CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

# Innovation, effectiveness and compliance in H&N cancers

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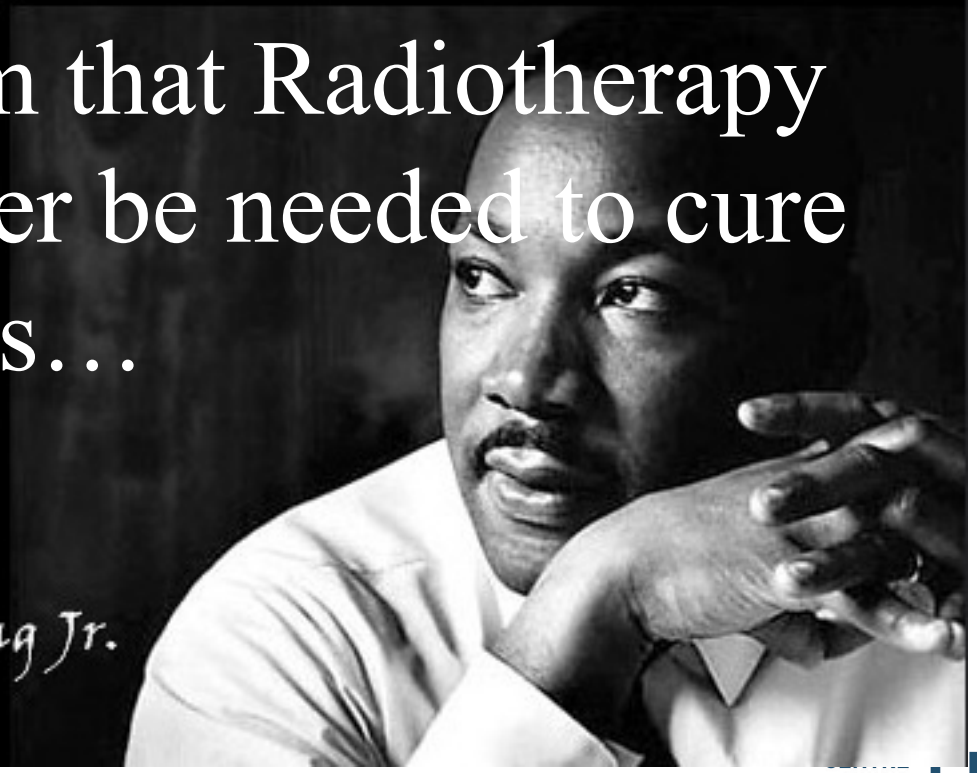
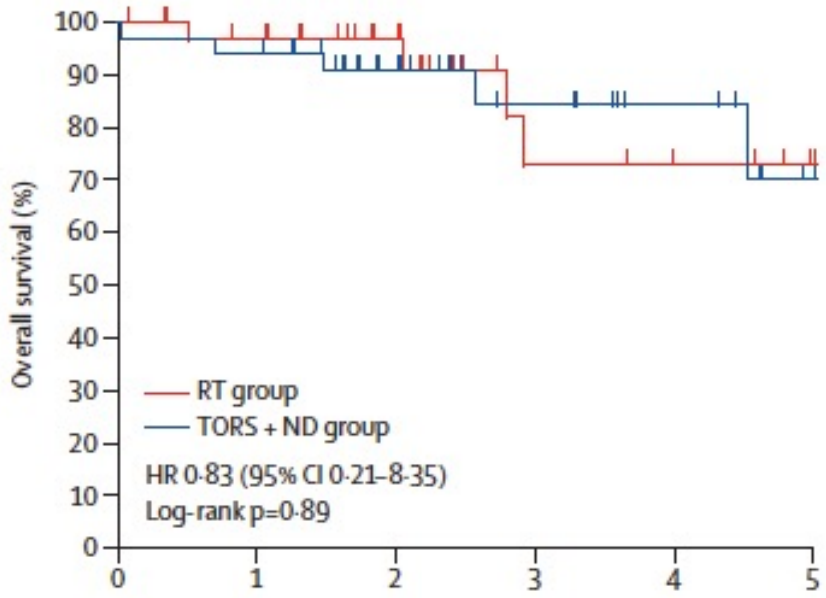
Centre Léon Bérard, Lyon, France

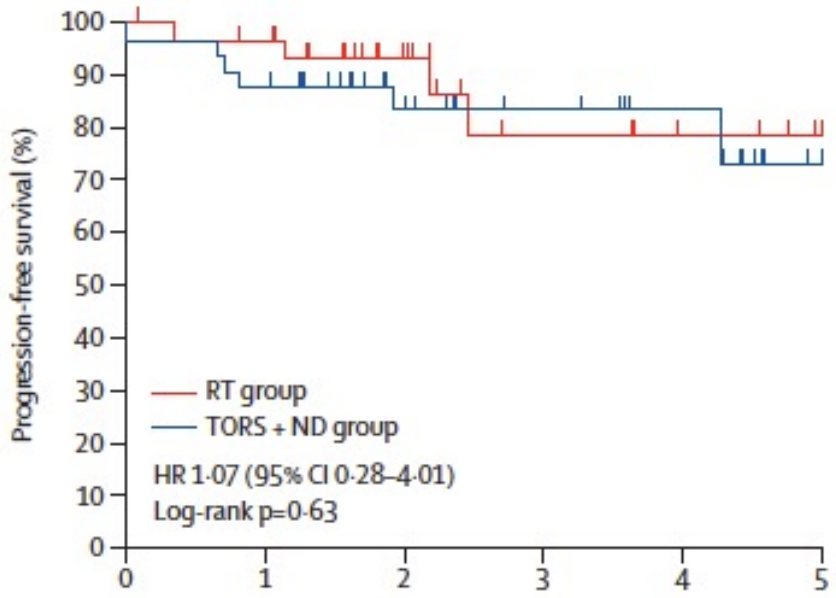
"I have a dream that my four little children will one day live in a nation where they will not be judged by the color of their skin, but by the content of their character."

