CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

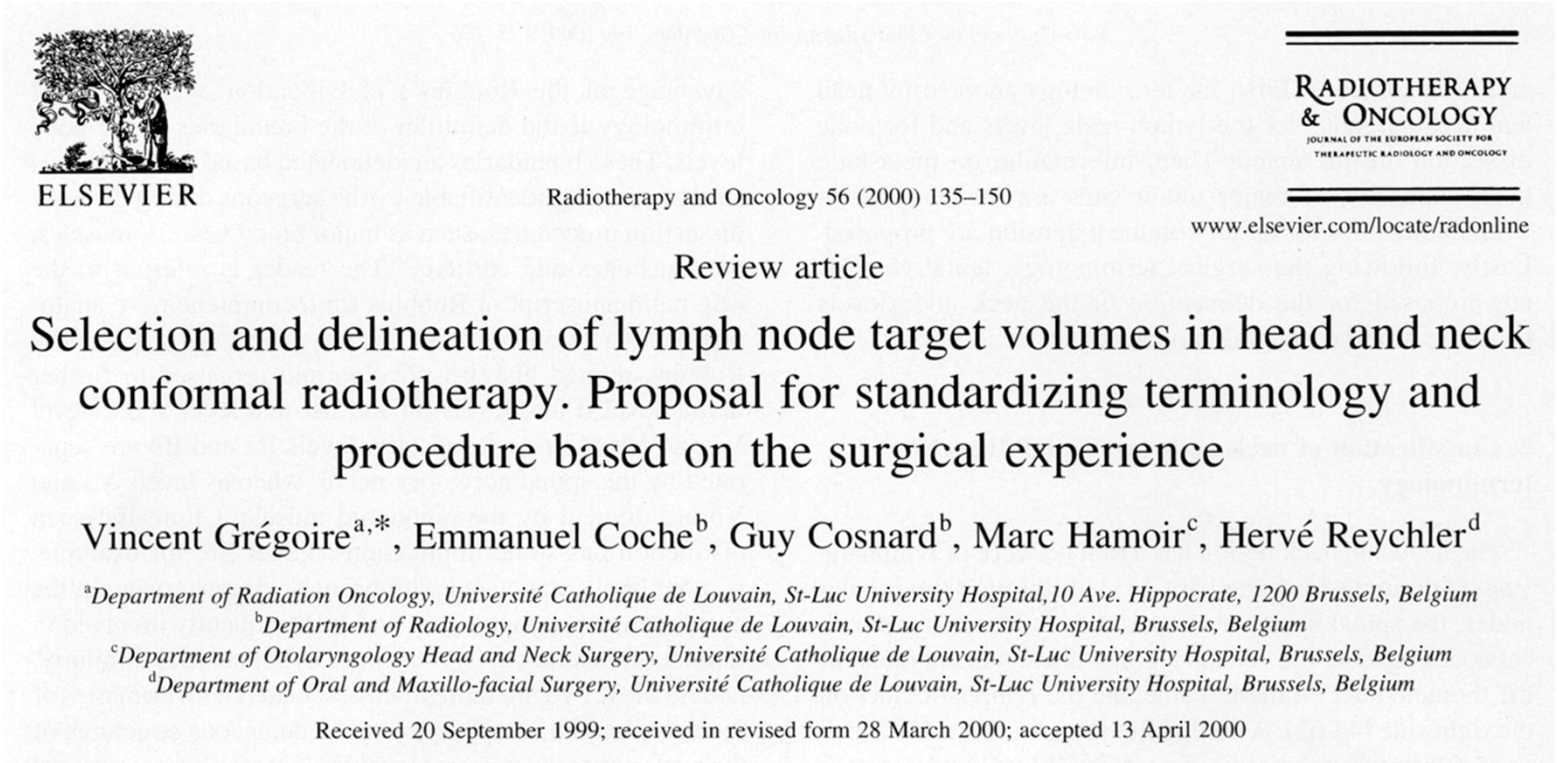
Target volumes in H&N tumors: what are the needs for modern treatments

Vincent GREGOIRE, MD, PhD, Hon FRCR (UK, IE)

Radiation Oncology Department, Centre Léon Bérard, Lyon, France

Gemelli, Oct. 2023

IMRT/VMAT in Head and Neck Tumors



ELSEVIER

Radiotherapy and Oncology 56 (2000) 135–150

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Review article

Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience

Vincent Grégoire[a,*], Emmanuel Coche[b], Guy Cosnard[b], Marc Hamoir[c], Hervé Reychler[d]

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[b]*Department of Radiology, Université Catholique de Louvain, St-Luc University Hospital, Brussels, Belgium*
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Grégoire et al, R&O, 2000

Clinical Target Volumes (CTV) delineation in the neck

ELSEVIER

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines ☆

Vincent Grégoire [a,*], Kian Ang [b], Wilfried Budach [c], Cai Grau [d], Marc Hamoir [e], Johannes A. Langendijk [f], Anne Lee [g], Quynh-Thu Le [h,i], Philippe Maingon [j], Chris Nutting [k], Brian O'Sullivan [l], Sandro V. Porceddu [m], Benoit Lengele [n]

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Grégoire et al;, R&O, 2013

Clinical Target Volumes (CTV) delineation in the neck

Radiotherapy and Oncology 134 (2019) 1–9

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update

Julian Biau [a,b,*], Michel Lapeyre [b], Idriss Troussier [a], Wilfried Budach [c], Jordi Giralt [d], Cai Grau [e], Joanna Kazmierska [f], Johannes A. Langendijk [g], Mahmut Ozsahin [a], Brian O'Sullivan [h], Jean Bourhis [a,1], Vincent Grégoire [i,*,1]

Biau, Grégoire et al, R&O, 2019

IMRT/VMAT in Head and Neck Tumors

Primary Tumour Clinical Target Volumes (CTV_p)

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines

Vincent Grégoire [a,*], Mererid Evans [b], Quynh-Thu Le [c], Jean Bourhis [d], Volker Budach [e], Amy Chen [f], Abraham Eisbruch [g], Mei Feng [h], Jordi Giralt [i], Tejpal Gupta [j], Marc Hamoir [k], Juliana K. Helito [l], Chaosu Hu [m], Keith Hunter [n], Jorgen Johansen [o], Johannes Kaanders [p], Sarbani Ghosh Laskar [j], Anne Lee [q], Philippe Maingon [r], Antti Mäkitie [s], Francesco Micciche' [t], Piero Nicolai [u], Brian O'Sullivan [v], Adela Poitevin [w], Sandro Porceddu [x], Krzysztof Składowski [y], Silke Tribius [z], John Waldron [v], Joseph Wee [aa], Min Yao [ab], Sue S. Yom [ac], Frank Zimmermann [ad], Cai Grau [ae]

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Gemelli, Oct. 2023

Grégoire et al, R&O, 2018

Where to go from here?
GTV primary tumors

Automatic AI-based GTV delineation

Comparing different CT, PET and MRI multi-modality image combinations for deep learning-based head and neck tumor segmentation

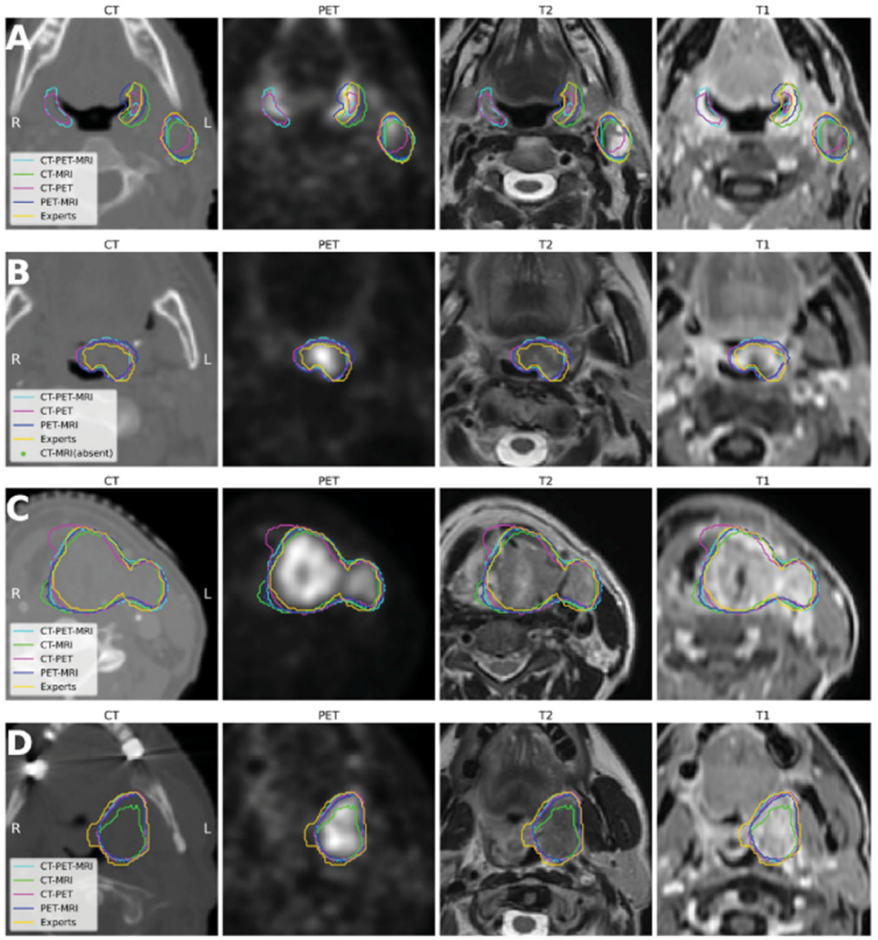
Jintao Ren[a,b,c], Jesper Grau Eriksen[a,d], Jasper Nijkamp[a,b*] and Stine Sofia Korreman[a,b,c*]

[a]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [b]Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; [d]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

- 153 patients with pharyngo-laryngeal SCC
- 60% T1-T2; 75% N^+
- CT, coronal MRI-T1, axial MRI-T2, mDixon MRI, FDG-PET acquired with an immobilization mask

