Cervical Esophageal Cancer Radiation Therapy

Francesca Arcadipane

Radioterapia U

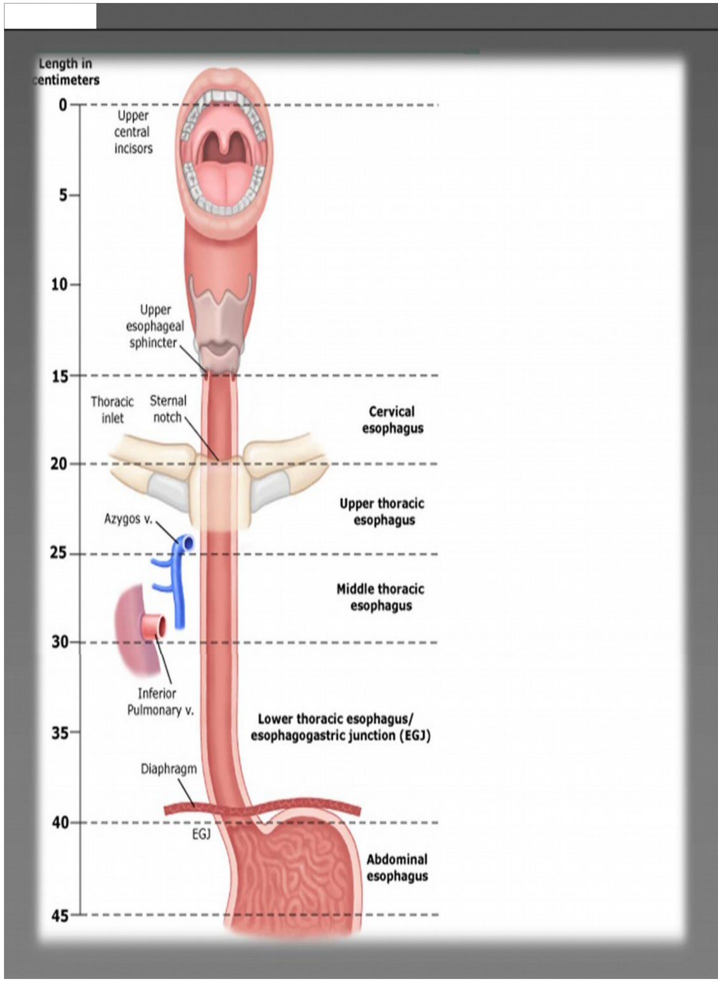
AOU Città della Salute e della Scienza

Introduction

EC is the short part of the esophagus between the lower border of the cricoid cartilage and the thoracic inlet, **15-20 c**m from the incisor teeth

Japanese classification: begins at esophageal orifice and extending to the level of the sternal notch

Carcinoma of EC, usually squamous cell carcinoma, is uncommon, 2%–10% of all esophageal carcinomas



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Diagnosis and Staging

- Endoscopy and biopsy
- Endoscopic ultrasonography 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
- 18F-FDG-PET CT is highly recommended to detect potential tumor invasion into adjacent structures and lymph node or distant metastases
- Bronchoscopy, with endobronchial ultrasound and biopsy, can be used to assess infiltration in adjacent structures, e.g. trachea
- Most are locally advanced at the time of diagnosis, with ~55% being TNM stage III or IV tumors and 27% stage II tumors

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Drainage

Esophagus is characterized by a rich, longitudinal,lymphatic drainage network

A higher incidence of cervical lymph node metastasis is observed

Node classification	Description	Patients [*n* (%)] with EC lesion	
		Cervical	Upper thoracic
Level II	Upper jugular	1 (1.0)	0
Level III	Middle jugular	14 (14.4)	8 (2.2)
Group 1	Supraclavicular	30 (30.9)	76 (20.5)
Group 2 R/L	Upper paratracheal	11 (11.3)	51 (13.7)
Group 3P	Posterior mediastinal (upper para-esophageal)	23 (23.7)	145 (39.1)
Group 4 R/L	Lower paratracheal	8 (8.2)	45 (12.1)
Group 5	Aortopulmonary	8 (8.2)	65 (17.5)
Group 6	Anterior mediastinal	7 (7.2)	21 (5.7)
Group 7	Subcarinal	3 (3.1)	48 (12.9)
Group 8	Middle para-esophageal	0	10 (2.7)
Group 9	Pulmonary ligament	0	2 (0.5)
Group 10 R/L	Tracheobronchial	0	8 (2.2)
Group 15	Diaphragmatic	0	0
Group 16	Paracardiac	0	2 (0.5)
Group 17	Left gastric arterial	2 (2.1)	10 (2.7)
Group 18	Common hepatic arterial	0	0
Group 19	Splenic arterial	0	0
Group 20	Celiac	0	0

RTOG = Radiation Therapy Oncology Group; EC = esophageal cancer; R/L = right or left.

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Surgery

Study	Year	Ce/Hp	5ySR (%)	Morbidity *n* (%)	Hospital mortality *n* (%)
Wei et al. [5]	1998	32/37	24	34(49)	6(9)
Triboulet et al. [6]	2001	78/131	24	42(33.1)	10(4.8)
Wang et al. [7]	2006	15/26	31.5	19(46.3)	4(9.8)
Daiko et al. [8]	2007	74/0	33	25(34 %)	3(4 %)
Tong et al. [9]	2011	43/25	37.6(2y)		5(7.1)

Surgery is often impossible, or mutilating

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HISTOLOGY	TUMOR CLASSIFICATION[g]	PRIMARY TREATMENT OPTIONS FOR MEDICALLY FIT PATIENTS	
Squamous cell carcinoma	cT1b-cT2, N0[o]	Esophagectomy[c,d,t,u] (non-cervical esophagus) (T1b/T2, N0 low-risk lesions: <2 cm, well differentiated)	See Surgical Outcomes After Esophagectomy (ESOPH-6)
	cT1b-cT2, N+ or cT3-cT4a, Any N[w]	Preoperative chemoradiation[x,y] (non-cervical esophagus) (RT, 41.4–50.4 Gy + concurrent chemotherapy)	See Response Assessment (ESOPH-5)
		or Definitive chemoradiation[x,y] (only for patients who decline surgery) (recommended for cervical esophagus) (RT, 50–50.4 Gy + concurrent chemotherapy)	Follow-up (See ESOPH-9)
	cT4b[p]	Definitive chemoradiation[x,y] (RT, 50–50.4 Gy + concurrent chemotherapy)	See Response Assessment (ESOPH-5)
		Consider chemotherapy alone in the setting of invasion of trachea, great vessels, or heart[x] See Palliative Management (ESOPH-10)	

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Chemoradiation

CRT: positive impact on the QoL preserving larynx and esophagus

Optimal RT dose and fractionation have not yet been established: range 50-70 Gy

Most of the prospective randomized trials, investigating combined CRT for esophageal cancer, marginally enrolled, or excluded at all, patients with cervical localizations

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Chemoradiation

Study	Patients (n)	Dose (Gy/Fx)	CRT (%)	CTx	2-y LC/LRC (%) (definition)	2-y OS (%)
3DCRT						
Huang et al (15)	29	70/35	83	High-dose CDDP	48 (LRFS)	43
Yamada et al (17)	27	44-74	85	5-FU + CDDP	48 (LR)	45[*]
Gkika et al (18)	55	56-70	100[†]	CDDP + E/5-FU	55 (LRC)	35
Burmeister et al (14)	34	50.4-65	100	CDDP +5-FU or 5-FU alone	88 (LC)	65[*]
Stuschke et al (16)	17	60-66	100[‡]	CDDP + E	33 (LRC)	24
Tong et al (20)	21	60-68	100	CDDP + 5-FU	NR	47
Zenda et al (3)	33	60	100	CDDP + 5-FU	50 (LFFS)[*]	70[*]
IMRT						
Wang et al (22)	7	59.4-66	100[§]	Mixed	66 (LC)	NR
Cao et al (21)	64	60-76	34	CDDP	75 (LFFS)	42.5