# I had a dream that Radiotherapy may no longer be needed to cure H&N cancers…



# I had a dream that robotic surgery replaces RT in early-stage H&N SCC…




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| RT group | 34 (0) | 30 (3) | 19 (14) | 8 (22) | 5 (25) | 2 (28) |
| TORS + ND group | 34 (0) | 32 (0) | 21 (10) | 12 (18) | 8 (22) | 2 (27) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 34 (0) | 30 (3) | 18 (14) | 8 (22) | 5 (25) | 2 (28) |
| | 34 (0) | 32 (0) | 19 (10) | 12 (17) | 8 (21) | 2 (26) |

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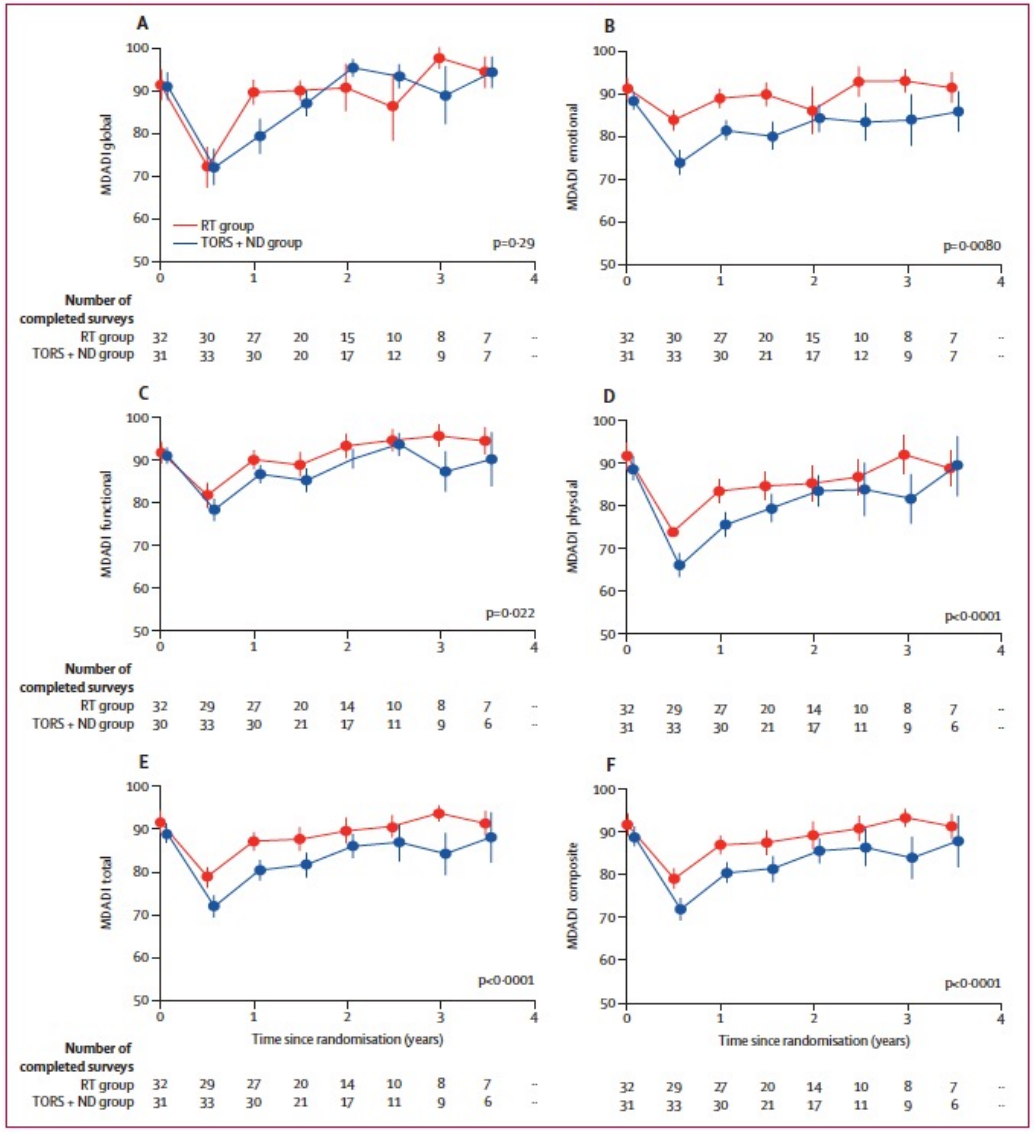
Nichols et al, Lancet Oncol, 2019