Ren et al, Acta Oncol, 2021

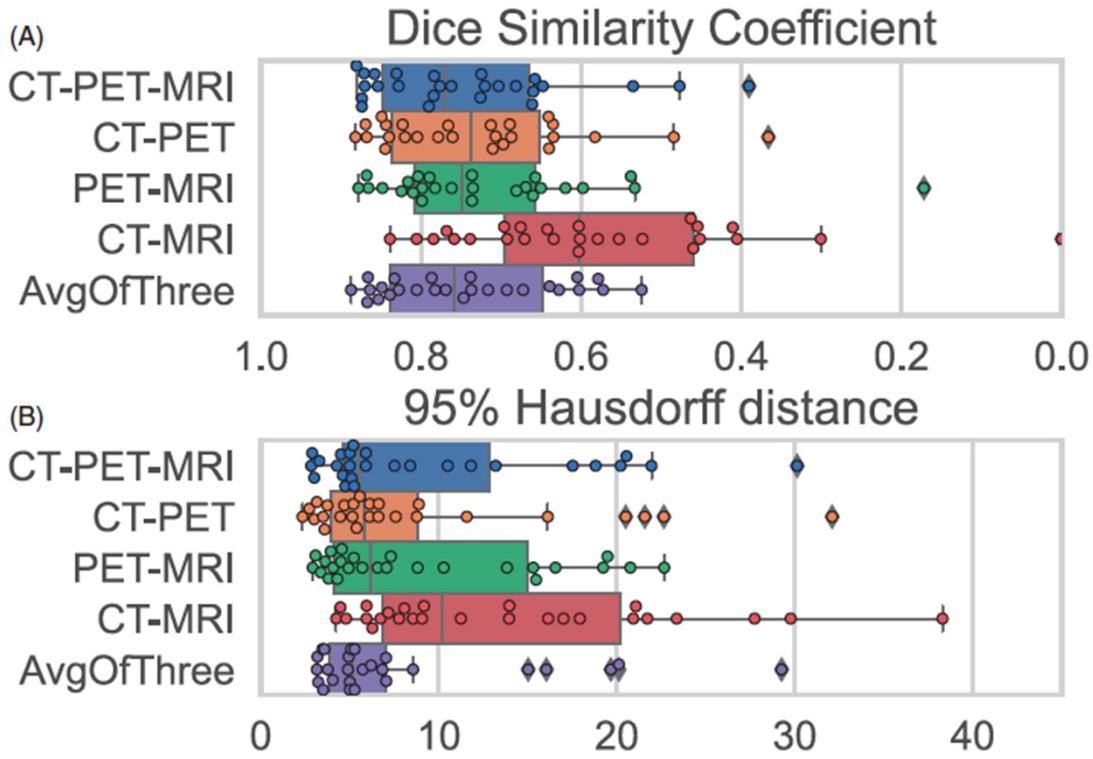
Automatic AI-based GTV delineation



Gemelli, Oct. 2023

Ren et al, Acta Oncol, 2021

Automatic AI-based GTV delineation



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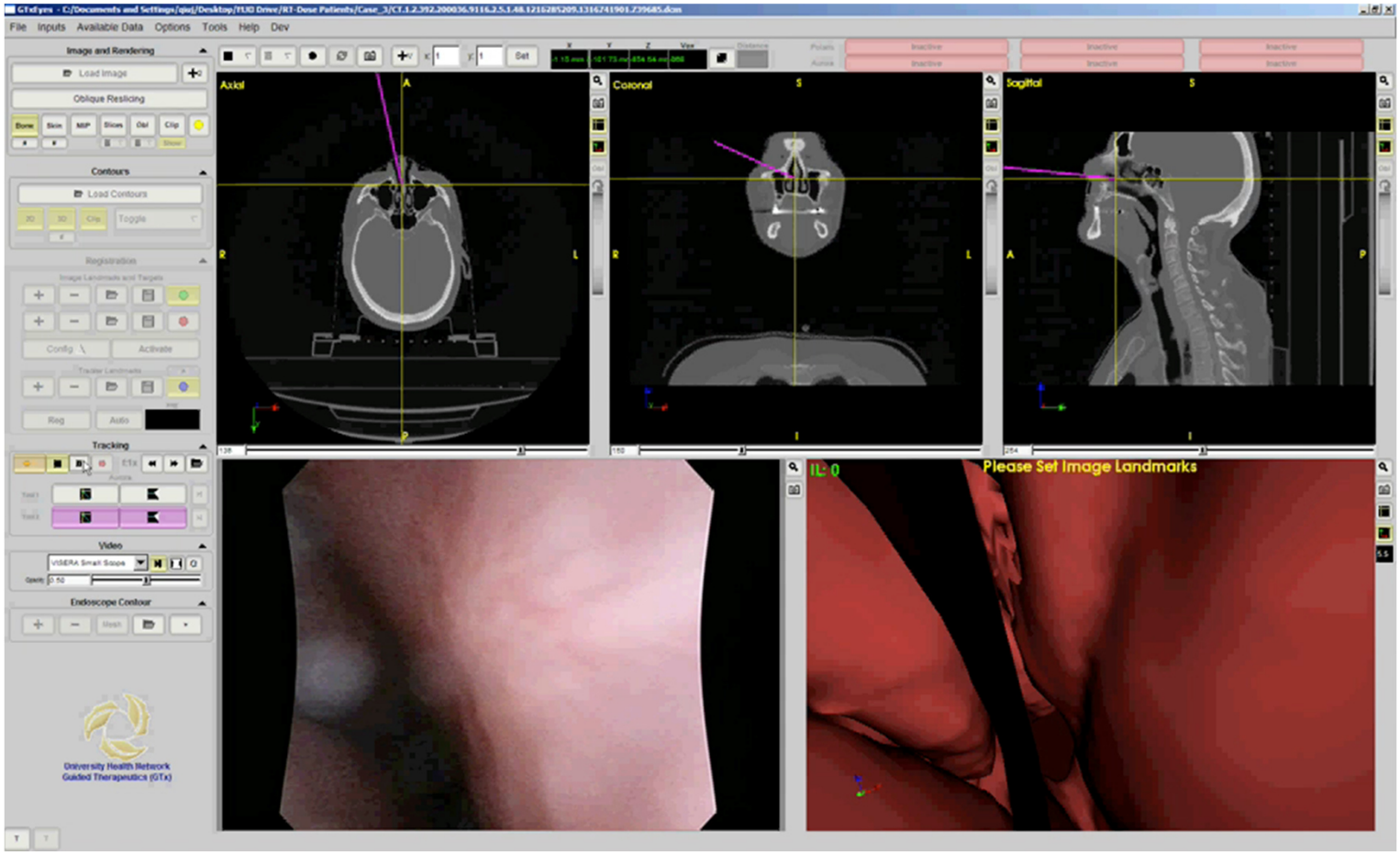
Ren et al, Acta Oncol, 2021

And in the “foreseeable” future… Augmented reality?