Outcome of RT has been reported in several studies

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Dose Constraints

- ✓Spinal cord: 45 Gy
- ✓Lungs: V20 <20%, V5< 50%, Dmean <18 Gy
- ✓Thyroid: Dmean<35-45Gy
- ✓Larynx: Dmean <40-45 Gy
- ✓Brachial Plexus: Dmax < 66Gy

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Target delineation

RT includes prophylactic lymph node stations:

✓Bilateral supraclavicular

✓Mid-deep cervical

✓Paraesophageal

✓Recurrent nerve extending as far as the subcarina

When EC invaded pharynx: upper deep cervical station

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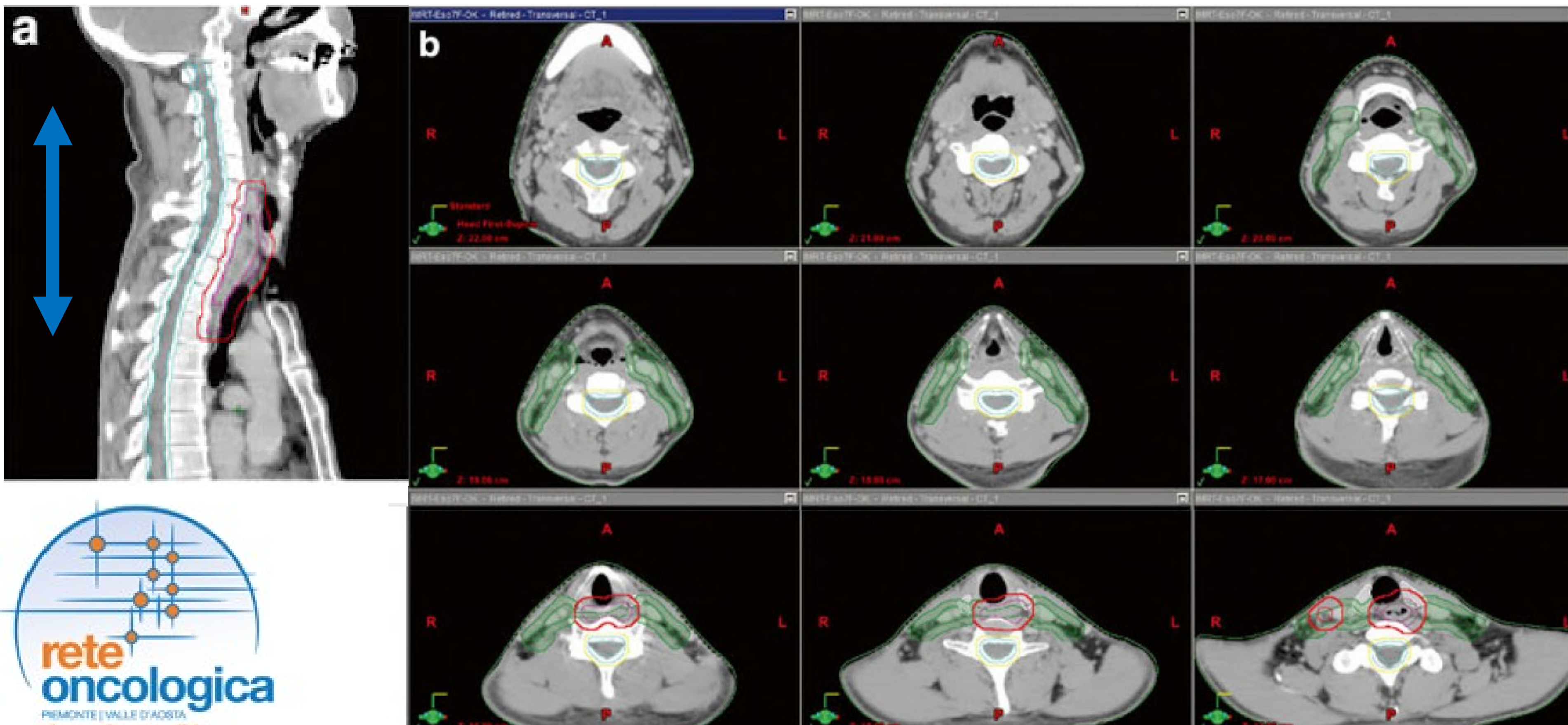
Target delineation