# I had a dream that robotic surgery replaces RT in early-stage H&N SCC…




Median FU:
27 months

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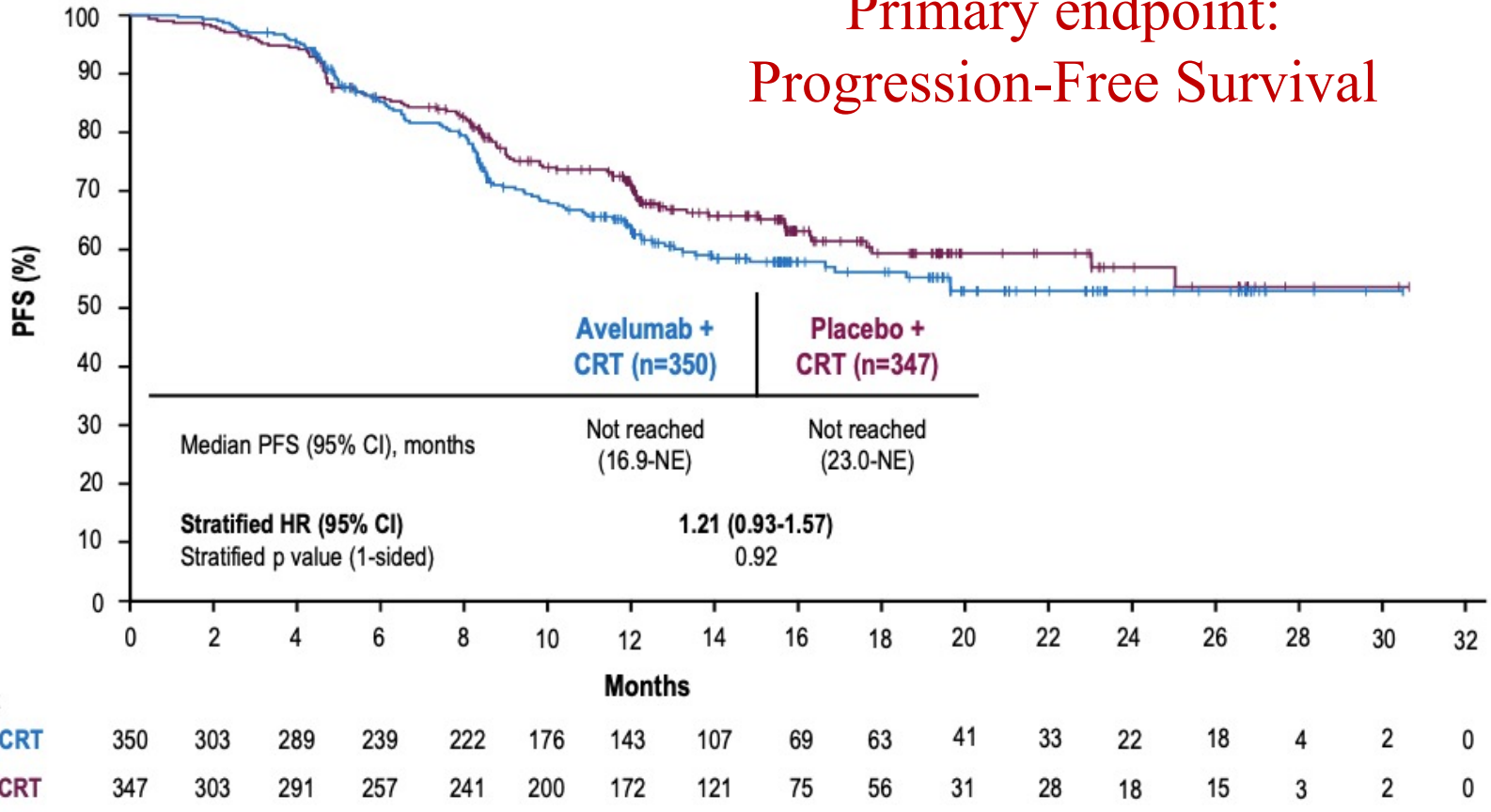
Nichols et al, Lancet Oncol, 2019

# I had a dream that immune therapy replaces RT in H&N SCC…

Primary endpoint:
Progression-Free Survival

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Lee et al, Lancet Oncol, 2021

The Truth is rarely pure and never simple …

Oscar Wilde

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# My dream of Radiation Oncology for H&N Cancer in 2025…

# Radiation Oncology for H&N Cancer in 2025…

- Revisiting target volume selection
- Revisiting target volume delineation
- Revisiting OAR delineation
- Revisiting dose prescription
- Revisiting dose distribution: the role of protontherapy

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# Selection of node levels in Head and Neck Tumors

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]