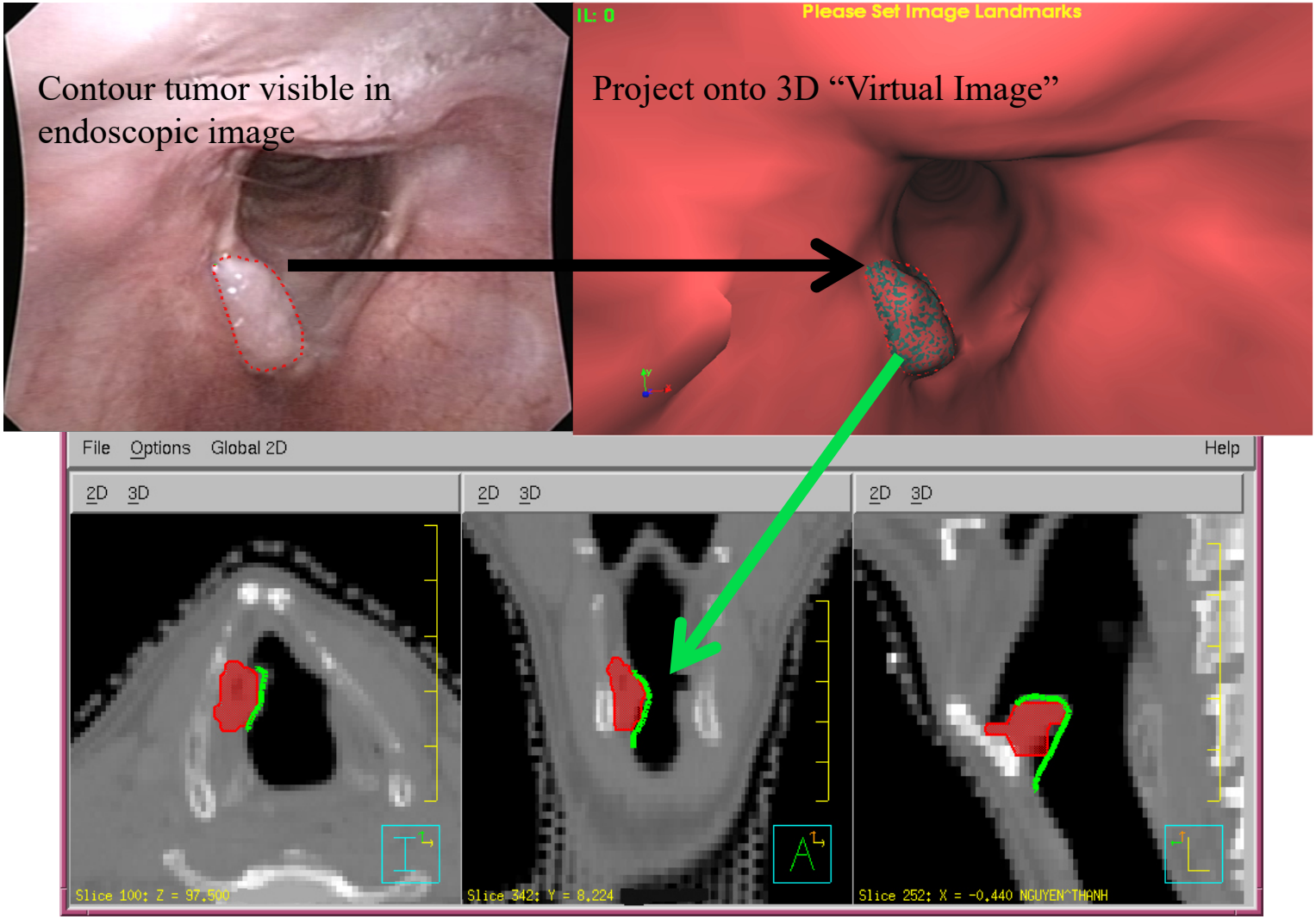


Gemelli, Oct. 2023

Weersink et al Med. Phys 38 6458, 2011

Weersink, US Patent: 9,138,597

Endoscopic Contouring



Weersink et al Med. Phys 38 6458, 2011

Weersink, US Patent: 9,138,597

Where to go from here?
CTV primary tumors

From primary tumor GTV to CTV

Geometrical margins

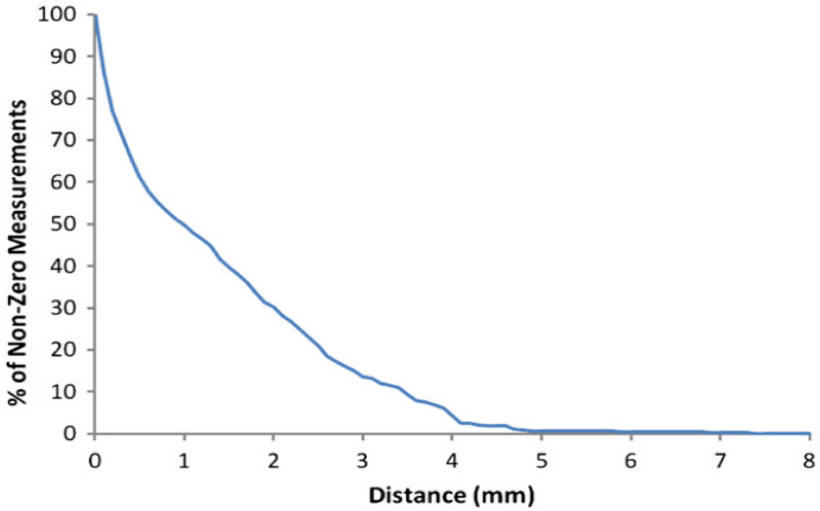


Fig. 8. Graph showing the percentage of nonzero measurements against distance from the gross tumor volume.

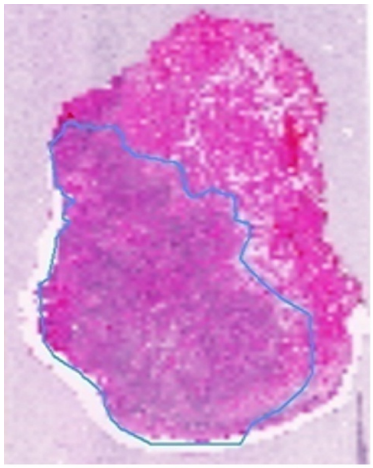


Fig. 4. Image at ×4 magnification and naked eye resolution with gross tumor volume contoured in blue.

Of 88 slides from 10 patients with oral cancers, 44 (50%) had signs of microscopic extension. The maximum distance from the border was 7.8 mm. Ninety-nine percent of all MD was within 4.75 mm and 95% was within 3.95 mm of the GTV.

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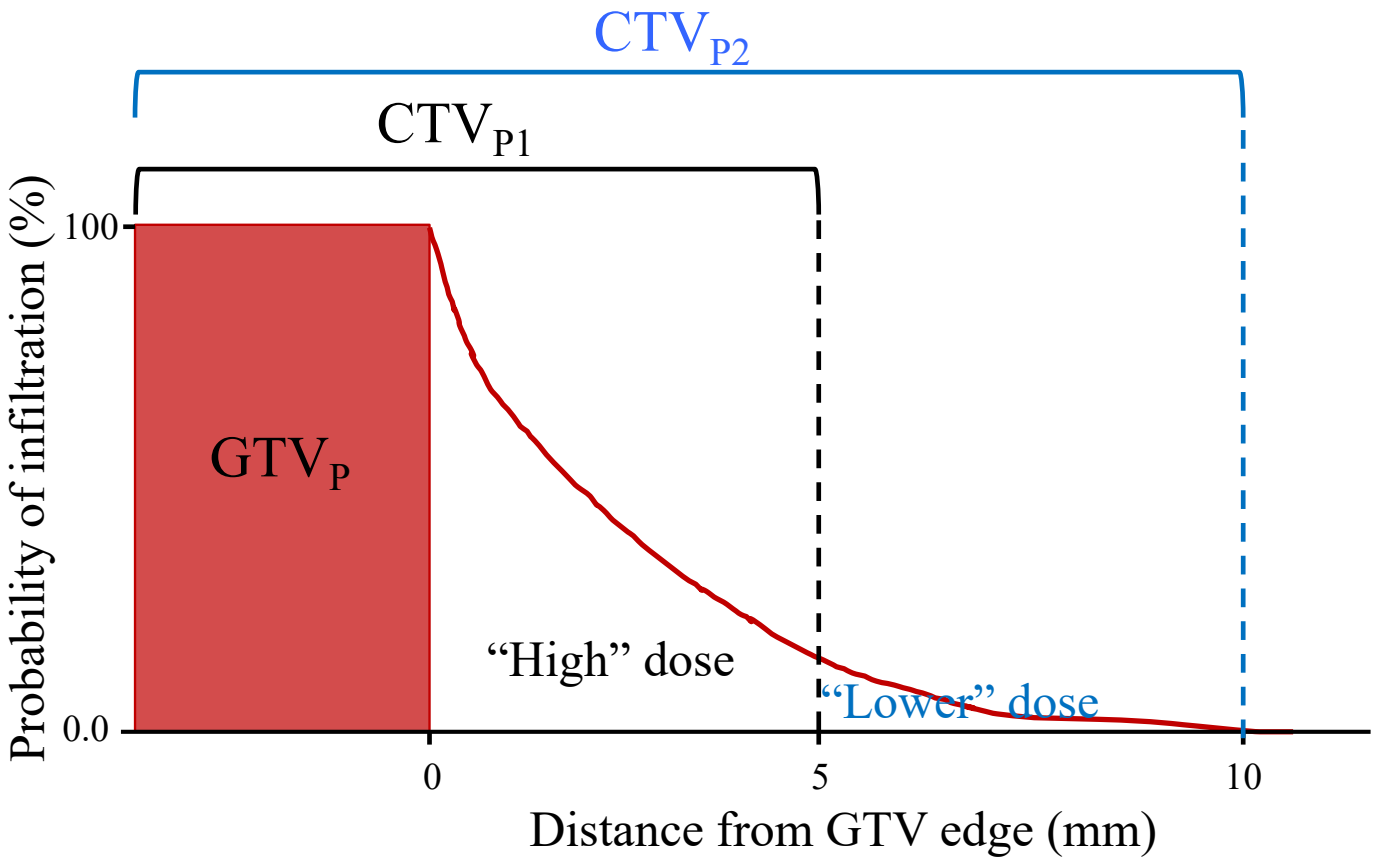
Gemelli, Oct. 2023

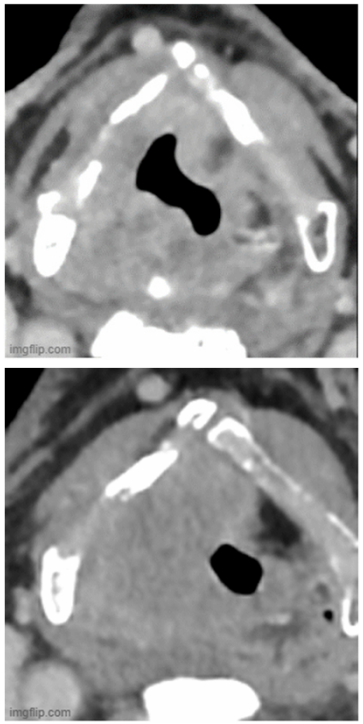
Campbell et al. IJROBP, 2012

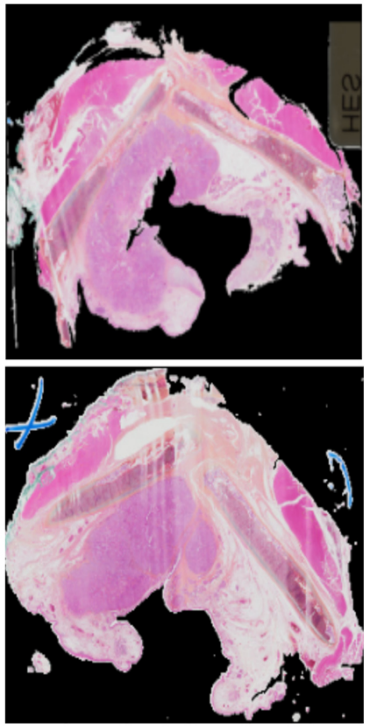
From primary tumor GTV to CTV



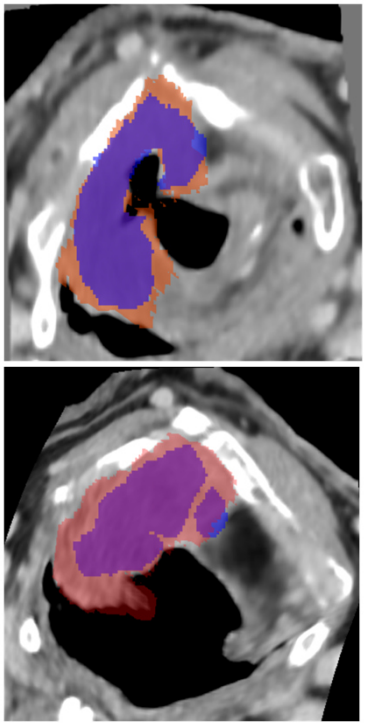
From primary tumor GTV to CTV

AI-based target volume delineation





Pathologic specimen



Registration of CT and histology

Courtesy of A. Leroy, 2023

Where to go from here?
CTV neck nodes

Neck irradiation

- How could neck irradiation evolve in the coming years?
  - Personalization of the selection of the elective neck node levels
  - Automatic target volume delineation

Personalization of the selection of the elective neck node levels

IOP Publishing Phys. Med. Biol. 64 (2019) 165003 (17pp) https://doi.org/10.1088/1361-6560/ab2a18

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

PAPER

A Bayesian network model of lymphatic tumor progression for personalized elective CTV definition in head and neck cancers

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Keywords: CTV, Bayesian network, head and neck cancer, lymph nodes, elective nodal irradiation

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Gemelli, Oct. 2023

Unkelbach, R&O, 2020

Personalization of the selection of the elective neck node levels

ELSEVIER

Radiotherapy and Oncology
Volume 153, December 2020, Pages 15-25

Review Article

The role of computational methods for automating and improving clinical target volume definition

