30 < 33% Mean < 25 Gy
Small bowel	11	85	D max (37–54 Gy) V15–45	9 4	D max 54 Gy V45 < 193ccm

n: number of centers, Gy: Gray, Dmax: Maximum point dose, Vx: volume receiving less than x Gy

Regarding target volume definitions, centers were specifically asked to report axial and longitudinal PTV margins for the primary tumor and suspicious LNs in cases of dose escalation. When both (CTV and PTV) margins were reported, these margins were summed. For the primary tumor, the median axial and longitudinal margins were 15 mm (range 5–25 mm) and 21 mm (range 5–50 mm), respectively. For suspicious LNs, margins were usually isotropic and smaller, with a median of 12.5 mm (range 6–20 mm).

Treatment procedure

All centers reported to use volumetric intensity-modulated radiation therapy (VMAT). Participants were asked to provide information on routinely contoured organs at risk (OAR) and the application of specific dose constraints (see Table 6).

Some form of image-guidance is performed by all centers (100%), but technique and timing vary. Most departments indicate daily imaging ($n = 8$, 61%), which is performed using cone-beam CT (CBCT) in four and portal imaging in four institutions. In the latter group, portal imaging is complemented by weekly CBCT in 3 institutions. 5 centers perform daily CBCT during the first 3–5 treatment fractions and subsequently adapt the IGRT strategy based on the initial results.

Systemic chemotherapy

No center reported the use of induction chemotherapy. All institutions indicated the use of concurrent chemotherapy regimes in neoadjuvant and definitive settings. In n-CRT, Carboplatin/Paclitaxel according to the CROSS trial is administered in 11 centers (85%), while one center reported using Cisplatin/5-Fluorouracil (5-FU). Carboplatin/Paclitaxel is also the most frequently used regimen in d-CRT ($n = 9$), with only 3 centers still applying Cisplatin/5FU. In both settings, 1 center each reported using either 5-FU/Capecitabine or Cisplatin as monotherapy.

Adjuvant chemotherapy is given only in 2 centers (both using Cisplatin/5 FU), although both centers indicated the use of Carboplatin/Paclitaxel during radiotherapy.

Systemic therapy is administered in the radiation oncology department in 69% and in the medical oncology department in 31% of the centers.

Additive immunotherapy with nivolumab after d-CRT is offered in 3 centers: either individually in cases of residual tumor in one center or as part of the SKYSCRAPER 07 trial (NCT 04543617) in two centers. After n-CRT, additive immunotherapy is given in 12 centers for patients without pCR or with R1/2 resections ($n = 9$), based on the CheckMATE 577 study [13].

Regarding treatment logistics, only two centers (15%) perform CRT entirely on an outpatient basis. Eight centers (61%) offer hospitalization in the event of major side effects, while 3 centers (23%) treat all patients as inpatients.

Follow-up

Specific follow-up visits in the radiation oncology department are offered in 12 centers (93%) and are accompanied by follow-up visits in the medical oncological department in 11 centers. Exclusive follow-up in the surgical department is provided by one center, while another performs follow-up only in the radiation oncology department.

Follow-up is offered regularly for 5 years in 10 centers (77%) and for 10 years in 2 centers; one institution did not answer this question. Visits are scheduled every three months during the first year in all institutions, every 3–6 months in the second year, and every 6–12 months in the third year in 92% of all centers. The examinations included into the follow-up visits are listed in Table 1. In case of incomplete clinical remission after d-CRT, 85% of centers perform biopsies to rule out residual disease three months after the end of radiation therapy. In one center, biopsies are performed at six months, while one center never performs biopsies in this context.

Discussion

CRT is a commonly used treatment approach in esophageal SCC, either as neoadjuvant or as definitive treatment. It results in increased complete resection rates (R0) and improved OS compared to surgery alone and represents the standard of care for inoperable patients based on randomized trials [2, 4–7]. However, beyond the therapeutic strategy itself, several aspects of treatment lack general consensus. Topics like work-up, dose and fractionation, target volumes or chemotherapy regimens are particularly affected, also because not every relevant question can be addressed within randomized trials. This may lead to variations in the patterns of care across the population. With its "centralized" healthcare system with only 14 centers covering the radiotherapeutic care of roughly 9 million inhabitants, Austria offers a good opportunity to evaluate such patterns of care on a nationwide level. We therefore assessed areas of agreement and disagreement among centers using a national survey and compared current practice with the recommendations of major international guidelines, namely NCCN [17] and ESMO [16] in its latest version.

With a response rate of 93%, the present survey provides a complete and representative overview of the current clinical practice, clearly outperforming response rates reported in similar studies from other countries.