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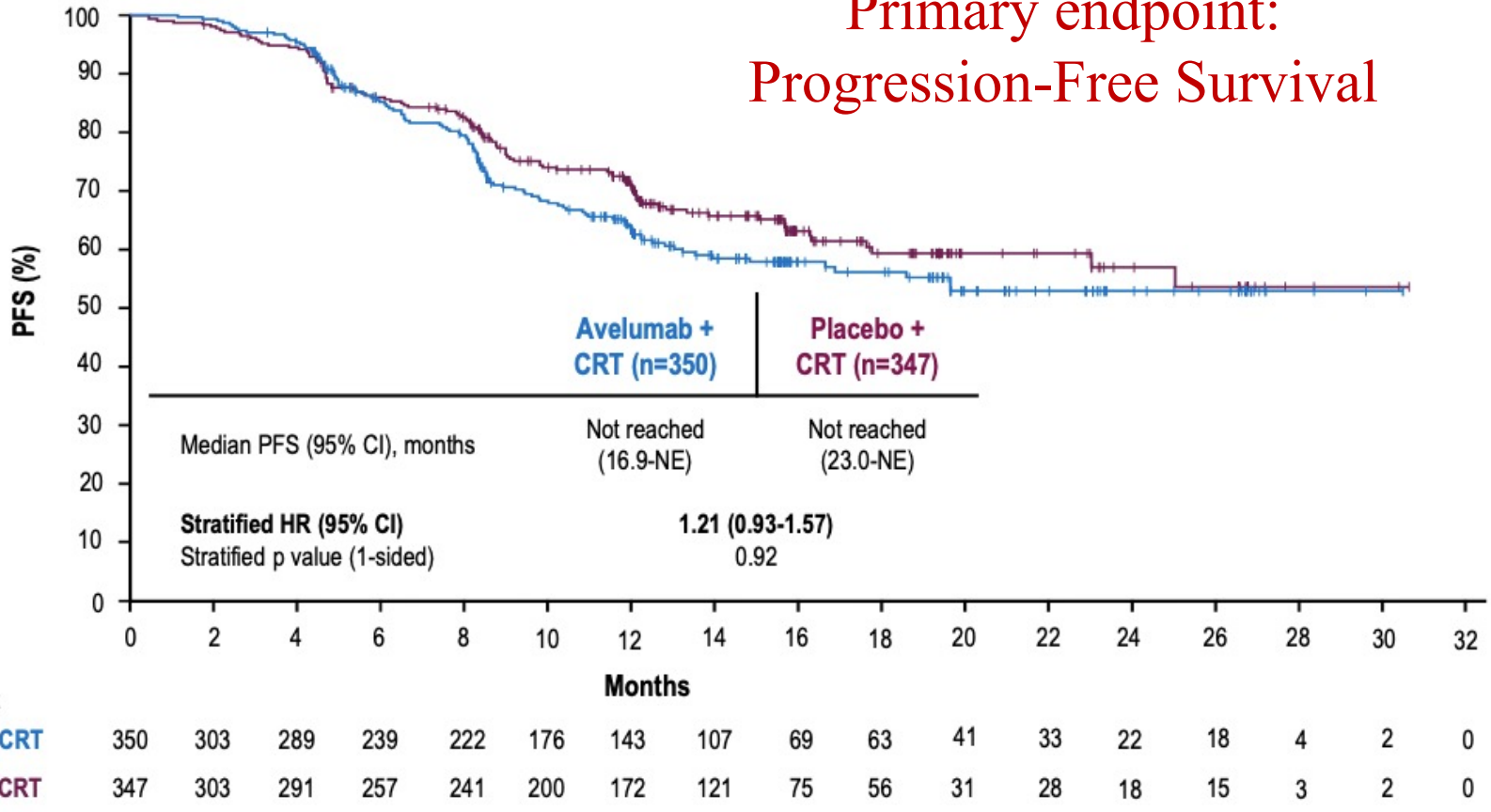
# Could bilateral irradiation have killed the immune effectors cells in the Javelin-100 trial?

Primary endpoint:
Progression-Free Survival

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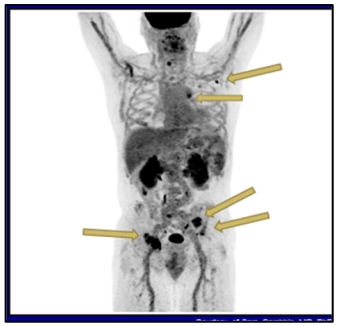
Lee et al, Lancet Oncol, 2021

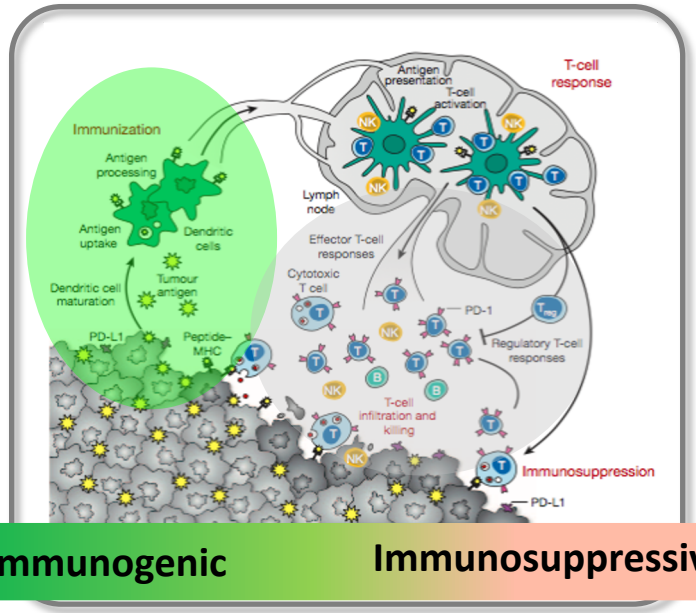
# Love and Hate relationship between Radiotherapy and the Immune System

**Immunogenic RT Effects**

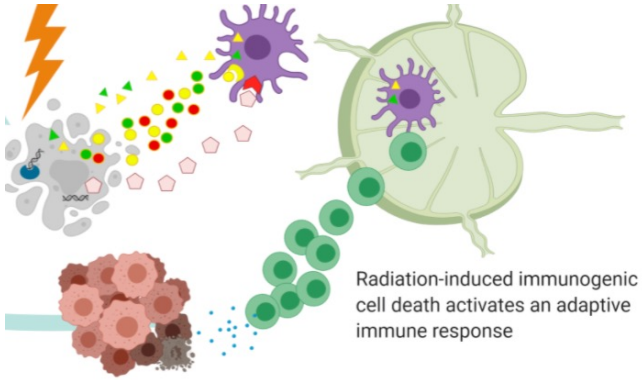
- Antigen release/ cross-priming
- Inflammation
- Immune stimulation, enhanced vascular permeability



*Deutsch et al. Lancet Oncol, 2019*

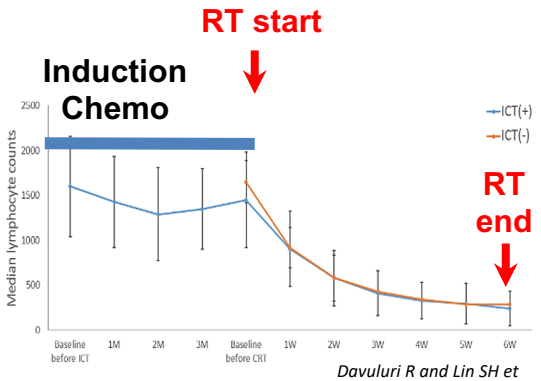



**Immunogenic** ⟵ ⟶ **Immunosuppressive**




**Immunosuppressive RT Effects**

- **Direct killing of lymphocytes**
- Altered cytokine expression patterns
- Inflammation
- Anergy
- Immunosenescence