Jan Unkelbach [a], Thomas Bortfeld [b], Carlos E. Cardenas [c], Vincent Gregoire [d], Wille Hager [e], Ben Heijmen [f], Robert Jeraj [g], Stine S. Korreman [h], Roman Ludwig [a], Bertrand Pouymayou [a], Nadya Shusharina [b], Jonas Söderberg [i], Iuliana Toma-Dasu [e], Esther G.C. Troost [j, k, l], Eliana Vasquez Osorio [m]

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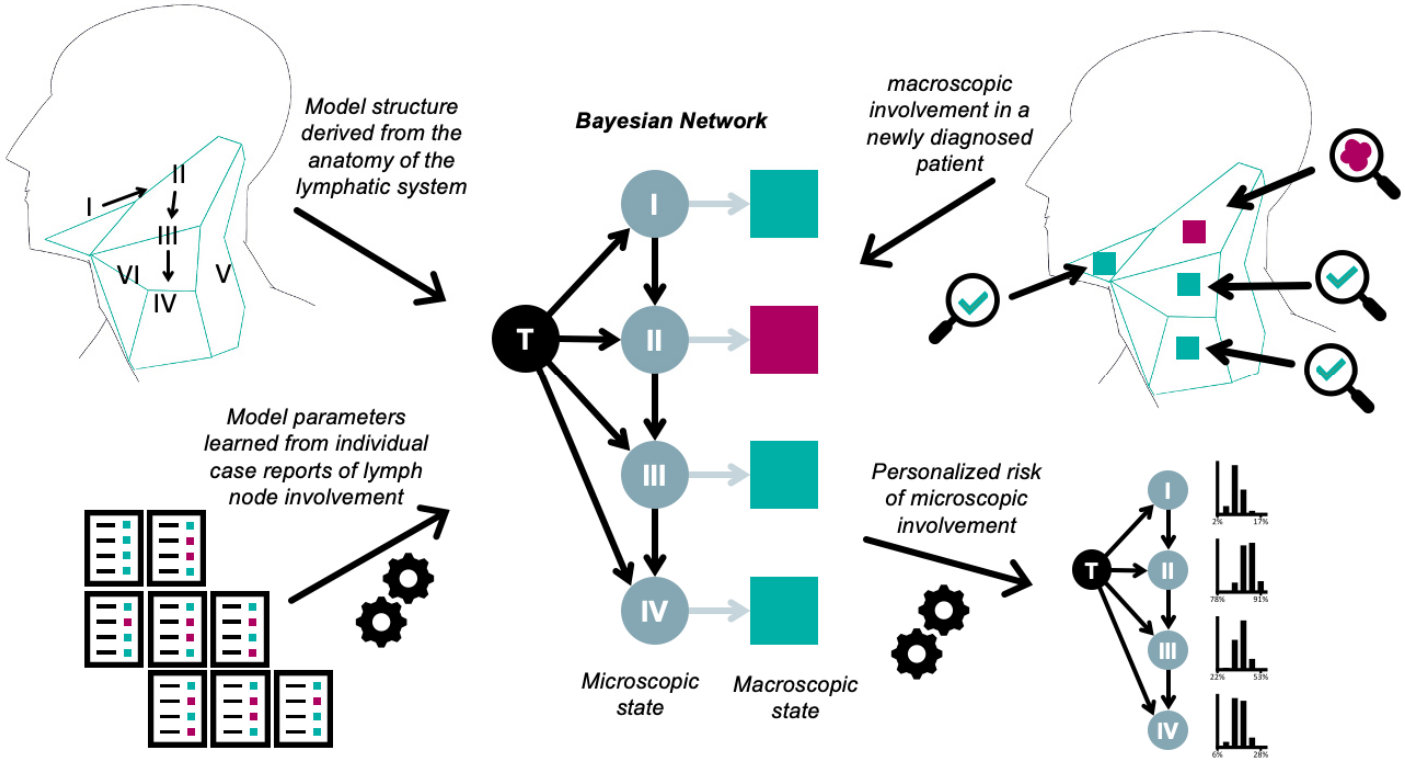
Gemelli, Oct. 2023

Unkelbach, R&O, 2020

Personalization of the selection of the elective neck node levels

From population-based to individual probability



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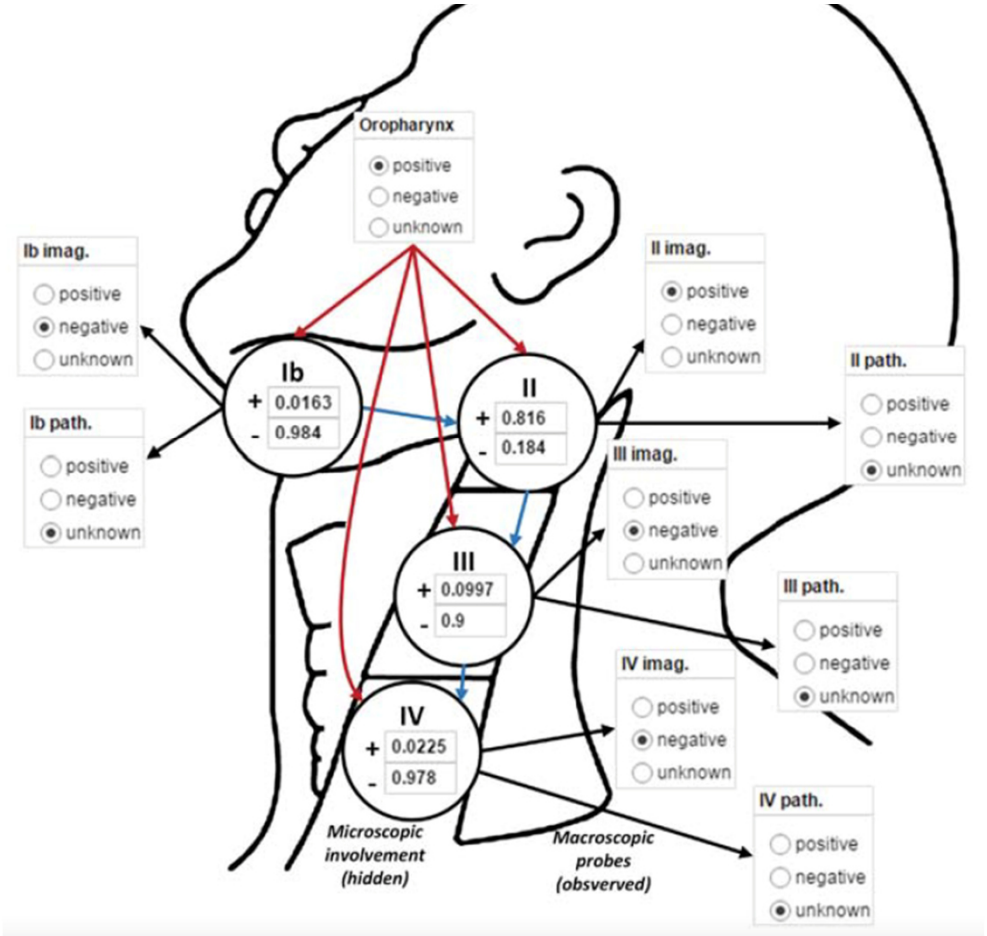
Unkelbach, R&O, 2020

Personalization of the selection of the elective neck node levels

From population-based to individual probability



Gemelli, Oct. 2023

Pouymayou, PMB, 2019

Optimization of the selection of the elective neck node levels

Meta-analyses of the Negative Predictive Value of different imaging modalities for neck staging

Author	# necks	N-staging	CT	MRI	FDG-PET	US-FNA	SLN
Kyzas, 2008	1236	N0 & N^+	0.92	0.94	0.95	0.87	-
Lian-Ming Wu, 2012	878	N0 & N^+	-	0.93* (0.96 for DW-MRI)*	-	-	-
Thompson, 2013	766	N0 & N^+	-	-	-	-	0.96 (0.94-0.99)
Li-Jen Liao, 2016	181-2469	N0	0.87	0.88	0.87	0.90	0.96

*NPV were calculated for a prevalence of 0.2

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Optimization of the selection of the elective neck node levels

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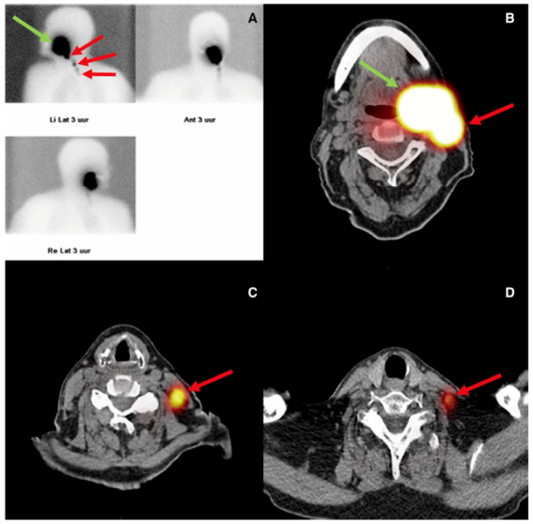
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

SPECT/CT-guided elective nodal irradiation for head and neck cancer is oncologically safe and less toxic: A potentially practice-changing approach



Gemelli, Oct. 2023

de Veij Mestdagh et al, R&O, 2020

Optimization of the selection of the elective neck node levels

- #pts = 50; 2015-2017
- SCC of oral cavity, oropharynx ($p16^+$ and $p16^-$), hypopharynx, larynx not crossing the midline
- Any T (except T1 glottic), any N (except N2c and N3)
- Stage I-II (24%) and III-IV (76%)
- VMAT, 70 Gy / 54.25 Gy ± concomitant CH (20%)
- Matched pair cohort of patients with bilateral neck irradiation