Work-up

Multidisciplinary discussion prior to treatment is routinely performed in all Austrian institutions as recommended by both guidelines [16, 17]. Moreover, we observed a high level of agreement regarding the most important staging procedures: CT Staging (either alone or as part of a PET-CT scan) and endoscopy with biopsy are used in all institutions on a regular basis [16, 17].

In contrast, PET-CT itself is performed for staging in only 54% of centers (possibly due to limited access) although it is recommended by NCCN [17] for both neoadjuvant and definitive treatment (if available) and by ESMO [16] for neoadjuvant treatment planning. PET-CT may offer advantages in staging accuracy, patient stratification, and target volume delineation. A systematic review reported, that PET-CT outperformed other staging modalities in detecting distant metastasis with a sensitivity of 69%–81% and a specificity of 91%–93% [18], thus preventing several patients from undergoing aggressive local treatments. Moreover, several retrospective studies have demonstrated clear associations of changes in FDG-PET-CT parameters (e.g. SUVmax, MTV, or TLG) and treatment response and/or OS after n-CRT [19–22] or d-CRT [21, 23,24, 25], which may guide treatment decisions even during therapy [22]. In addition, PET-CT scan can be helpful in target volume delineation during radiotherapy planning [18, 26, 27].

The use of EUS, bronchoscopy (at least for supra- or bifurcal tumor localizations) and pretreatment pulmonary function testing appears to be underrepresented in Austrian institutions. Only 61% perform EUS in addition to endoscopy, although it is strongly recommended in neoadjuvant settings and at least conditionally recommended in definitive settings by both guidelines [16, 17].

EUS seems valuable for patient stratification and radiotherapy planning, demonstrating very high sensitivity (82–92%) and specificity (97–99%) for T-stage differentiation, including the detection of invasion into surrounding organs (T4 stage) [28–30]. Moreover, EUS offers excellent sensitivity (up to 97%) for detecting nodal involvement, especially when combined with fine needle aspiration biopsy, thereby guiding treatment stratification from ER to multimodal approaches [30]. With regard to RT treatment planning, EUS may further help in defining tumor length and suspicious lymph nodes [28].

Only 69% of Austrian institutions routinely perform pretreatment bronchoscopy for tumors at or above the tracheal bifurcation to rule out direct airway invasion with an increased risk for fistula/perforation during CRT, despite recommendations in both guidelines [16, 17].

Only 46% of the Austrian institutions assess pulmonary function prior to initiating multimodal treatment, although this is recommended by the ESMO-guidelines [16]. Interestingly, NCCN guidelines recommend pulmonary function testing only when surgery is being considered [17]. Pulmonary function testing enables risk evaluation of pulmonary outcome after CRT and/or surgery and is essential to determine appropriate dose constraints for RT planning. Consequently, it was mandatory

in most recent multimodal treatment protocols incorporating radiation [2, 3, 15].

ENT examination is performed in 85% of all Austrian centers for cervical tumor localizations as recommended in the ESMO guideline [16] for all SCC. Interestingly, the NCCN guidelines [17] do not include such a recommendation, despite a roughly 7% pooled synchronous and metachronous prevalence of head and neck cancer among EC patients according to a meta-analysis of Asian trials [31].

Nutritional assessment and counselling prior to therapy are recommended in both guidelines [16, 17], as weight loss is associated with increased surgical risk, impaired quality of life and poor survival in advanced disease [32]. Although this topic was not explicitly addressed in our survey, it was subject of a free-text field. As only one center reported its routine implementation, this represents an area with potential for improvement in Austrian institutions. Prophylactic PEG tube insertion is suggested in both guidelines [16, 17] for operable patients and, according to the NCCN guideline [17], for patients with cervical tumors undergoing d-CRT. In contrast, Austrian centers generally reserve PEG tube placement for patients who develop impaired oral intake (54%) or aspiration (31%) during treatment. Similarly, esophageal stent placement is performed only by 2 centers on an individual basis, while 3 centers consider it a contraindication for CRT. These practices are in line with ESMO, NCCN and European Society of Gastrointestinal Endoscopy (ESGE) recommendations, which restrict stent placement mainly to palliative settings [16, 17, 33]. Although data regarding the facilitation of CRT-related complications is conflicting [34], stent placement may worsen prognosis without improving on nutritional status [16, 33, 35, 36].