*Davuluri R and Lin SH et al., IJROBP 2017*

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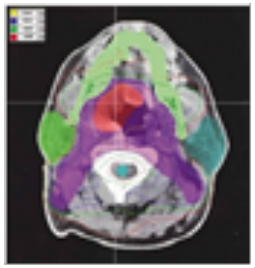
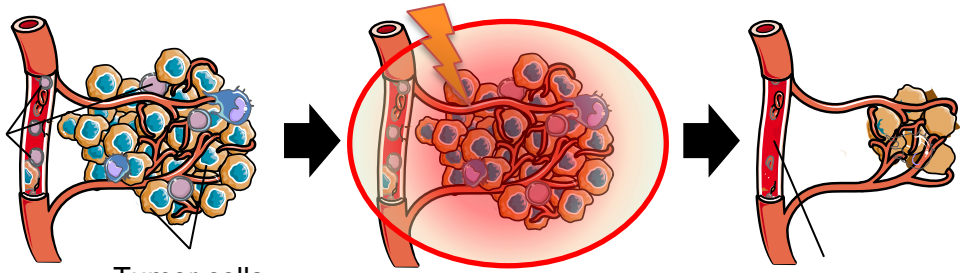
# Refinement in nodal target volume selection

## From conventional to lymphocyte-sparing radiotherapy

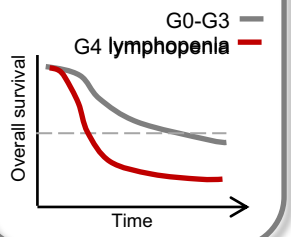
Example: head and neck tumors



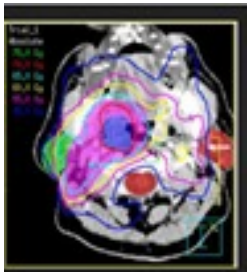
T cells

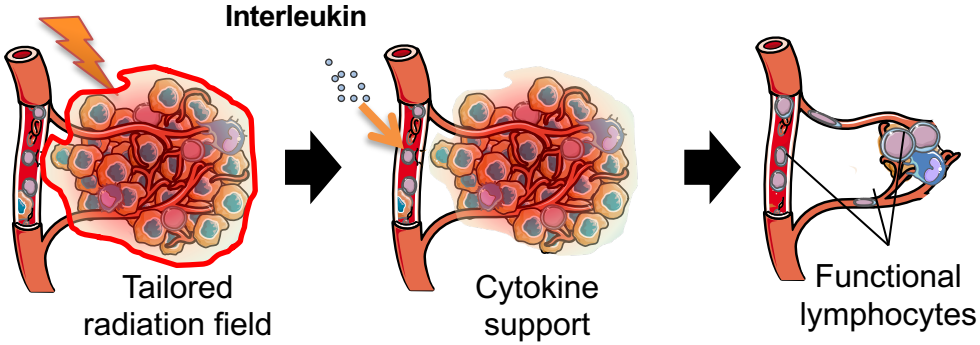



Negative impact on survival

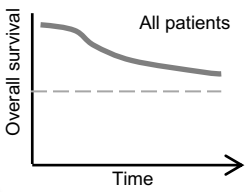



Proof-of-concept: Head and neck






Positive impact on survival

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Deutsch, Grégoire et al, 2021

# Selection of node levels in Head and Neck Tumors: 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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# Optimization of the selection of the elective neck node levels

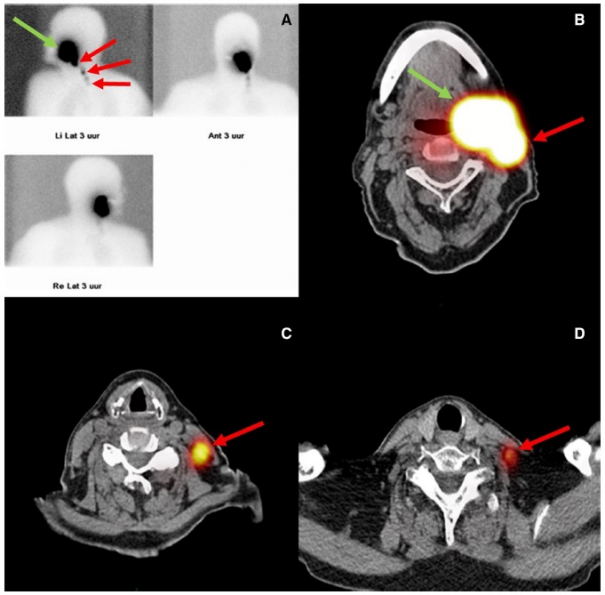
Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