CTV: GTV + 2 cm C-C + 0,5 cm radial margin

CTV over trachea and bone is CUT unless there is direct invasion of T

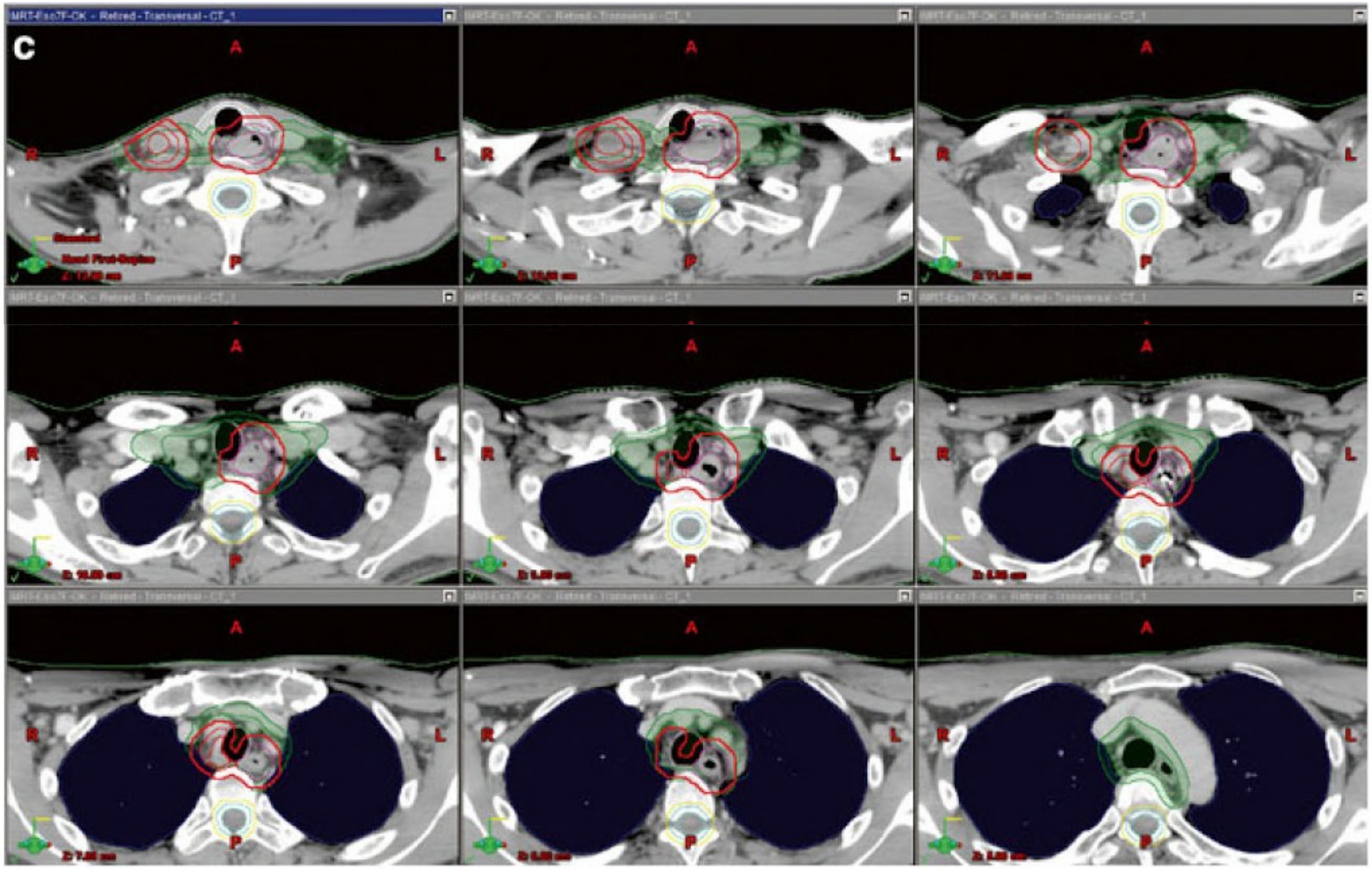
PTV-T >>

PTV-N >>



Target delineation

PTV-T >>
PTV-N >>



Target PET-guided

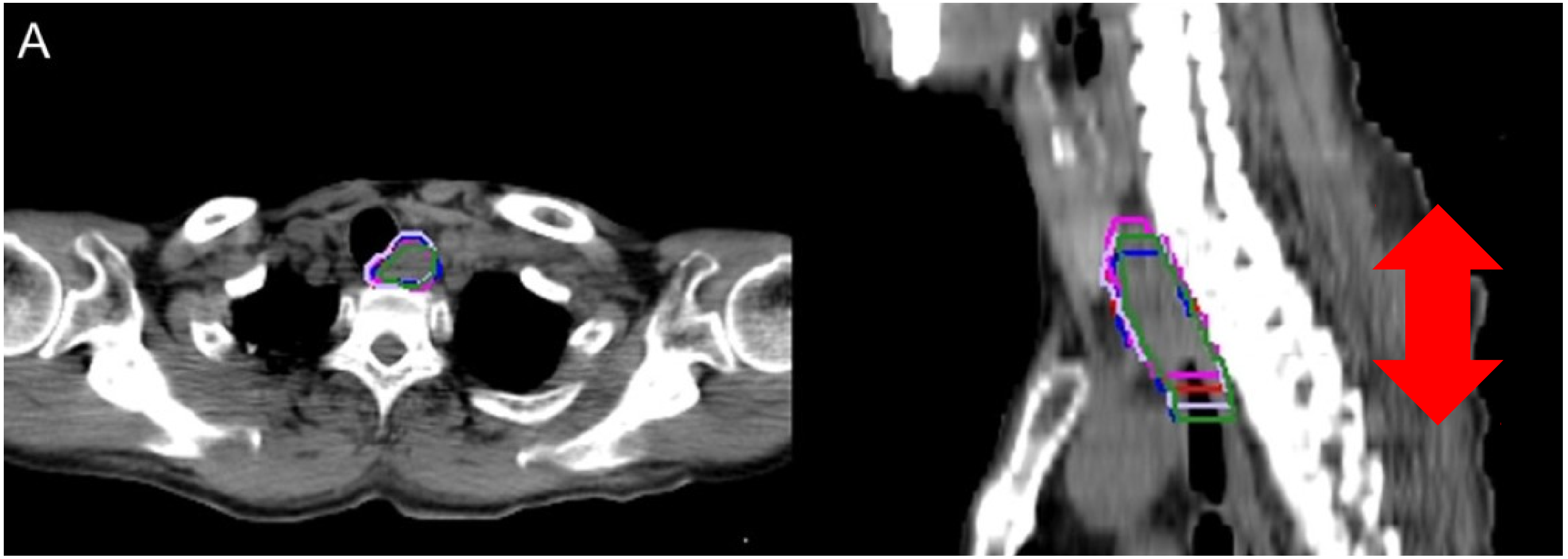
Journal of Radiation Research, Vol. 60, No. 3, 2019, pp. 348–352
doi: 10.1093/jrr/rrz004
Advance Access Publication: 13 March 2019

Journal of Radiation Research

OXFORD

Impact of hybrid FDG-PET/CT on gross tumor volume definition of cervical esophageal cancer: reducing interobserver variation

R. Toya, Kumamoto University



EC: cT3N0M0 ,interobserver variation CI: **ratio of the intersection of the GTVs to their union**
GTVs defined by 5 observers based on CT
Conformality index was 0.41