Treatment algorithm

T1/T2 N0

Good concordance with major international guidelines was observed regarding treatment recommendations for treatment of T1N0 squamous-cell EC, as all centers recommended either ER or esophagectomy [16, 17]. In T2 N0 tumors, 46% recommended esophagectomy, 16% n-CRT followed by esophagectomy and 31% favored an individual decision between both approaches based on patient- and tumor-related factors. In contrast, both guidelines recommend primary esophagectomy, based on the lack evidence for an OS benefit with n-CRT in this stage. Noteworthy, the NCCN guideline prefer n-CRT in the presence of additional risk factors and ESMO advocates at least individualized discussion. ESMO further proposes to discuss each case in a multidisciplinary team with careful consideration of potential risks and benefits. Patients unable or unwilling to undergo surgery should be treated with d-CRT [16]. Moreover, both guidelines, as well as the majority of Austrian centers (77%), recommend d-CRT for EC with cervical localization even in early-stage disease.

T3 N0/T1b-3 N + and T4/N+

Since the publication of the CROSS trial, n-CRT with carboplatin and paclitaxel followed by surgery is considered the standard of care in advanced but resectable esophageal SCC, based on the demonstration of improved locoregional control (LC) and long-term OS compared to surgery alone [3, 37, 38]. Although only patients with clinical stage T1N1 or T2- N0-1 were eligible for the CROSS trial [2], both guidelines recommend n-CRT followed by surgery also for T4N0-N+ disease, provided that tumors are deemed technically resectable at least after restaging [16, 17]. Definitive CRT is recommended only for technically unresectable or medically inoperable patients, those with cervical tumor localization, or patients unwilling to undergo surgery [16, 17]. Austrian centers show good accordance with these recommendations in general: 69% routinely recommend n-CRT followed by surgery for T3N0 and T1b-3 N+ disease, whereas a minority of centers individualize treatment decisions between n-CRT and d-CRT, and only one center routinely prefers d-CRT (see Table 2).

However, most Austrian centers appear to use a more conservative approach in T4 tumors. The majority preferred d-CRT either routinely or based on individual factors for T4aN0-N+ tumors (31% and 24%, respectively), with this tendency even more pronounced for T4bN0-N+ tumors (46% and 24%). Two centers reported using either d-CRT or CHT alone in T4b disease, in line with the NCCN recommendations [17]. The overall less aggressive strategy may be attributed to a lack of evidence for a clear survival benefit when comparing d-CRT with n-CRT followed by surgery in T3-4N0-1 tumors in randomized trials. Although the addition of surgery resulted in improved LC, potential OS benefits appeared to be offset by increased surgical mortality, at least in patients responding to n-CRT [39, 40]. As surgical risks are likely to increase with more advanced T stage, these findings may explain the preference for d-CRT in this setting.

In contrast, most Austrian centers (69%) would not omit surgery after n-CRT even in case of a good response. Only a minority (24%) would switch to a watch-and-wait strategy after completion of a neoadjuvant total dose or delivery of an additional boost. The median interval to surgery after n-CRT in Austrian centers is 6 weeks (4–12 weeks), which is comparable to the CROSS protocol [2]. Neither guideline recommends a specific time interval between n-CRT and surgery.

Simulation/treatment planning/treatment procedure

Detailed recommendations specifically addressing RT treatment planning are only partially provided in international guidelines. Both guidelines mention 3D-conformal RT as a minimum requirement, while cautiously favoring intensity-modulated techniques in the absence of randomized data [16, 17]. In contrast, all Austrian centers reported the routine use of IMRT. The NCCN guidelines provide detailed dose constraints for all organs at risk [17], whereas the ESMO guidelines do not include comparable specifications [16]. Austrian centers mainly delineate the major OARs recommended by the NCCN, however reported dose constraints vary considerably among centers and only partially align with guideline proposals (see Table 6). While NCCN recommends the use of intravenous and/or oral contrast agents and motion management strategies for distal tumors, only a minority of Austrian centers adhere to these recommendations (approximately one third using contrast agents and fewer than 50% employing motion management strategies). NCCN [17] further advocates daily kV-image-guidance, a practice also preferred by the majority of Austrian centers (69%), implemented either via cone-beam CT or portal imaging.