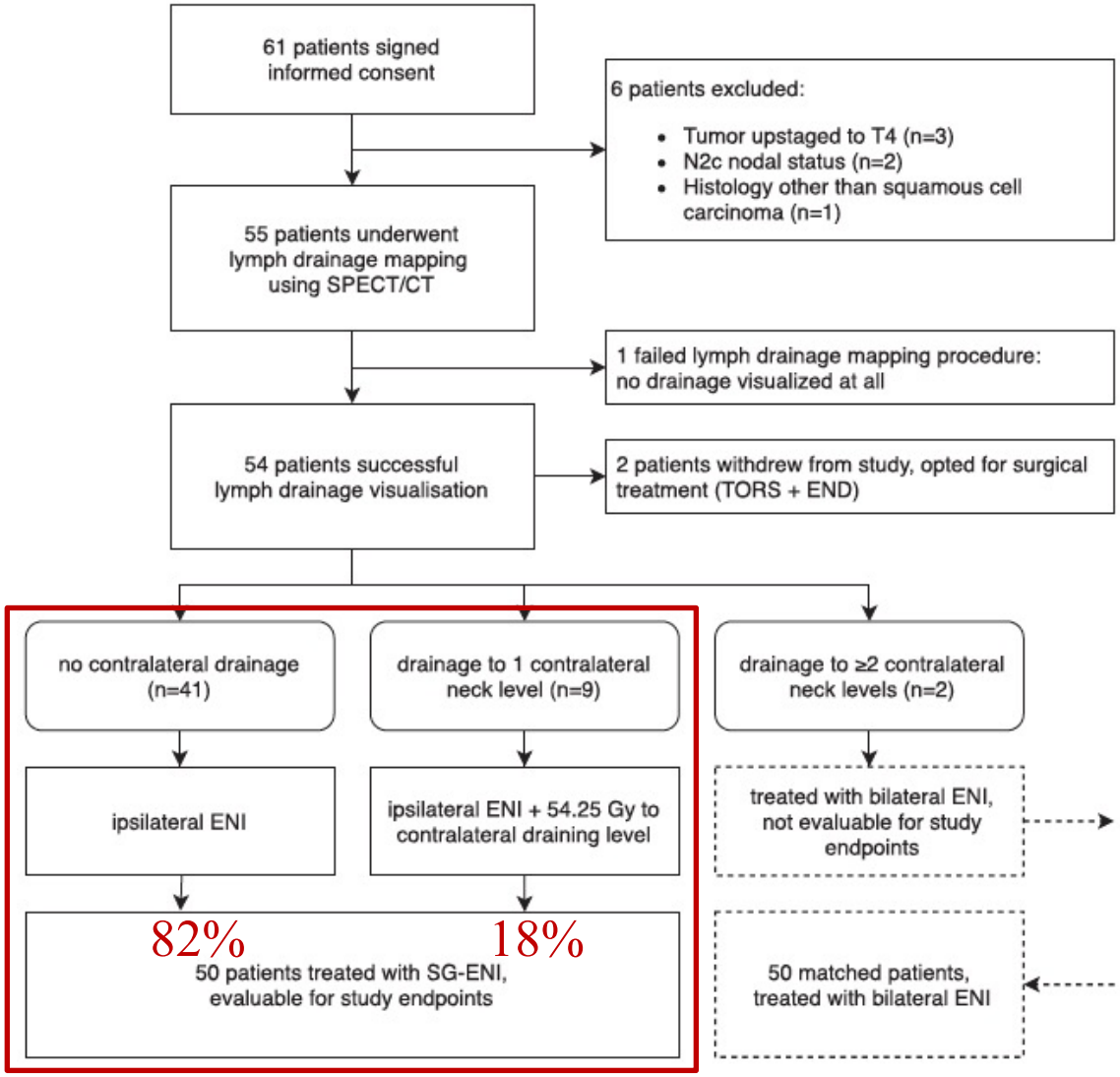
Original Article

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



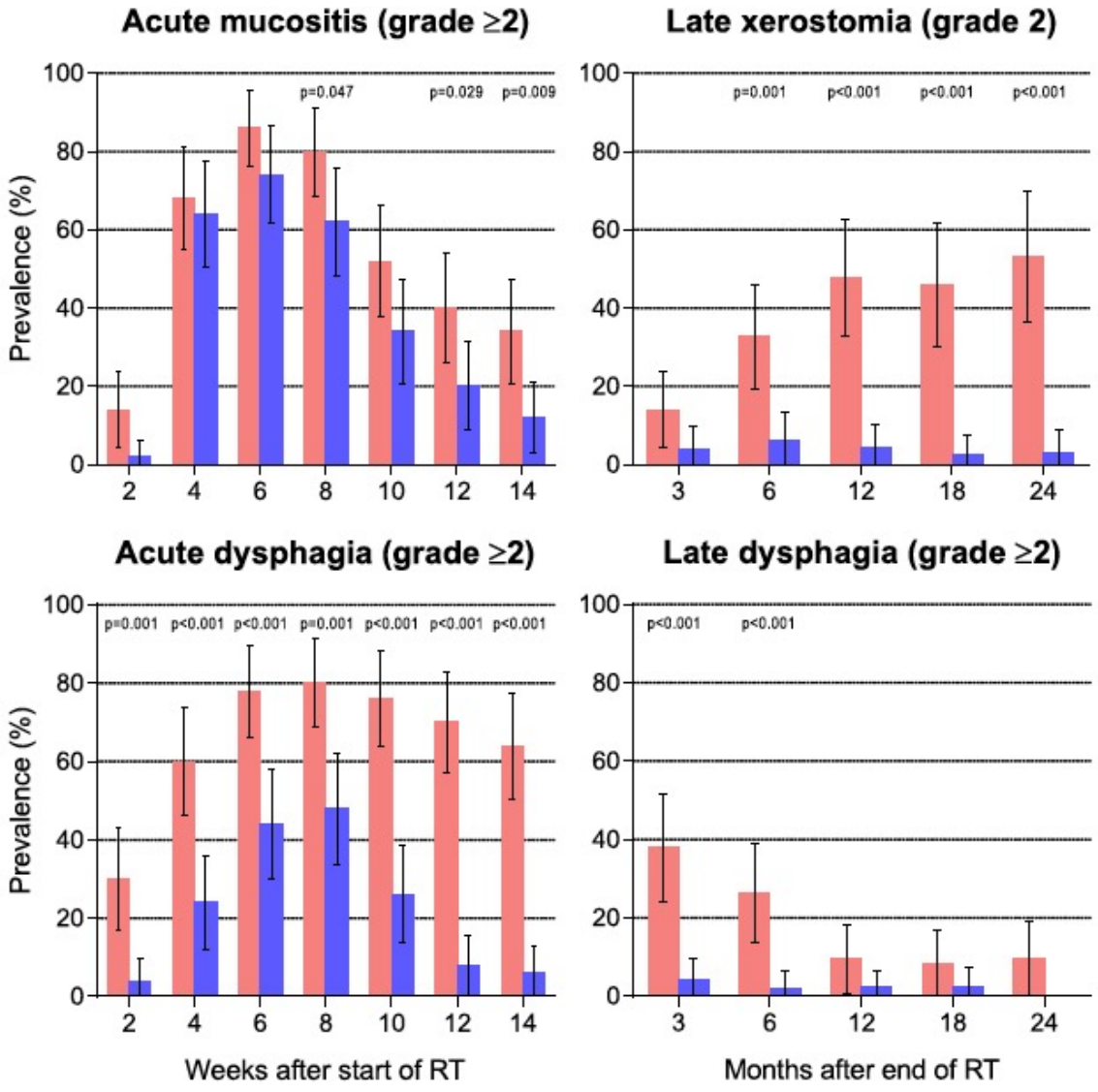

de Veij Mestdagh et al, R&O, 2020

# Optimization of the selection of the elective neck node levels




de Veij Mestdagh et al, R&O, 2020

# Optimization of the selection of the elective neck node levels




Radiation Toxicity

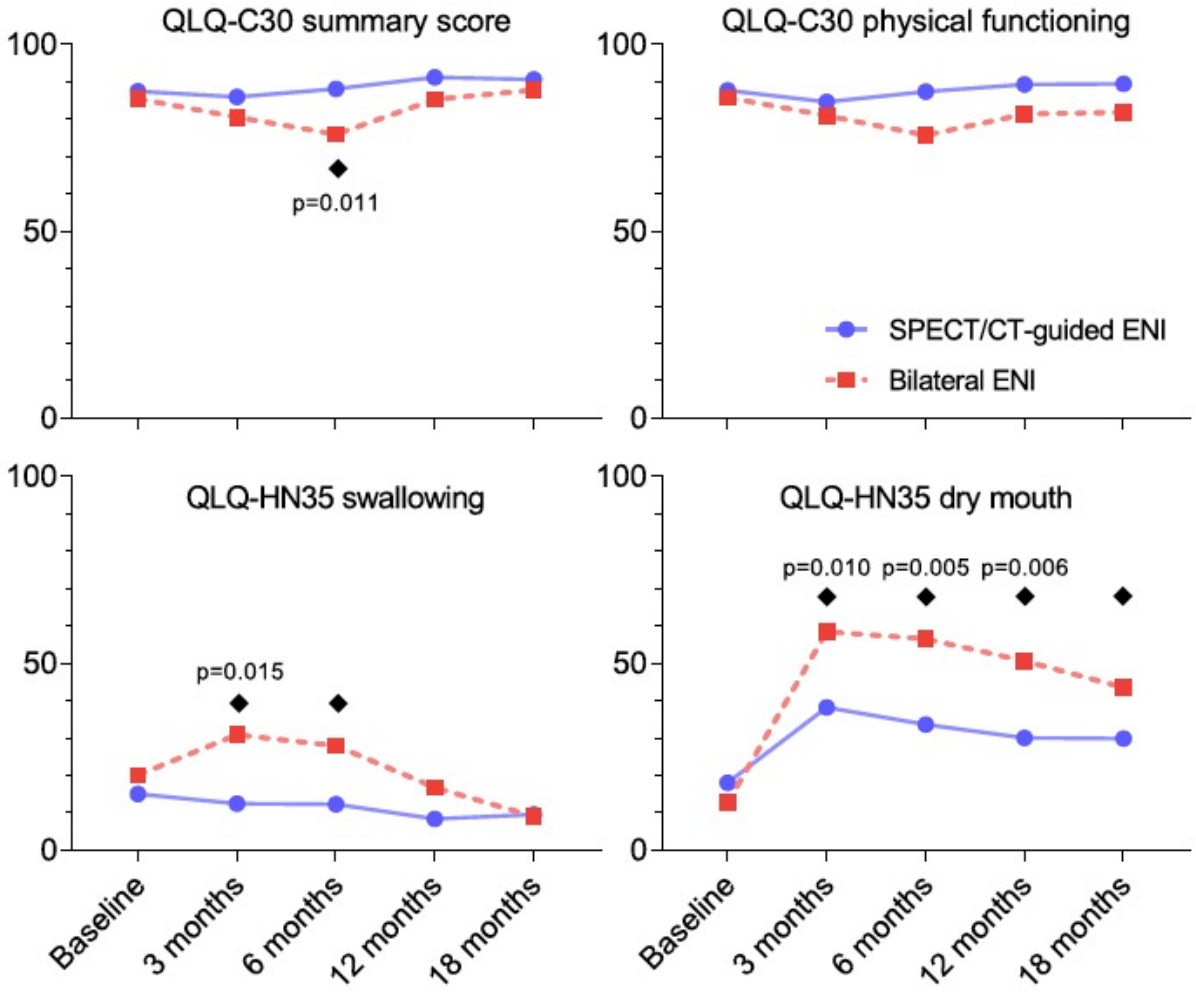
Bilateral ENI

SPECT/CT-guided ENI

de Veij Mestdagh et al, R&O, 2020