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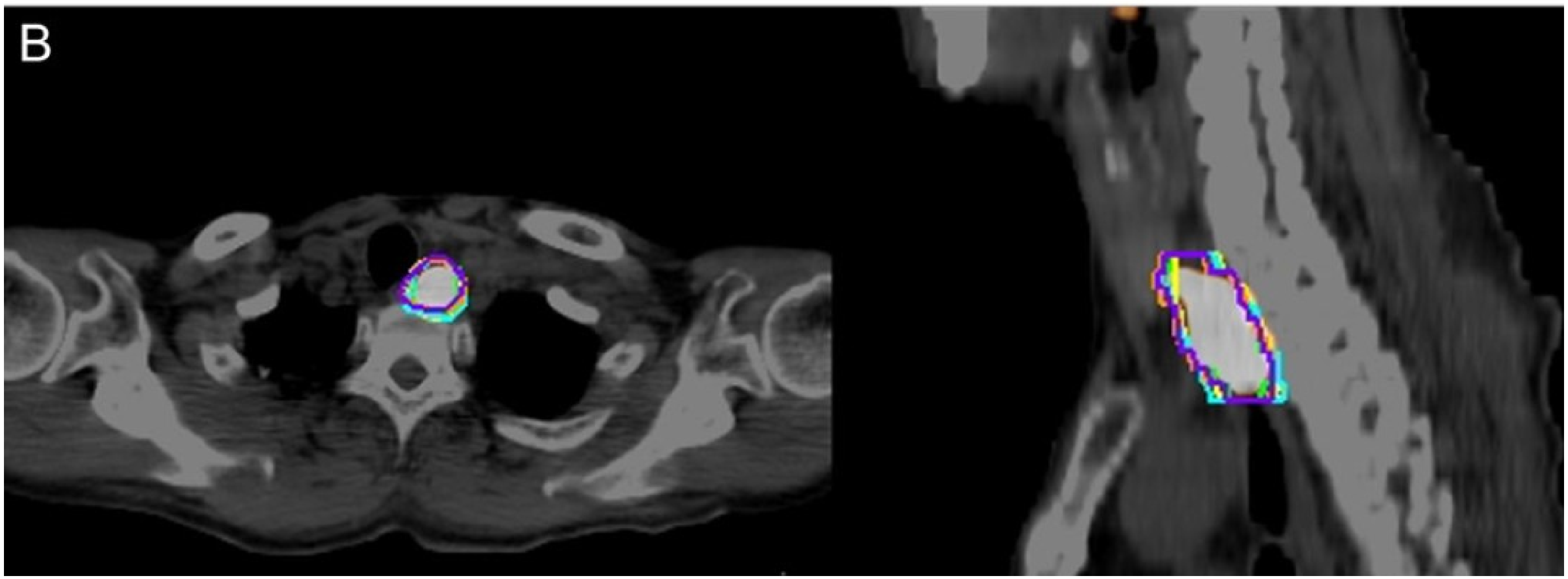
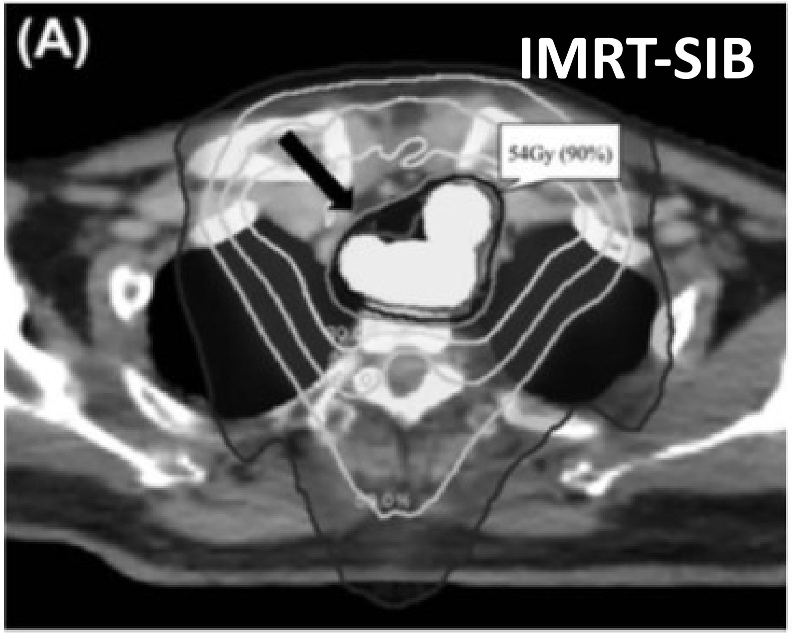
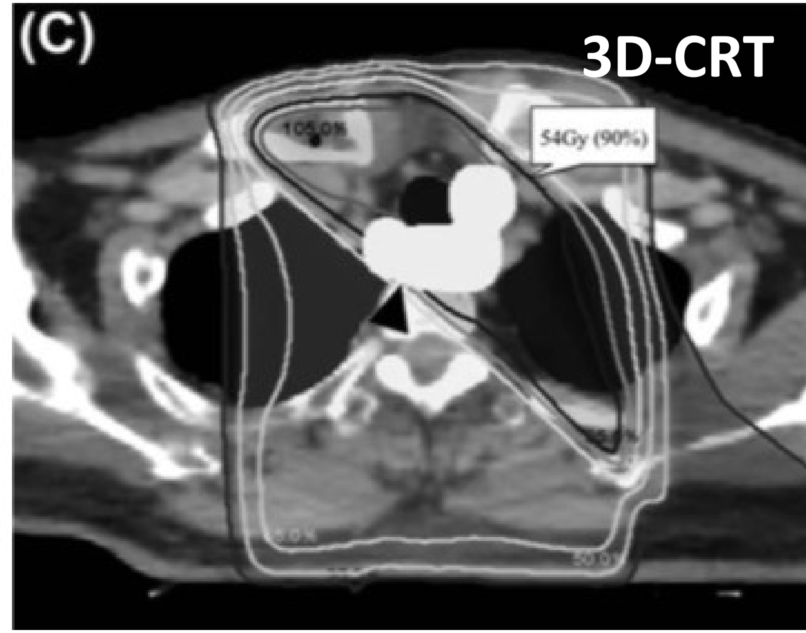


GTVs defined by 5 observers based on PET/CT
Conformality index improved to 0.59

IMRT vs 3D





Dose-coverage for PTV of both IMRT approach seemed to be better than 3DCRT

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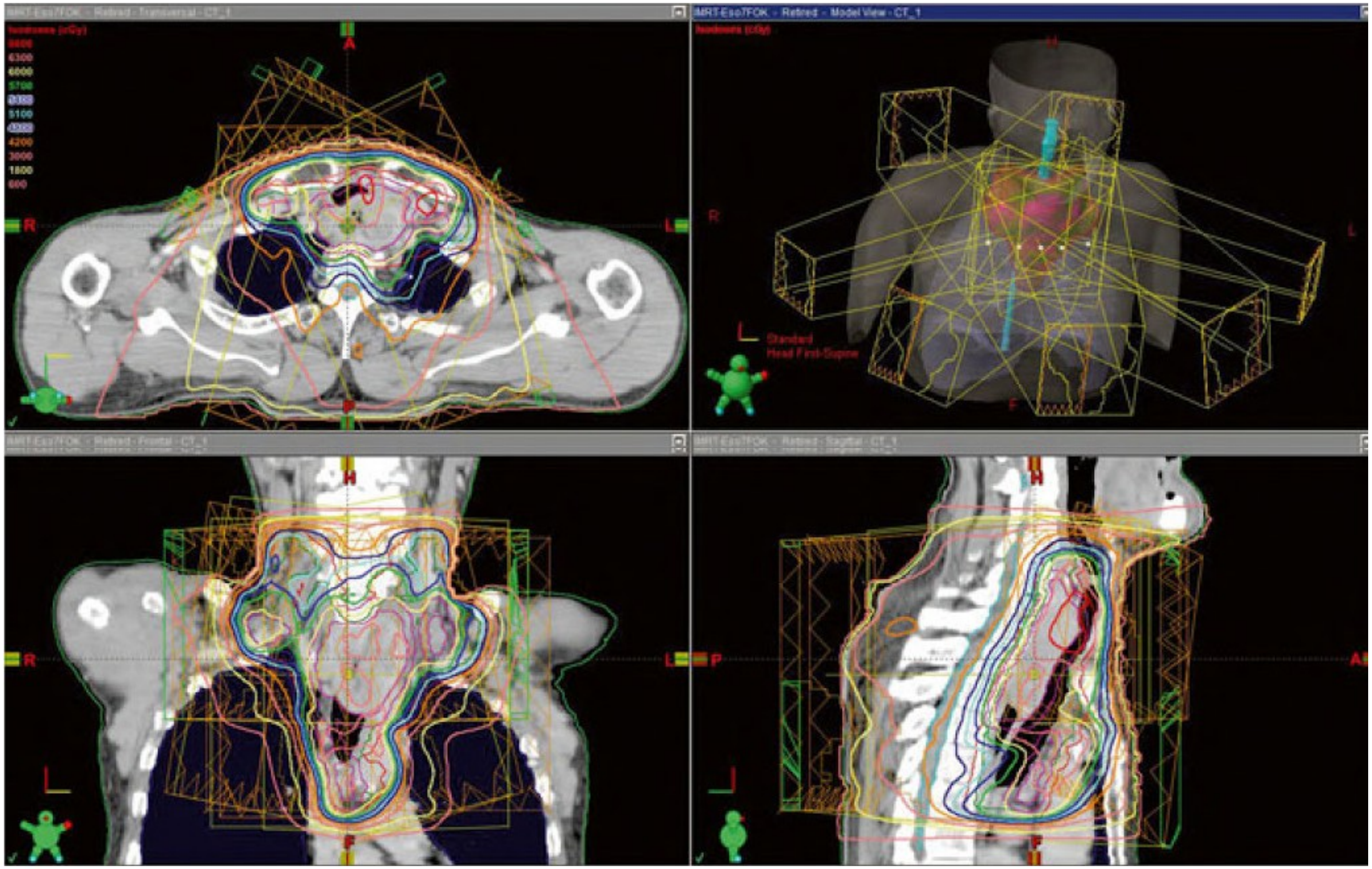
Planning IMRT