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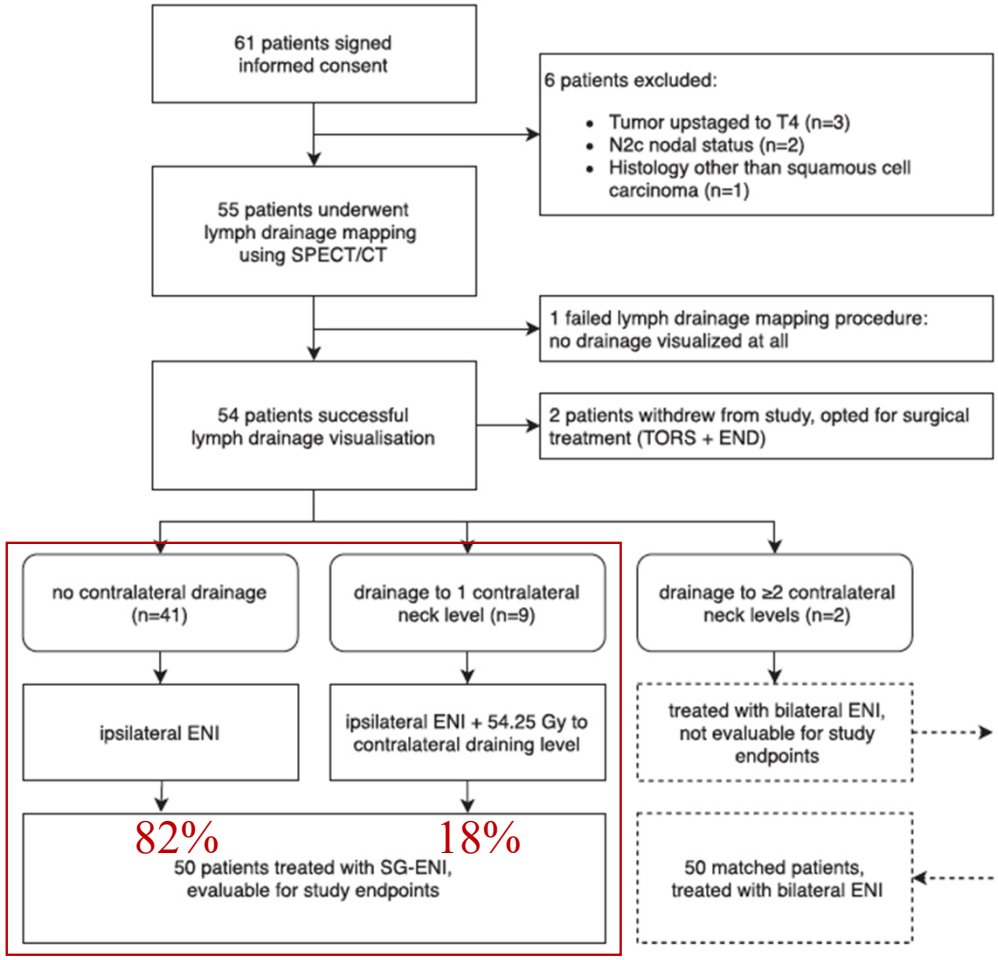
de Veij Mestdagh et al, R&O, 2020

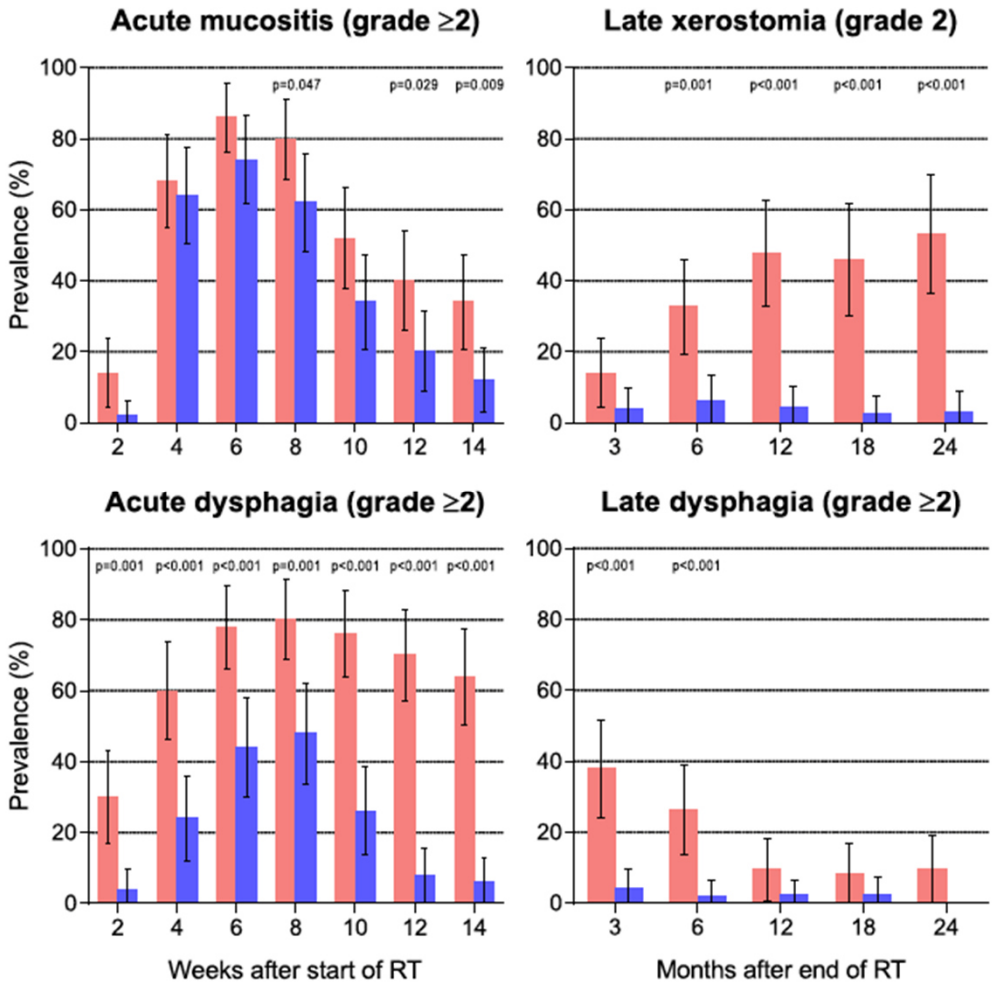
Optimization of the selection of the elective neck node levels



Gemelli, Oct. 2023

de Veij Mestdagh et al, R&O, 2020

Optimization of the selection of the elective neck node levels



Radiation Toxicity

Bilateral ENI

SPECT/CT-guided ENI

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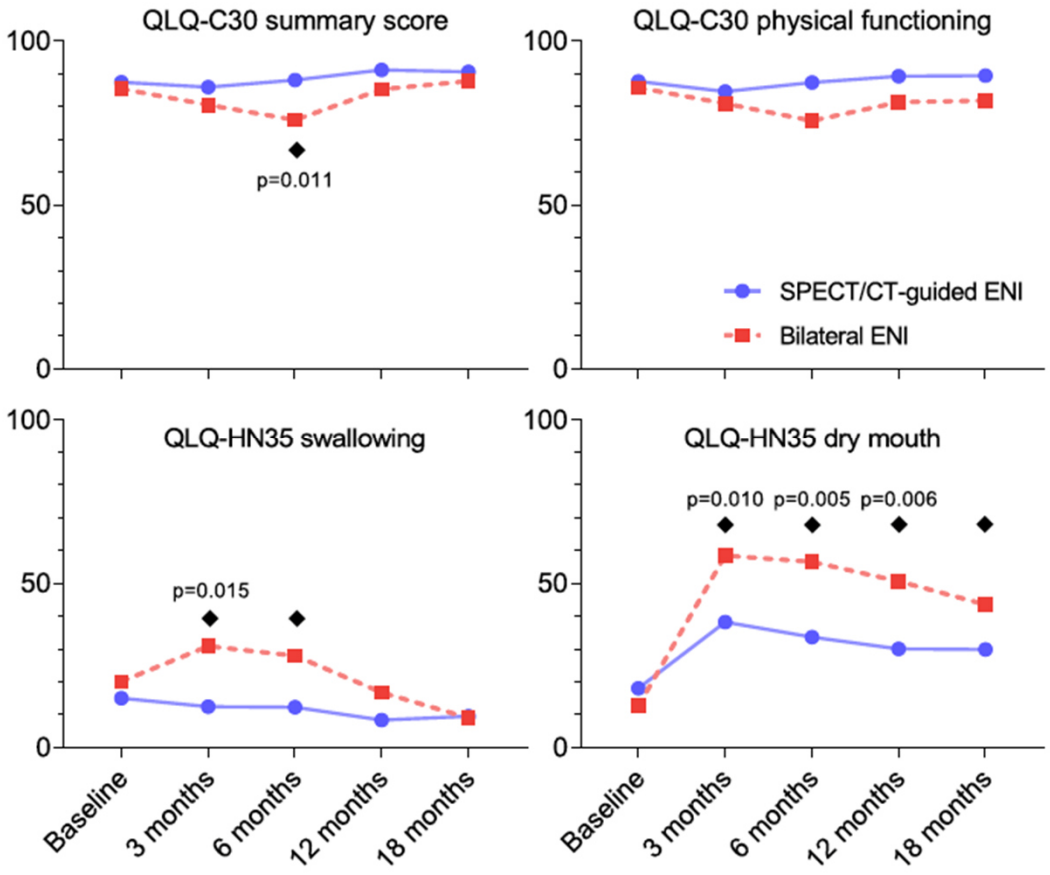
de Veij Mestdagh et al, R&O, 2020

Optimization of the selection of the elective neck node levels

Quality of Life (EORTC scale)



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de Veij Mestdagh et al, R&O, 2020

Optimization of the selection of the elective neck node levels

Outcome

Endpoint	
2-year incidence of local failure	4.3% (95% CI: 0-10%)
2-year incidence of regional failure	4.0% (95% CI: 0-9%)
2-year incidence of distant failure	8.6% (95% CI: 0-16%)
2-year overall survival	81.6% (95% CI: 71-95%)

de Veij Mestdagh et al, R&O, 2020

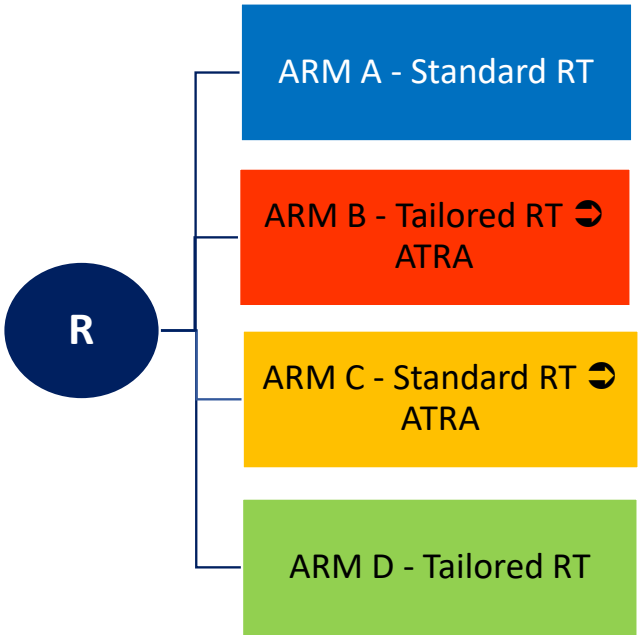
Optimization of the selection of the elective neck node levels