Target volume definition/dose prescription

ESMO guidelines do not provide recommendations regarding target volume definition [16]. In contrast, the NCCN guidelines offer detailed instructions on defining the GTV (primary and positive nodes), the CTV (primary tumor plus 3–4 cm in cranio-caudal direction and 1 cm radially; nodal GTV plus 0.5–1.5 cm) and the PTV (CTV plus 0.5–1 cm). Furthermore, the NCCN guidelines recommend ENI irrespective of nodal status or CRT intent and define elective nodal volumes according to tumor localization [17]. These recommendations are of particular interest, as the landmark trial for n-CRT (CROSS) did not include ENI, and there is increasing evidence against its use also for d-CRT [41]. Consequently, there is no general consensus on the use of ENI among Austrian centers. Approximately half of the centers routinely include ENI in the neoadjuvant setting and, at least in N0 disease, also in the definitive setting. In contrast, none of the centers reported the use of ENI in node-positive patients undergoing d-CRT. In this situation, 69% favor a moderate form of involved nodal irradiation (INI) treating the primary tumor and involved nodes with safety margin within a single target volume. This approach may reflect the perceived limited benefit of elective nodal volume treatment in node-positive patients, who are at higher risk for distant failures, or a cautious attitude toward treatment-related toxicity associated with larger target volumes in patients who are often in poorer general condition than surgical candidates.

With regard to single and total doses for n-CRT, both guidelines recommend similar concepts (NCCN: 41.4–50.4 Gy, in 1.8–2.0 Gy per fraction and ESMO 41.4 Gy in 1.8 Gy fractions) [16, 17]. Austrian centers largely adhere to these recommendations (reported range 41.4–50 Gy, median 45 Gy), which are well supported by several large trials [2, 3, 14, 37, 38, 42].

In the definitive treatment setting, both guidelines consistently recommend total doses of 50–50.4 Gy in 1.8–2.0 Gy fractions [16, 17]. These recommendations are mainly based on several randomized trials that failed to demonstrate a clear benefit from further dose escalation [15, 43]. While the earlier trial [43] employed outdated radiation techniques and has been heavily criticized with regard to the interpretation of its results, the more recent ARTDECO trial [15] was conducted using modern techniques. Nevertheless, it likewise failed to demonstrate significant improvements in LC or OS with dose escalation to 61.6 Gy to the primary tumor, despite an absolute increase in LC rates without excess toxicity. In contrast, more than two thirds of Austrian centers still use apply escalation to the primary tumor (median 57.7 Gy, range 50–66 Gy) and/or involved lymph nodes (median 54 Gy, range 50–66 Gy). This practice may reflect adherence to the general radiobiological principle "more dose, more control", which holds true in most malignancies treated with definitive radiotherapy. Even in the light of the negative ARTDECO results, this topic may warrant further investigation, particularly regarding response-adapted dose escalation or de-escalation strategies. Organs at risk definition and particularly dose constraints are not harmonized across Austrian centers and represent a potential target for further standardization and more evidence-based practice.

Systemic chemotherapy

Nearly all Austrian centers are in agreement with international guidelines in using Carboplatin/Paclitaxel according to the CROSS protocol for neoadjuvant concurrent chemotherapy [2, 3, 16, 17, 37, 38]. In contrast to ESMO, the NCCN guidelines list additional options, such as the FOLFOX regimen, based on its use in the definitive setting [44]. There is some evidence that FOLFOX may induce more pronounced tumor responses compared with Carboplatin/Paclitaxel [45], therefore this regimen may represent an area of further research interest.

Interestingly Carboplatin/Paclitaxel is also frequently used in definitive setting in Austrian centers (69%). Only 3 centers still reported using Cisplatin/5-Fu based on the RTOG 85 – 01 protocol by Herscovic et al. [46, 47], despite this regimen being recommended as the primary option in both guidelines. Carboplatin/Paclitaxel is recommended in the definitive setting only by the NCCN [17], whereas both guidelines list FOLFOX as alternative

based on a phase II/III trial [16, 17, 44]. The preferential use of Carboplatin/Paclitaxel over other regimes may again reflect concerns about increased toxicity in this often less resilient patient population and the comparable outcome suggested by retrospective data [48].

Adjuvant or additive chemotherapy after d-CRT is rarely used in Austrian centers ($n = 2$), and not recommended by either guideline [16, 17], although it was part of the RTOG 85 – 01 trial [46, 47].

Immunotherapy

Boths guidelines recommend additive immunotherapy in case of residual tumor or R1-resection after n-CRT and surgery [16, 17], based on the results of the CheckMate 577 trial [13] demonstrating a clear disease-free survival benefit (22.4 vs. 11months) with the addition of Nivolumab. Accordingly, most Austrian centers add immunotherapy after surgery in case of incomplete resection ($n = 12$) or absence of a pathological complete response ($n = 9$).

Additive immunotherapy after d-CRT is not (yet) recommended; however, it is currently evaluated in the ongoing phase III SKYSCRAPER 07 trial (NCT 04543617). Consequently, the two Austrian centers participating in the trial reported its use within the study protocol, while 1 center indicated routine off-trial use of additive immunotherapy after d-CRT (off trial) and 2 centers reported its use in cases of residual disease.