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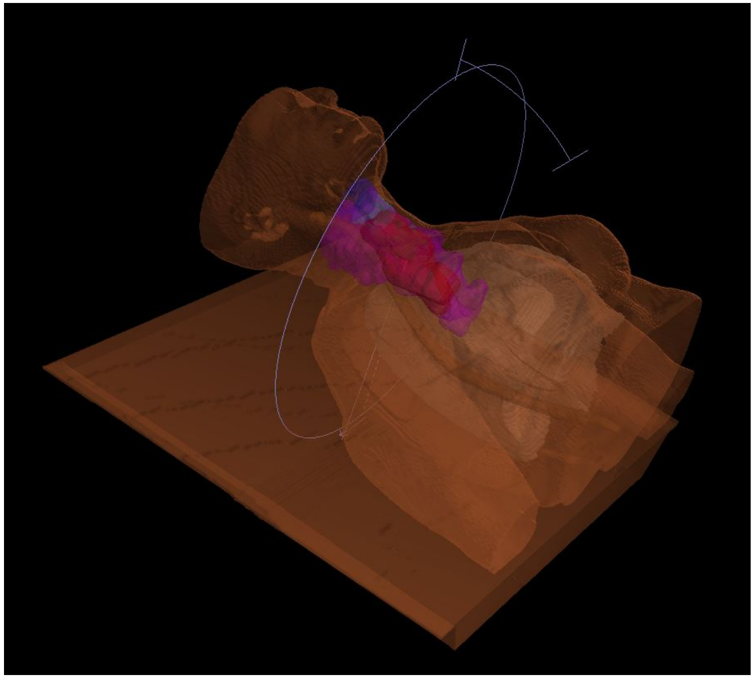
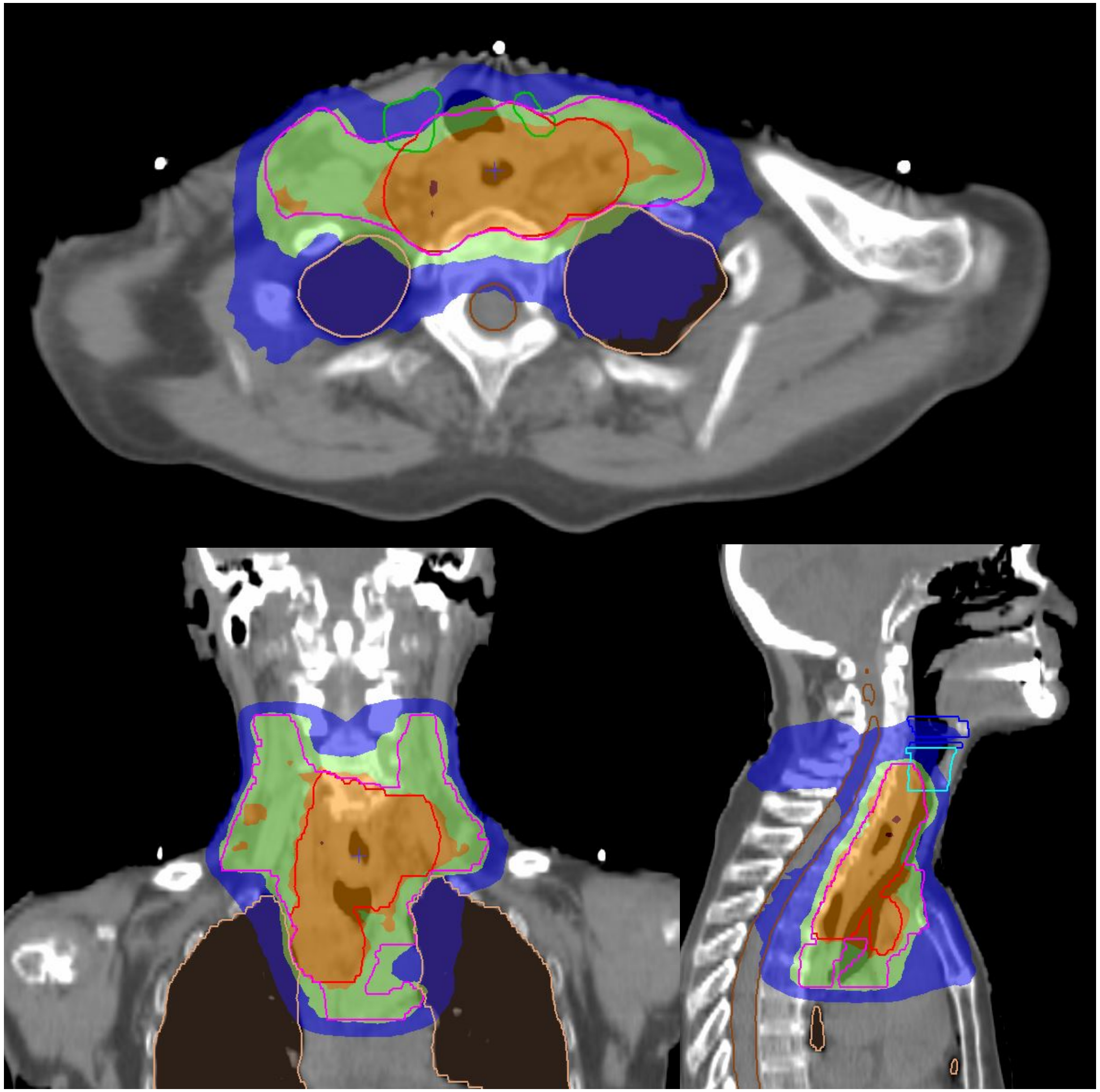
Planning VMAT





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IMRT

Short distance between esophagus and spinal cord at level of neck, it’s difficult to deliver an adequate dose avoiding OaR

Differences in thickness of body at neck and chest make it diffucult to achieve an even dose distribution

IMRT:

- Improve target volume coverage and conformity
- Reduce dose to spinal cord and lungs

VMAT vs fixed-beam IMRT improves dose distribution and large reduction in MU, but increase low-dose to lungs

IMRT vs 3D

Clinical Investigation

Effect of Intensity Modulated Radiation Therapy With Concurrent Chemotherapy on Survival for Patients With Cervical Esophageal Carcinoma