Concept validation

- Adult pts with primary head and neck tumor up to, but not crossing the midline, previously untreated with histologically-confirmed squamous cell carcinoma of
  - the oropharynx $p16^-$, larynx or hypopharynx : T1/N2a-N2b, T2/N0-N2b, T3/N0-N2b (UICC 8th ed)
  - the oropharynx $p16^+$: T1/N1 (multiple nodes), T2-T3/N0-N1 (UICC 8th ed)

- Unilateral lymph node drainage i.e. ipsilateral sentinel node mapping, or non-contralateral FDG-PET/CT

- Amenable to treatment with RT or concomitant chemo-radiotherapy



Primary endpoint
- Event free survival

Secondary endpoints
- Local relapse Free survival
- Regional relapse free survival
- Metastase free survival
- Overall survival
- Rate of pathologically positive lymph nodes at neck node dissection performed at 4 months after the completion of (chemo)-radiotherapy
- Safety according to NCI-CTCAE V5.0
- Patient 'QoL (EORTC QLQ-C30, HN-43)

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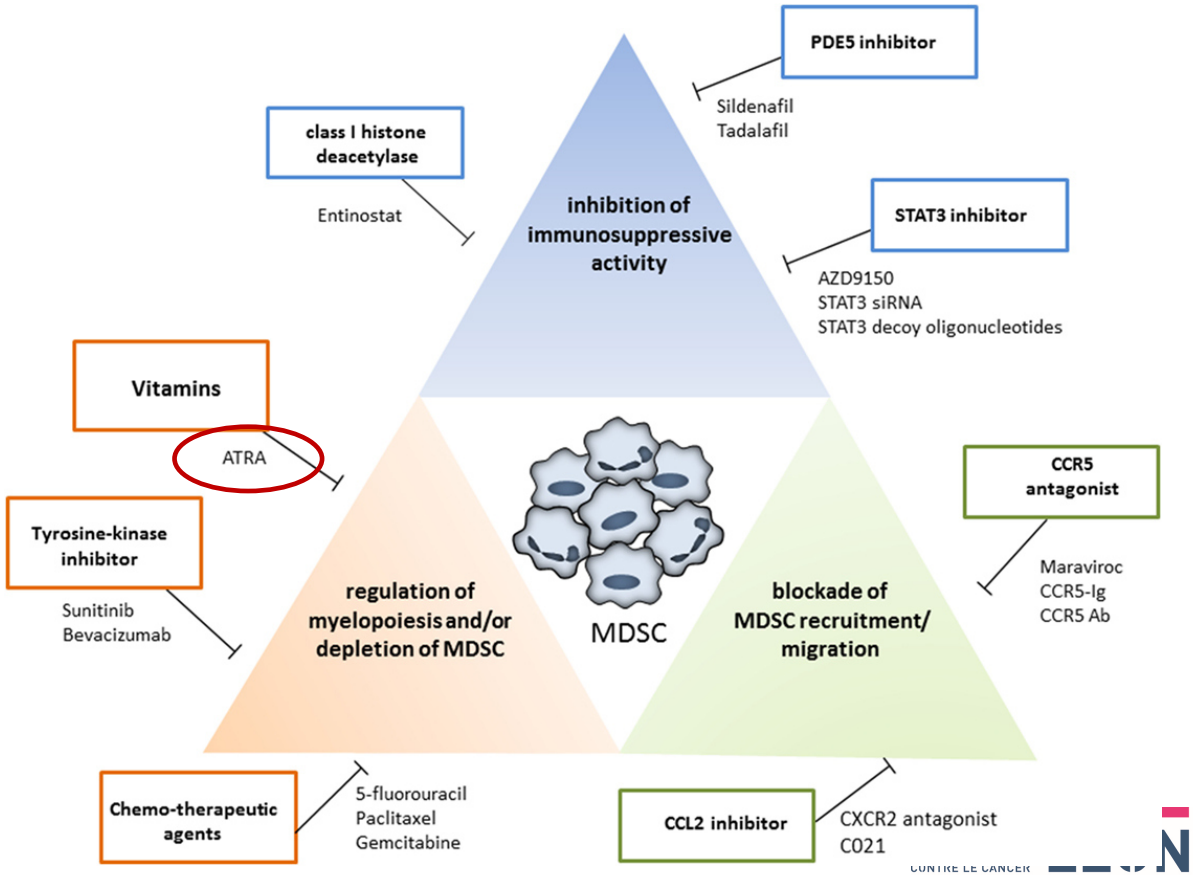
Gemelli, Oct. 2023

Deutsch, Grégoire, Paragios, 2021

Optimization of the selection of the elective neck node levels

Myelo-Derived Suppressor Cells (MDSC)

- Immature myeloid cells
- Immuno-suppressive function
- Inhibition of T-cells and NK-cells
- Stimulate angiogenesis and promote metastatic niches
- Enrichment of MDSC correlated with worse outcome

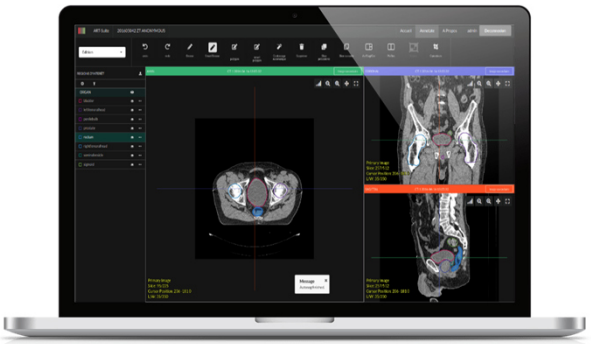


Gemelli, Oct. 2023

Fleming et al, Front. Immunol, 2018

Could AI-based software further improve human-based processes?

What can our AI actually do?



1

Plan preparation

Multi-modal, multi-organ organ segmentation through Unique combination of Deep and transfer learning

Auto-identify organs at risks and tumors in patients anatomy in a few minutes with medical accuracy

2

Dose Optimization:

Unique combination of parallel multi-objective Master-Slave optimization & reinforcement learning

Produce the best possible treatment plan in minutes instead of hours /days, protecting 30% more organs at risk

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

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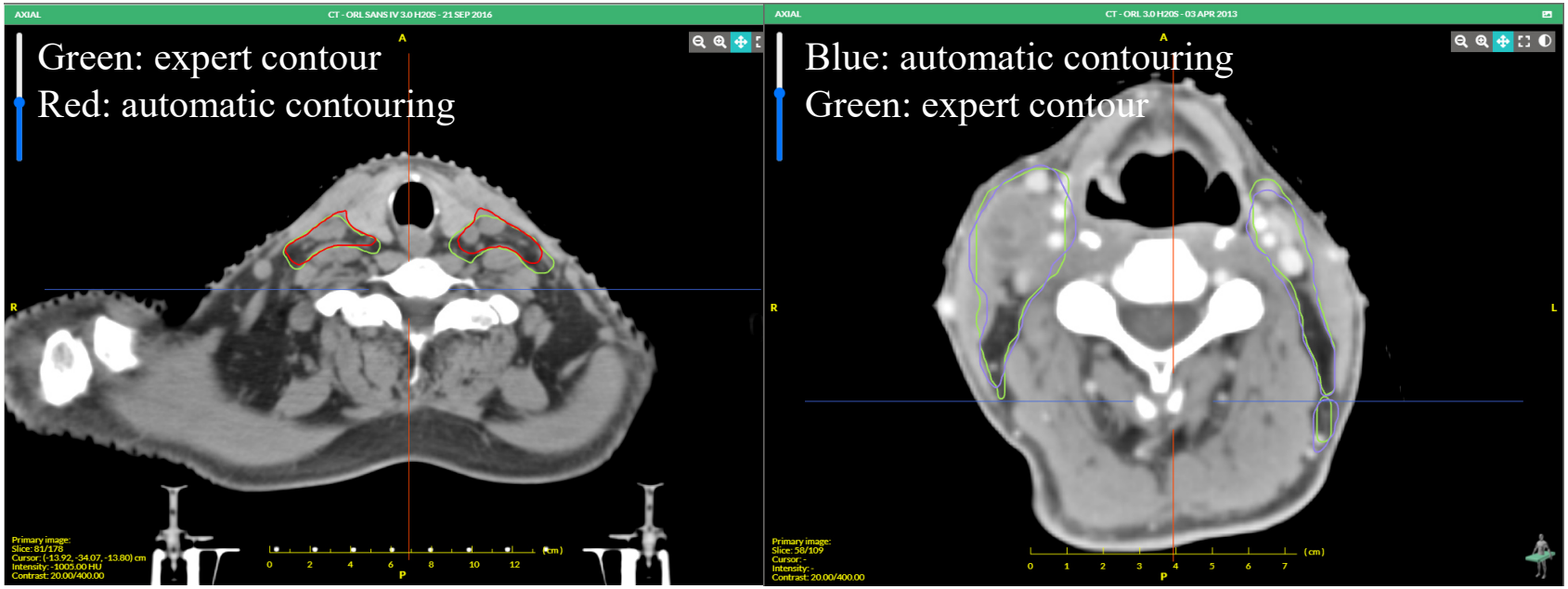
Courtesy of N. Paragios, 2021

Could AI-based software further improve human-based processes?