# Optimization of the selection of the elective neck node levels

## Quality of Life (EORTC scale)




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%) |

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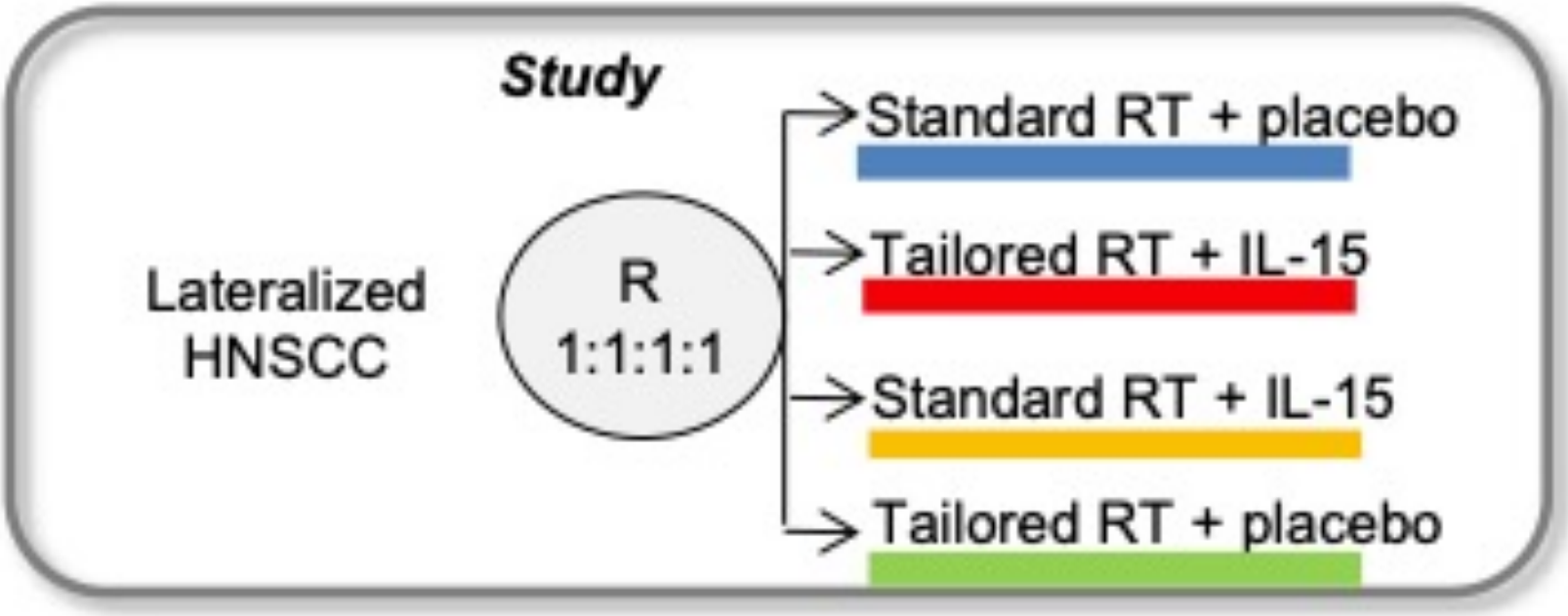
de Veij Mestdagh et al, R&O, 2020

# Optimization of the selection of the elective neck node levels

## Concept validation






Deutsch, Grégoire, Paragios, 2021

# Radiation Oncology for H&N Cancer in 2025…

- Revisiting target volume selection
- Revisiting target volume delineation
- Revisiting OAR delineation
- Revisiting dose prescription
- Revisiting dose distribution: the role of protontherapy