International Journal of Radiation Oncology biology • physics

CrossMark

L.J. McDowell

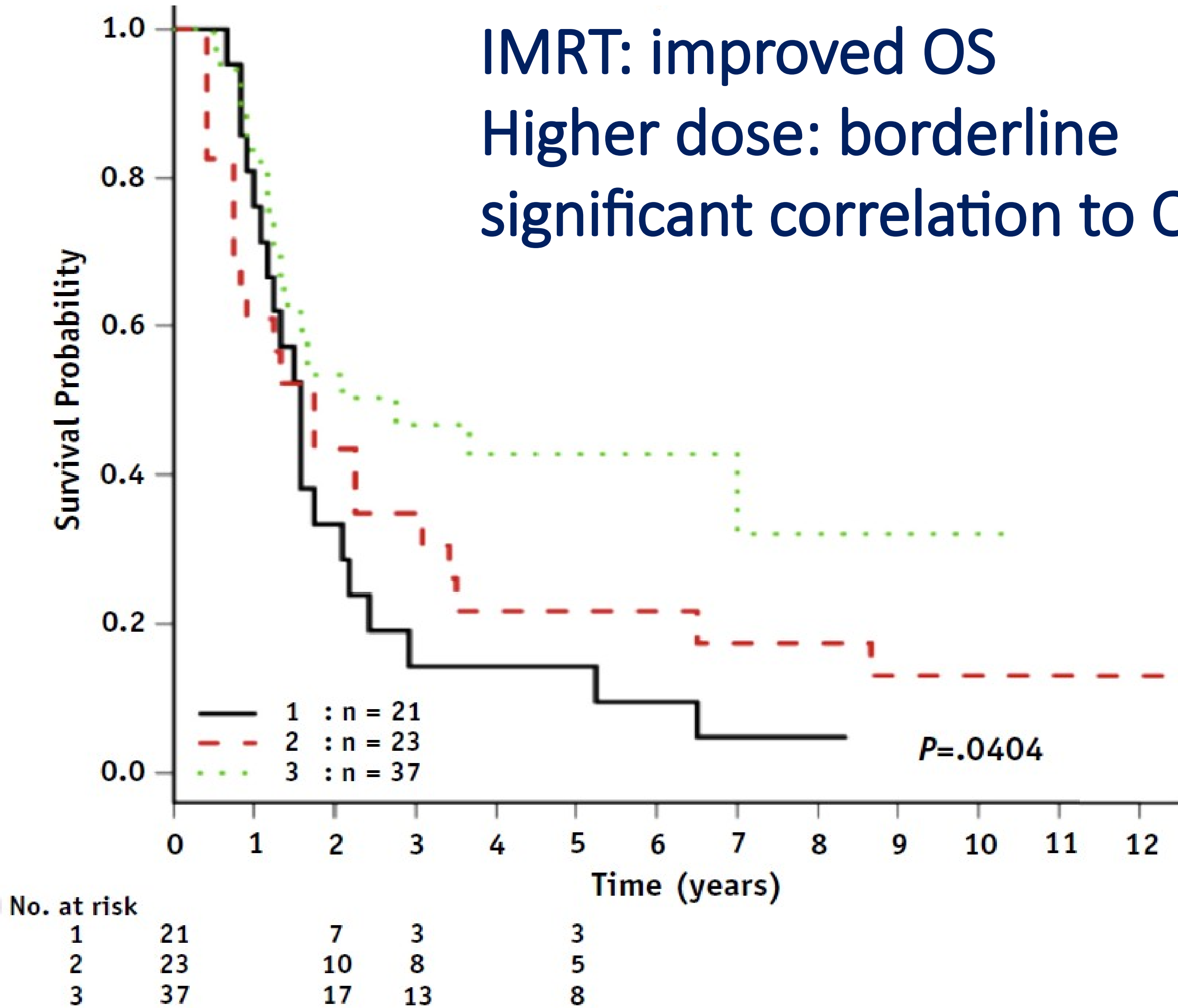
1997-2013, 81 patients
3 consecutive protocols

Variable	Protocol 1	Protocol 2	Protocol 3
Era	1997-2001	2001-2005	2005-2013
Treatment planning	Fluoroscopic or CT	CT	CT
Radiation dose (BED)	54 Gy/20 Fx (BED 68.6)	Preferred: 70 Gy/35 Fx (BED 84 Gy)	Preferred: 70 Gy/35 Fx (BED 84 Gy)
RT technique	2DRT	3DRT	IMRT
RT plan	2 Phase	2-3 Phase, shrinking field	Single-phase, simultaneous integrated boost
ENI	No	Yes	Yes
RT target volume	CTV, not defined; PTV, GTV + 2-5 cm margin to field edge	Primary: CTV1, 70 Gy/35 Fx to primary GTV + 1 cm expansion; CTV2, 50 Gy/25 Fx to entire CE with 3 cm below GTV LNs: CTV1, 70 Gy/35 Fx to gross LNs + 0.5-1.0 cm expansion; CTV2 (ENI), 50 Gy/25 Fx to superior mediastinal, bilateral supraclavicular, and level III/IV LNs and 1 echelon beyond any positive neck LNs; PTV, CTV + 0.5-1.0 cm expansion	Primary: CTV1, 70 Gy/35 Fx to primary GTV + 1 cm expansion; CTV2, 56 Gy/35 Fx to entire CE with 3 cm below GTV LNs: CTV1, 70 Gy/35 Fx to gross LNs + 0.5-1.0 cm expansion; CTV2 (ENI), 56 Gy/35 Fx to superior mediastinal, bilateral supraclavicular, and level III/IV LNs and 1 echelon beyond any positive neck LNs; PTV, CTV + 0.5-1.0 cm expansion
Concomitant CTx	5-FU and MMC or cisplatin	High-dose cisplatin (100 mg/m^2, weeks 1, 4, 7)	High-dose cisplatin (100 mg/m^2, weeks 1, 4, 7)

IMRT vs 3D

IMRT: improved OS
Higher dose: borderline significant correlation to OS

	P value
RT technique	
2DRT/3DR	
IMRT	
BED	.0029
Median	
Range	
Protocol vari	.006
Either CTx	
CTx	
RT	
OS (%)	.04
2-y	
95% CI	
LRC (%)	.24
2-y	
95% CI	
DC (%)	.97
2-y	
95% CI	



L.J. McDowell

IMRT vs 3D

Received: 7 February 2017 | Revised: 22 June 2017 | Accepted: 6 July 2017
DOI: 10.1002/hed.24909

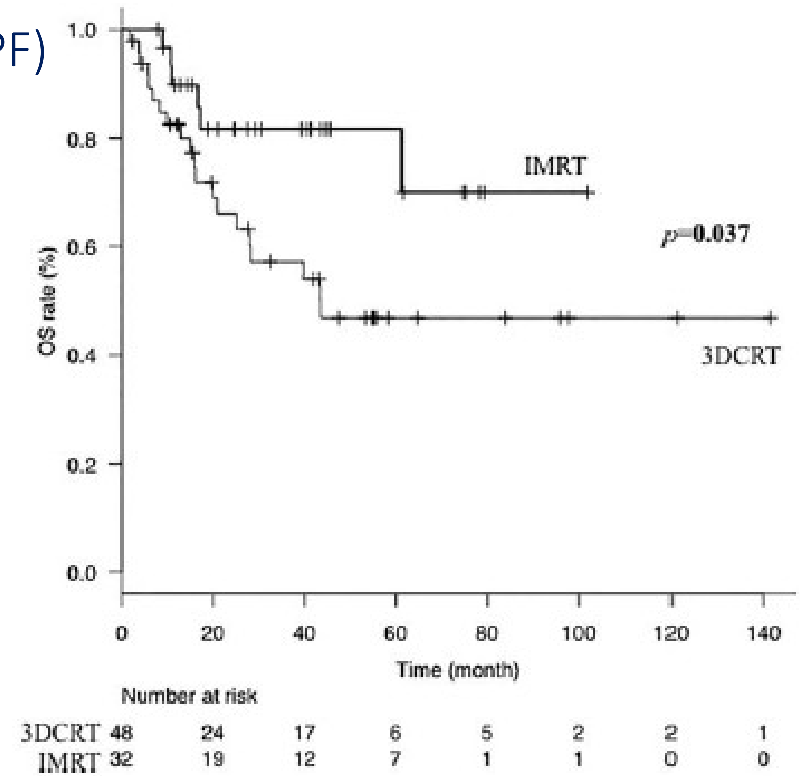
ORIGINAL ARTICLE

WILEY

Clinical results of definitive chemoradiotherapy for cervical esophageal cancer: Comparison of failure pattern and toxicities between intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy

M. Ito et al.

80 patients , 2002- 2014, 25 ICT (CDDP+5FU or TPF)
Concomitant CT: 5-FU (700 mg/m2 i.v.; days 1-4)
and Cisplatin (70 mg/m2 i.v.; day 1)
Dose 60Gy/30 Fr
IMRT n 32, 3DCRT n 48
3-year OS 66%, IMRT 81%, 3DCRT 57%