Follow-up

Recommendations regarding follow-up investigations after CRT in EC remain controversial. In the absence of a clear and validated impact on survival, ESMO recommends symptom-driven follow-up only [16], whereas the NCCN [17] propose an algorithm that aims at balancing benefits and risks according to tumor stage in this unfavorable patient cohort. In contrast, most Austrian centers strongly believer in the value of regular long-term follow-up. The majority offers scheduled surveillance for at least 5 years (77%), and some even up to 10 years ($n = 2$), including endoscopy and/or cross-sectional imaging at gradually increasing intervals (every 3 during the first year, every 3–6 months during the second year, and every 6–12 months from the third to the fifth years or beyond). Given the generally limited overall survival observed in historical cohorts of patients with metastatic esophageal cancer, the cost-effectiveness of repeated follow-up examinations warrants further evaluation.

To date, there is no clear evidence demonstrating if (and to what extent) early detection of metastastaic disease - and thus earlier initiation of salvage therapies (e.g. local ablative treatments, immunotherapy or targeted therapies)- translates into improved prognosis. Nevertheless, earlier detection of (oligo-)metastatic spread may enable the use of local ablative approaches, which have been associated with improved OS in several tumor entities.

Summary

In summary, we observed a high level of agreement among Austrian centers and substantial concordance with major international guidelines regarding the key aspects of work-up, treatment and follow-up for CRT in esophageal SCC. Nevertheless, PET-CT, EUS, bronchoscopy and pulmonary function testing appear to be used less frequently during work-up than recommended. All centers employ modern radiation therapy techniques (e.g. IMRT) with image-guidance. High agreement and guideline concordance were also found for the management of early-stage disease. In contrast, many centers tend to favor d-CRT more often than recommended for T4 tumors. Substantial variability was observed in target volume definition, particularly with regard to the inclusion of elective nodal volumes (ENI). While Austrian centers largely adhere to guideline-recommended dose concepts in the neoadjuvant setting, many still prefer dose escalation beyond 50 Gy in d-CRT. Marked discrepancies were also noted in the definition of organs at risk and, even more pronounced, in the applied dose constraints. The choice of concurrent and adjuvant systemic therapy regimens aligns well with guideline recommendations, although a clear preference for Carboplatin/Paclitaxel is evident even in the d-CRT setting. Supportive care during and after CRT is highly variable and insufficiently addresses in major guidelines, despite being an integral component of comprehensive treatment. Follow-up practices in Austrian centers are generally more intensive than currently recommended.

Advanced staging procedures, dose prescription in definitive CRT, the role of involved versus elective nodal irradiation, OAR dose constraints, and follow-up strategies were identified as the main areas of inter-center variability and discordance with major international guidelines. These domains may represent promising targets for future harmonization efforts and focused clinical research.

Abbrevations

AC	Adenocarcinoma
CBCT	Cone beam computed tomography
CHT	Chemotherapy
CR	Complete response
CRT	Chemoradiation
CT	Computed tomography
CTV	Clinical target volume
d-CRT	Definitive chemoradiation
DIBH	Deep inspiration breathhold
EC	Esophageal cancer
EGD	Esophagoduodenoscopy
ENI	Elective nodal irradiation
ENT	Ear -nose- throat
ER	Endoscopic resection

ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society of Medical Oncology
EUS	Endoscopic ultrasound
FOLFOX	Chemotherapy regimen including 5-Fluorouracil, oxaliplatin and leucovorin
GTV	Gross tumor volume
Gy	Gray
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
INI	Involved nodal irradiation
kV	Kilovoltage
LC	Locoregional control
LN	Lymph node
mm	Millimeter
MTV	Metabolic tumor volume
NCCN	National Comprehensive Cancer Network
n-CRT	Neoadjuvant chemoradiation
OAR	Organs at risk
OS	Overall survival
ÖGRO-GIT	Gastrointestinal working group of the national radiation oncology society
PEG	Percutaneous feeding tube
PET-CT	Positron-emission tomography - computed tomography
PTV	Planning target volume
pCR	Pathologic complete response
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SCC	Squamous cell cancer
SIB	Simultaneous integrated boost
SUVmax	Maximum standardized uptake volume
SOP	Standard operating procedures
TLG	Total lesion glycolysis
US	United states
VMAT	Volumetric intensity-modulated radiation therapy

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GS designed the survey, performed the statistics and drafted the manuscript. CP, SP, HP, JR, KO, KM, PK, RI, SR, SS, SH, VC answered the survey as representatives of their centers, provided valuable input for the manuscript draft and proofread the manuscript. RF supervised the design and critically reviewed the manuscript.

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