Automatic nodal target volume delineation



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Courtesy of N. Paragios, 2021

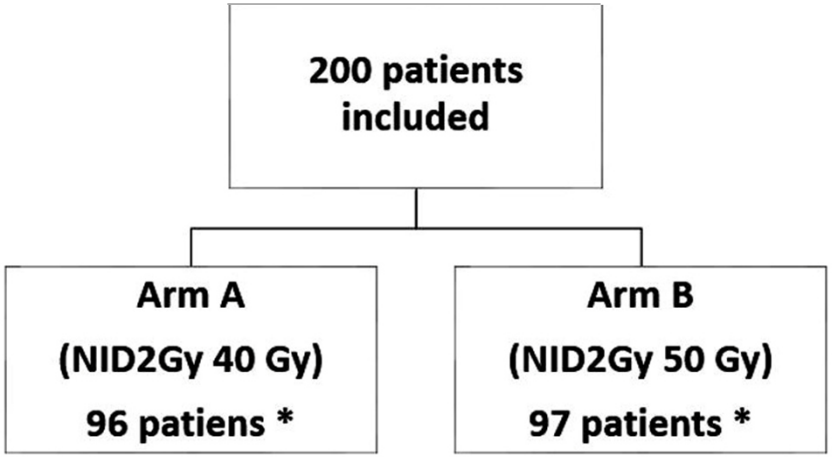
Conclusions

- Automatic GTV/CTV delineation in progress
- International guidelines for nodal target volume selection & delineation remain a standard of care
- Personalization of the selection of the neck node target volumes needs to be validated
- Elaboration of tools for automatic nodal target volume delineation is underway.

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Optimization of the radiation dose in the elective neck

- 2008-2011
- SCC of oral cavity, oropharynx, hypopharynx, larynx and CUP
- p16- (78%) and p16+ (22%) oropharyngeal tumors
- Stage I-II (12%) and III-IV (88%)
- IMRT, 70 Gy (EQD2) on primary tumor PTV ± concomitant CH (61%) and randomization for the elective PTV

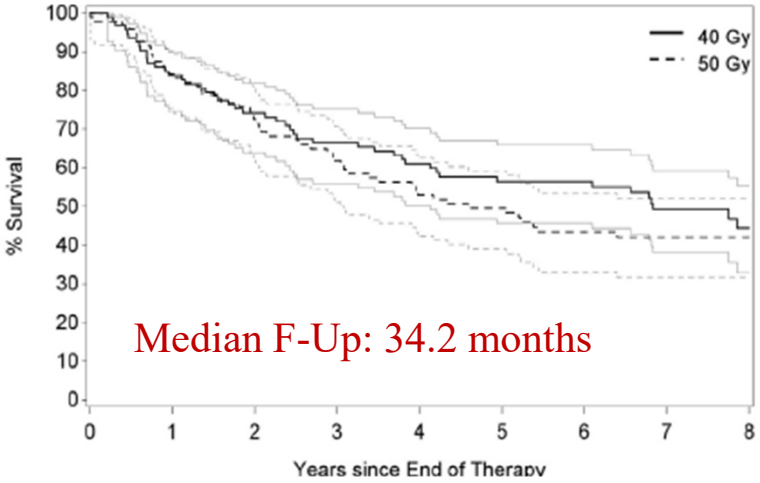


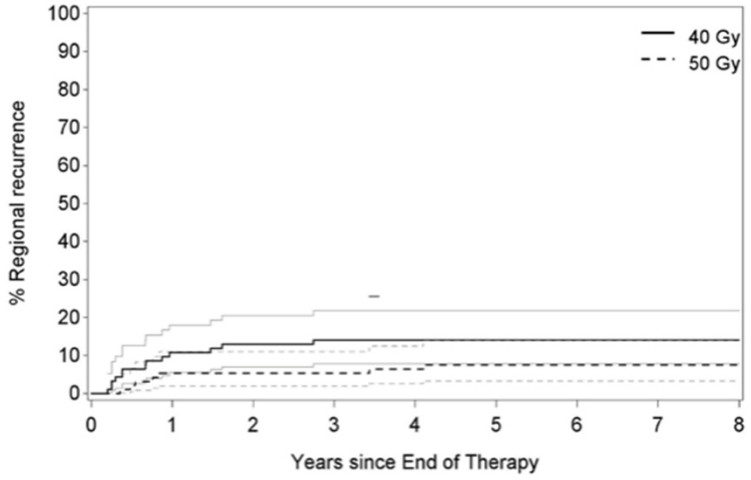
Gemelli, Oct. 2023

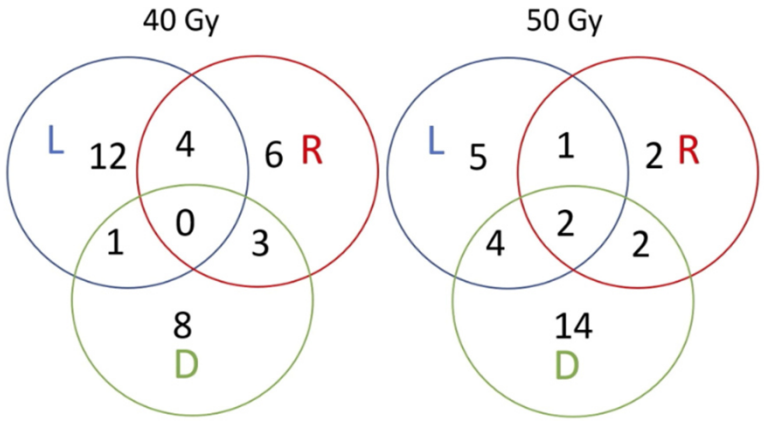
Nevens, R&O, 2017

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Optimization of the radiation dose in the elective neck







Regional recurrence	13/95	7/96 (p=ns)
Regional recurrence in PTV high dose	9/95	5/96
Regional recurrence in elective PTV	2/95	2/96

Gemelli, Oct. 2023

Deschuymer, R&O, 2020

Optimization of the radiation dose in the elective neck

Radiation toxicity

		⩾grade1 salivary gland toxicity	Total	P(GEE)	⩾grade3 salivary gland toxicity	Total	P(GEE)
Month 6	40 Gy	55 (68.7%)	80	0.01	2 (2.5%)	80	0.7
	50 Gy	63 (86.3%)	73		3 (4.1%)	73	
Month 12	40 Gy	47 (71.2%)	66	0.23	3 (4.5%)	66	1.0
	50 Gy	53 (80.3%)	66		2 (3.0%)	66	
Month 18	40 Gy	37 (63.8%)	58	0.03	2 (3.4%)	58	1.0
	50 Gy	49 (81.7%)	60		2 (3.3%)	60	
Month 24	40 Gy	34 (63.0%)	54	0.84	1 (1.8%)	54	1.0
	50 Gy	35 (64.2%)	54		0 (0.0%)	54	

Dysphagia							
	Randomisation	G 0	G 1	G2	G3	Total	P(GEE)
Month 6	40 Gy	48 (61.5%)	27 (34.6%)	3 (3.8%)	0	78	0.06
	50 Gy	37 (51.4%)	20 (27.8%)	15 (20.8%)	0	72	
Month 12	40 Gy	45 (67.2%)	14 (20.9%)	7 (10.4%)	1 (1.5%)	67	0.21
	50 Gy	37 (56.9%)	18 (27.7%)	6 (9.2%)	4 (6.1%)	65	
Month 18	40 Gy	39 (68.4%)	12 (21.0%)	6 (10.5%)	0	57	0.16
	50 Gy	33 (55.0%)	19 (31.7%)	8 (13.3%)	0	60	
Month 24	40 Gy	39 (73.6%)	12 (22.6%)	2 (3.8%)	0	53	0.15
	50 Gy	34 (63.0%)	12 (22.2%)	6 (11.1%)	2 (3.7%)	54	

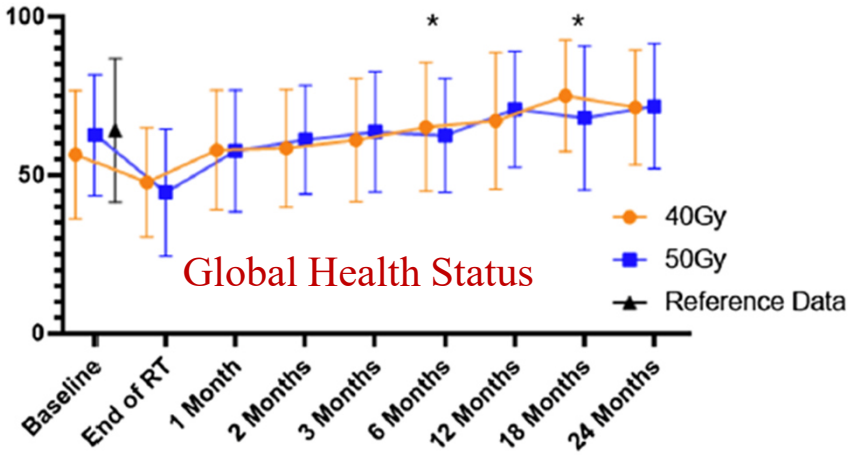
CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

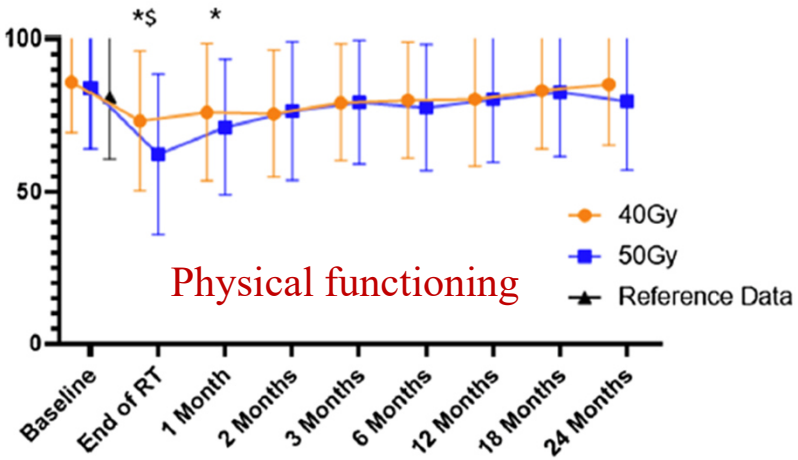
Gemelli, Oct. 2023

Deschuymer, R&O, 2020

Optimization of the radiation dose in the elective neck

Quality of Life (EORTC QLQ-C30)





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Neck node infiltration from H&N primaries

Sources of information

- Anatomy of the lymphatic system
- Lymph node distribution: clinical
  radiological
  pathological
- Pattern of failure after selective treatment

Neck node infiltration from H&N primaries

- Predictive pattern of lymph node involvement in HNSCC
- Selective neck treatment (irradiation or dissection) for selected N stage

Which CTV for the neck?
Oropharyngeal Carcinoma p16-

Nodal Category (AJCC/UICC 8th ed.)	Levels to be included in CTV-N-LR	
	Ipsilateral Neck	Contralateral Neck[1]
N0-1 (in level II, III, or IV)	(Ib)[2], II, III, IVa[3], +VIIa for posterior pharyngeal wall tumor	II, III, IVa, +VIIa for posterior pharyngeal wall tumor
N2a-b	Ib, II, III, IVa[3], Va,b, +VIIa, +VIIb[4]	II, III, IVa, +VIIa for posterior pharyngeal wall tumor
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IVa, Va,b, +VIIa, +VIIb[4]	II, III, IVa, +VIIa for posterior pharyngeal wall tumor

[2] in case of extension to the oral cavity
[3] Level IVb in case of infiltration in level IVa
[4] to be included in case of bulky infiltration of upper level II

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Biau, Grégoire et al., 2019

Any difference for p16-positive oropharyngeal SCC?