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IMRT vs 3D

M. Ito et al.

47 recurrence

26 (55.3%) locoregional failure, IMRT 60% 3DCRT 52%

15 (32.0%) distant metastasis, IMRT 30% 3DCRT 33%

6 (12.7%) both, IMRT 10% 3DCRT 15%

15 patients underwent salvage treatment:

IMRT 10 and 6 (60%) survived, 3DCRT 5 (20%) only 1 survived

Median DFS from surgery: IMRT 25 months, 3DCRT 11 months

IMRT group was comparable with 3D conformal RT group, with a better salvage rate, extended cervical ENI is recommended

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Toxicity

Esophagitis, Dysphagia, Dermatitis, Fatigue, **Weight loss**

Stenosis>60%, 2or3 dilations

Radiation pneumonitis: cough, dyspnea, distress 2-6months after

Risk factor: chemotherapy, V20, Dmean

Perforation of esophagus>> is life threatening

Symptoms: substernal chest pain, dyspnea, fever, hemorrhage

Perforation rate after CRT 5-10%, MS 0-3 months

Risk factors: T4 stage, reirradiation, lymph nodes ECE+

Correlation of Pulmonary Complications After Preoperative Chemoradiation for Esophageal Carcinoma

	Number Experiencing Pulmonary Complications (%)	*P*-Value
V_{10}		
>40%	8/23 (35)	0.014
<40%	3/38 (8)	
V_{15}		
>30%	7/21 (33)	0.036
<30%	4/40 (10)	
V_{20}		
>20%	7/22 (32)	0.079
<20%	4/39 (10)	

Lee H, Vaporciyan A, Cox J, et al. Postoperative pulmonary complications following preoperative CRT for esophageal carcinoma: correlation with pulmonary DVH. *Int J Radiat Oncol Biol Phys* 2003;57:1317–1322.

H. CHEN, Journal of Radiation Research, 2014

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IMRT and Dose Escalation

CANCER RESEARCH AND TREATMENT

Intensity-Modulated Radiotherapy versus Three-Dimensional Conformal Radiotherapy in Definitive Chemoradiotherapy for Cervical Esophageal Squamous Cell Carcinoma: Comparison of Survival Outcomes and Toxicities

Nai-Bin Chen[1,2,3], Bo Qiu[1,2,3], Jun Zhang[1,2,3], Meng-Yun Qiang[1,2,3], Yu-Jia Zhu[1,2,3], Bin Wang[1,2,3], Jin-Yu Guo[1,2,3], Ling-Zhi Cai[1,2,3], Shao-Min Huang[1,2,3], Meng-Zhong Liu[1,2,3], Qun Li[1,2,3], Yong-Hong Hu[1,2,3], Qi-Wen Li[1,2,3], Hui Liu[1,2,3]
[1]Department of Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

112 patients

Median follow-up 34.9 months: 3-year OS 3DCRT 49.6% vs IMRT 54.4% **(p=0.927)**

Similar G≥3 esophagitis, G≥2 pneumonitis, esophageal stricture and

Table 2. Dosimetric parameters

	3D-CRT	IMRT	p-value
Total radiation dose (Gy)	60 (60-70)	63.9 (60-70)	0.037
Fraction dose (cGy)	200 (165-232)	213 (180-229)	<0.001

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Chen et al. Cancer Res Treat. 2019

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IMRT and Dose Escalation

Table 7. Multivariate analysis of prognostic factors for tracheostomy dependence

Factor	Hazard ratio	95% CI for HR	p-value
Radiotherapy technique	0.09	0.01-0.79	0.030
Pretreatment hoarseness	0.12	0.02-0.70	0.018

HR, hazard ratio; CI, confidence interval.

8% patients developed dyspnea and required tracheostomy

Tracheostomy resulted correlated with IMRT than 3D-CRT group (14.3% vs.1.8%, p=0.032) and pretreatment hoarseness (HR, 0.12; 95% CI 0.02 to 0.70)

No survival benefits had been observed while comparing IMRT versus 3D-CRT in CEC patients

Hypofractionated IMRT and pretreatment hoarseness is related with a higher risk for tracheostomy

Dose escalation >60 Gy should be taken into account carefully when using IMRT with hypofractionation

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Chen et al. Cancer Res Treat. 2019

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University of Turin

IMRT vs 3D

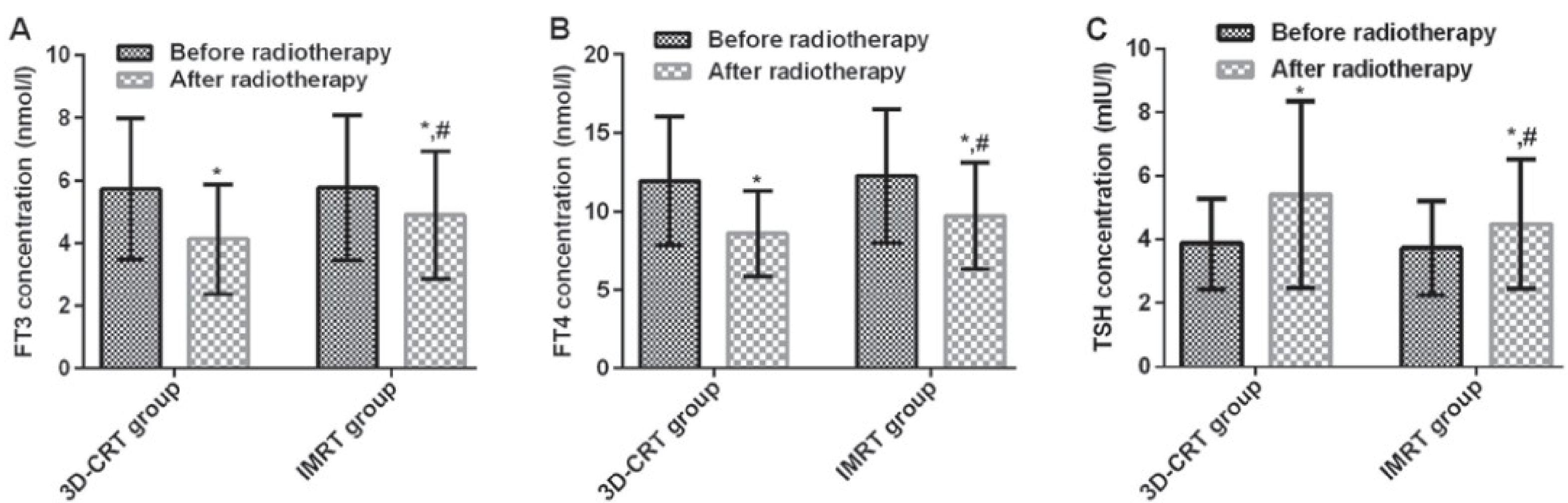
ONCOLOGY LETTERS 17: 3432-3438, 2019

Influence of 3D-CRT and conformal IMRT on thyroid function of patients with cervical and upper thoracic esophageal cancer and comparison of clinical efficacy

FEI CHEN[1*], JUN LI[1*], NIAN AI[1], HUAPING ZHANG[1], JUN LI[2] and YINGYING ZHU[3]

120 EC, 2015-2018; 3DCRT n60, IMRT n60

fT3,fT4 were higher before RT, and TSH lower: concentrations are higher after RT in IMRT group vs 3DCRT (p<0.05)



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IMRT vs 3D

Type	3D-CRT group (n=60)	IMRT group (n=60)	χ^2 value	P-value
Radiation esophagitis				
Grade I	7 (11.67)	4 (6.67)	0.901	0.529
Grade II	25 (41.67)	10 (16.67)	9.076	0.005
Grade III	7 (11.67)	3 (5.00)	1.745	0.322
Total incidence rate	39 (65.00)	17 (28.33)	16.205	<0.001
Radiation pneumonitis				
Grade I	9 (15.00)	6 (10.00)	0.686	0.582
Grade II	13 (21.67)	5 (8.33)	4.183	0.071
Grade III	2 (3.33)	1 (1.67)	0.342	0.909
Total incidence rate	24 (40.00)	12 (20.00)	5.714	0.028

Herrmann *et al. Radiation Oncology* (2017) 12:97
DOI 10.1186/s13014-017-0834-8

Radiation Oncology

RESEARCH Open Access

Outcome of proximal esophageal cancer after definitive combined chemo-radiation: a Swiss multicenter retrospective study

Evelyn Herrmann[1*], Nando Mertineit[1,5], Berardino De Bari[2,6], Laura Hoeng[3], Francesca Caparotti[4], Dominic Leiser[1], Raphael Jumeau[2], Nikola Cihoric[1], Alexandra D. Jensen[1], Daniel M. Aebersold[1] and Mahmut Ozsahin[2]

Median RT dose: 56Gy (28–72Gy)

ICHT: 58% of patients

Median follow up: 34 months

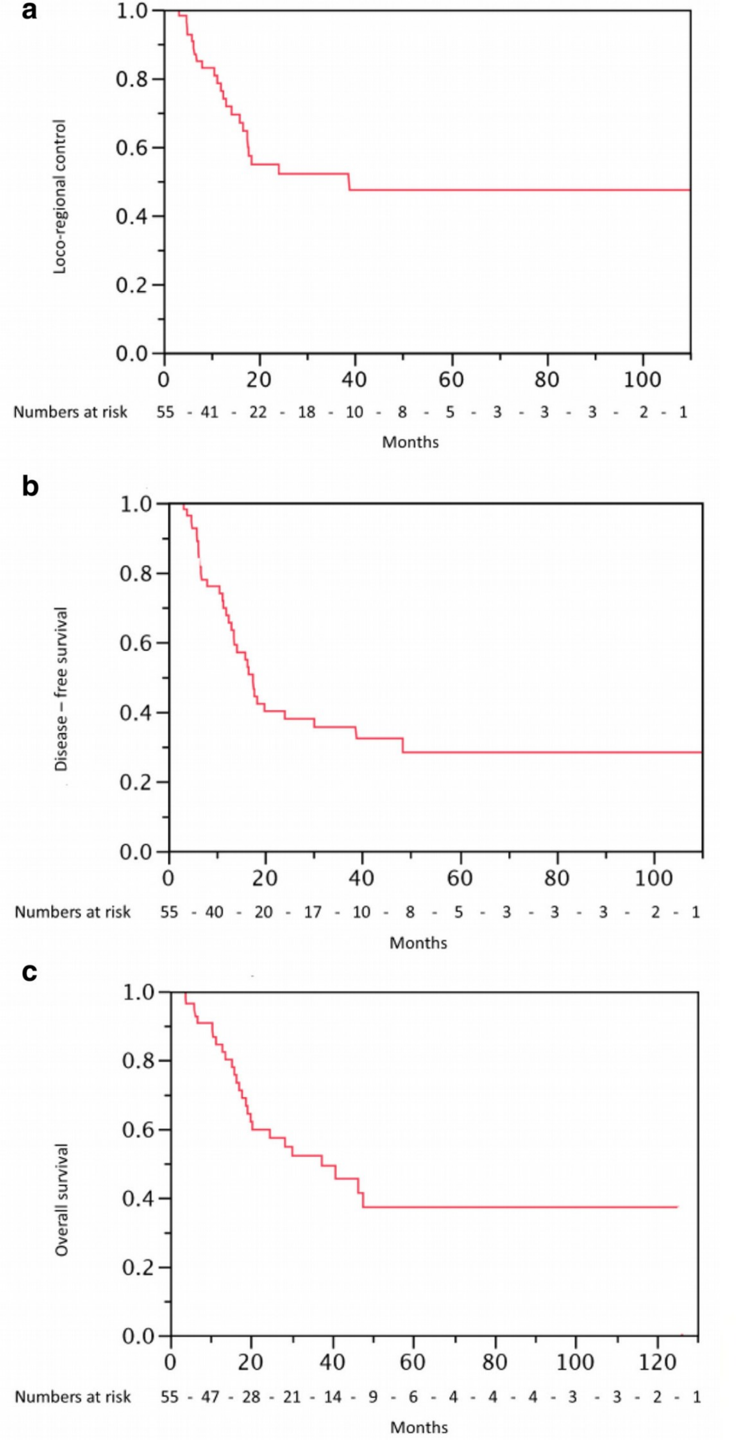
3-year LRC: 52% (95% CI: 37–67%)

3-year DFS: 35% (95% CI: 22–50%)

3-year OS: 52% (95% CI: 37–67%)

Time between diagnosis to CRT >78 days: prognostic factor for LRC

Dose >56Gy (p <0.006) and ICHT (p < 0.004): positive predictive factors for DFS and OS



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Toxicity

Herrmann *et al. Radiation Oncology* (2017) 12:97
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Radiation Oncology

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Characteristic	Number of patients [N]
Age (years), median (range)	64 (42-79)
Gender	
Male	42
Female	13
Acute Tox ≥ Grade 3	
Dysphagia	8
Skin	3
Pain	7
Haematological	5
Chronic Dysphagia	
Grade 1-2	30
Grade 3-4	5

Dysphagia G2: 45%, G3-4: 15%
Odynophagia G1-2 69%, G3 12%
Skin toxicity G3 in 5%

ICHT had no impact on odynophagia or on skin toxicity

HT: G1 20%, G2 33%, G3 9%

In ICHT group G2 HT was significantly higher, no differenceinG3
2 patients (4%) needed hospitalization for toxicity

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reviews

Annals of Oncology 27: 1664–1674, 2016
doi:10.1093/annonc/mdw183
Published online 26 April 2016

Cervical esophageal cancer: a gap in cancer knowledge

A. Hoeben[1], J. Polak[1], L. Van De Voorde[2], F. Hoebers[2], H. I. Grabsch[3,4] & J. de Vos-Geelen[1]*

[1]Department of Internal Medicine, Division of Medical Oncology; Departments of [2]Radiation Oncology (MAASTRO Clinic); [3]Pathology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; [4]Pathology & Tumour Biology, Leeds Institute of Cancer Studies and Pathology, University of Leeds, Leeds, UK

Key Points

- Early detection of precancerous conditions, molecular changes or early CEC would be desirable
- CEC is rare in Western countries, it is improbable a successful screening
- Taking the survival data and toxicity profiles the optimal treatment regimen is not yet defined
- Future studies: HN or esophageal protocol?
- ENI (cervical, supraclavicular, paratracheal lymph nodes) is suggested
- Patients need optimal nutritional and clinical support

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Editorial

Radiotherapy treatment strategies for squamous cell carcinoma of the cervical oesophagus: moving toward better outcomes

Pierfrancesco Franco[1], Francesca Arcadipane[2], Paolo Strignano[3], Renato Romagnoli[4], Umberto Ricardi[1]

- RT plays an important role in association with CRT
- Cancer-related mortality is due also to loco-regional relapse
- ENI is recommended
- IMRT and IGRT are able to deliver dose-escalated treatment with a more favorable toxicity profile and allow intense concomitant CT

Advances in early diagnosis and integration of RT with CT (including novel agents) and radical surgery remain strongly required to substantially improve clinical results

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Thank You

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