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journal homepage: www.thegreenjournal.com

Original Article

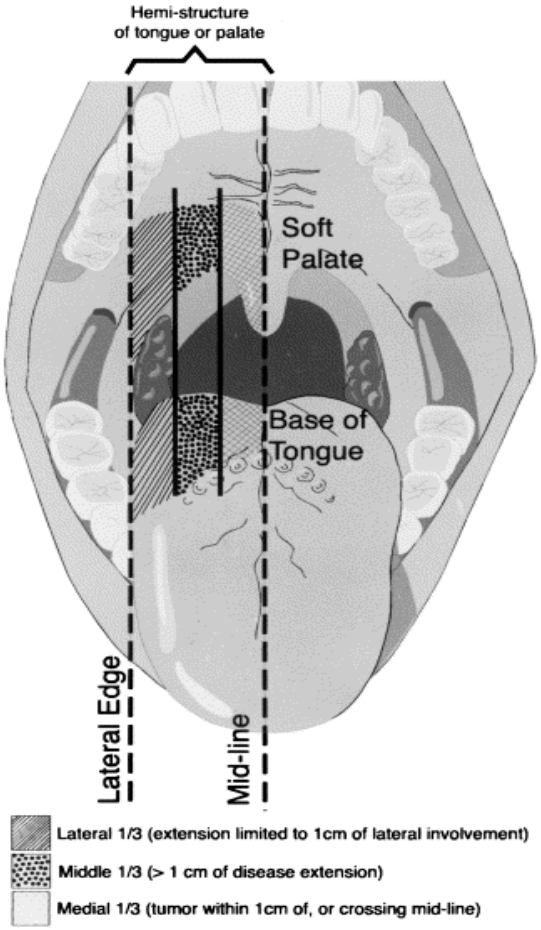
Prevalence and distribution of cervical lymph node metastases in HPV-positive and HPV-negative oropharyngeal squamous cell carcinoma

Laurence Bauwens [a], Aline Baltres [b], Danny-Joe Fiani [c], Philippe Zrounba [d], Guillaume Buiret [e], Bertrand Fleury [f], Nazim Benzerdjeb [g], Vincent Grégoire [a,*]

Unilateral or bilateral neck treatment?

- 228 tonsil SCC: T1-T3, N0 or unilteral N+
- Unilateral wedge-pair fields
- Contralateral neck failure: 8/228 (3.5%)

Unilateral treatment if < 1 cm soft palate and/or base of tongue infiltration



O'Sullivan B, IJROBP 2001

Guidelines for the treatment of the neck of patients with HNSCC: unilateral - bilateral?

Unilateral treatment

- lower gum
- lateral border of mobile tongue
- lateral floor of mouth
- retromolar trigone
- Cheek
- tonsillar fossa / tonsillar pillars
- lateral wall of piriform sinus

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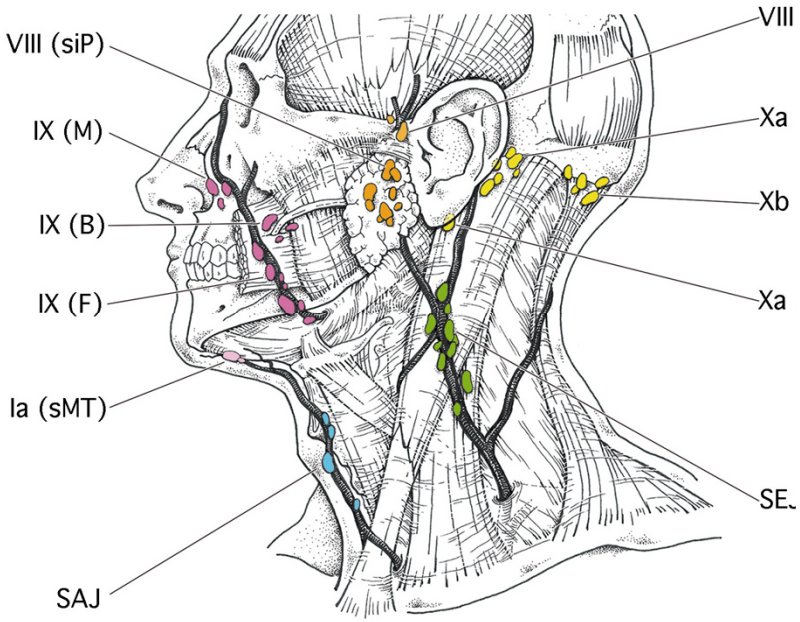
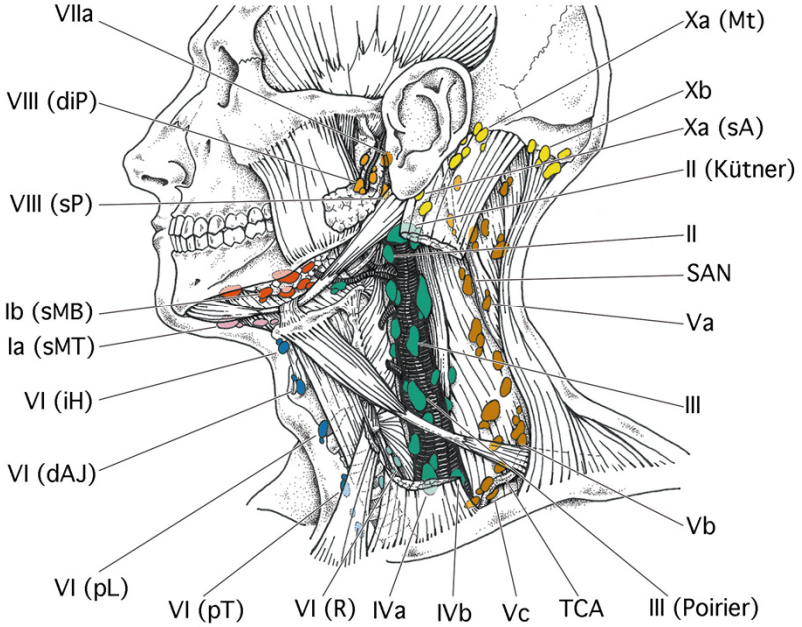
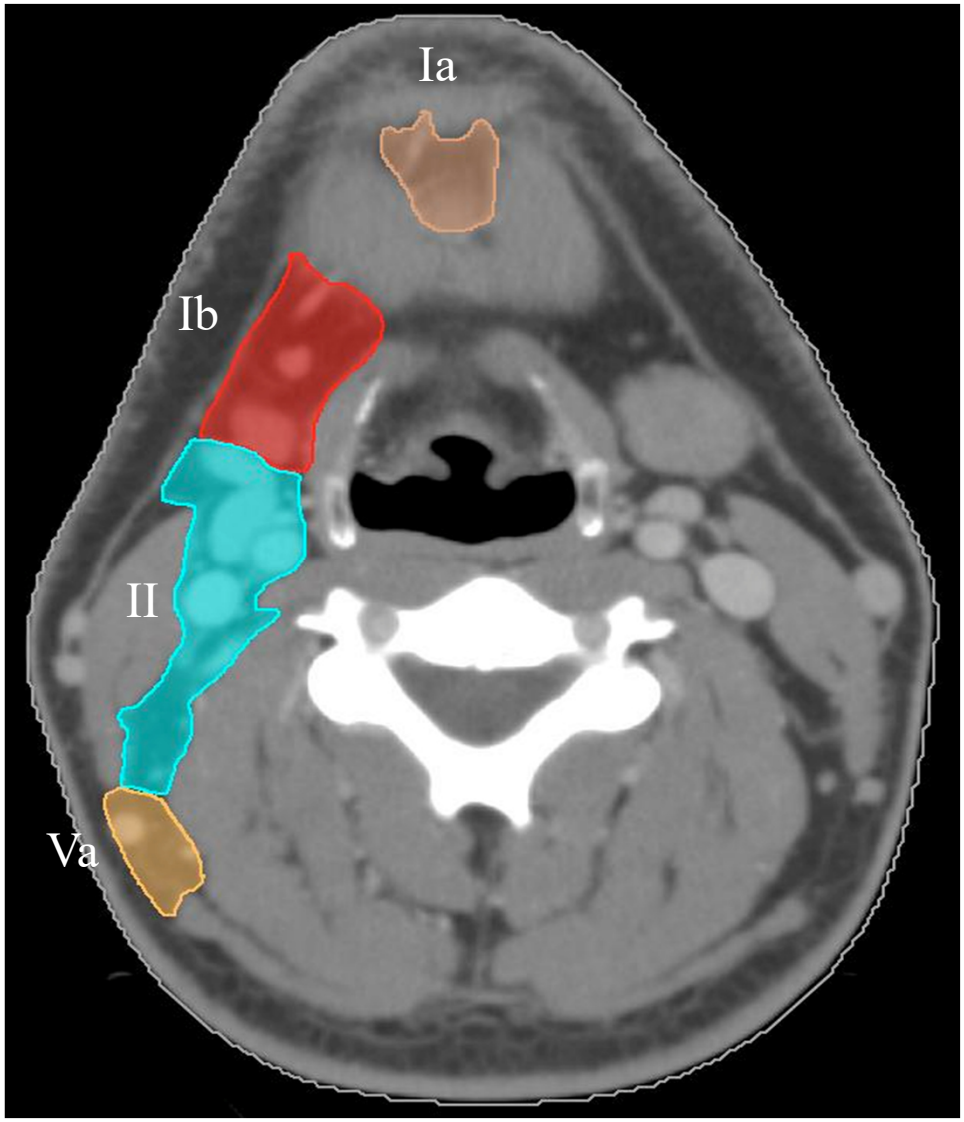
CT-based delineation of lymph node levels in the neck (revised version 2013)





Gemelli, Oct. 2023

Gregoire et al., 2013


Ia
Ib
II
Va