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# Artificial Intelligence

"A system's ability to correctly interpret external data, to learn from such data, and to use those learnings to achieve specific goals and tasks through flexible adaptation"

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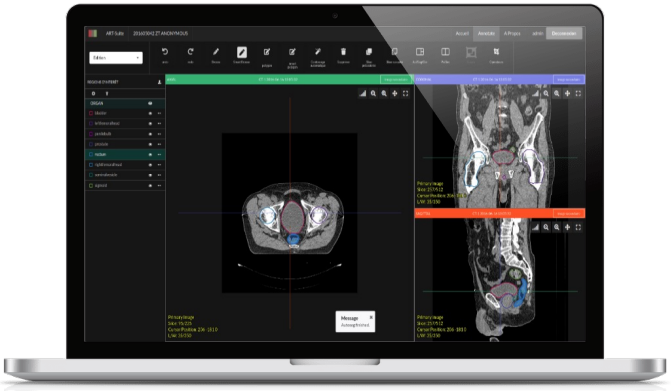
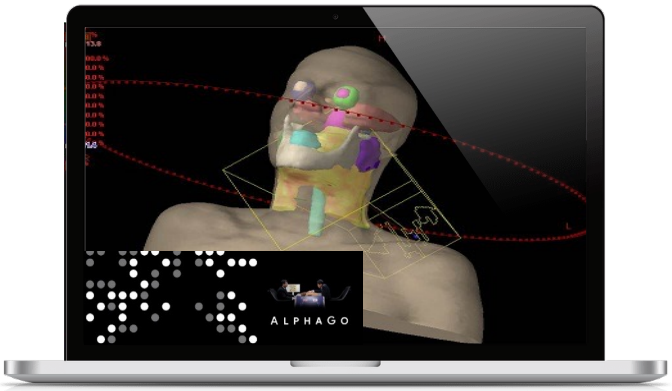
Kaplan & Haenlein, Business Horizons 2019

# 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

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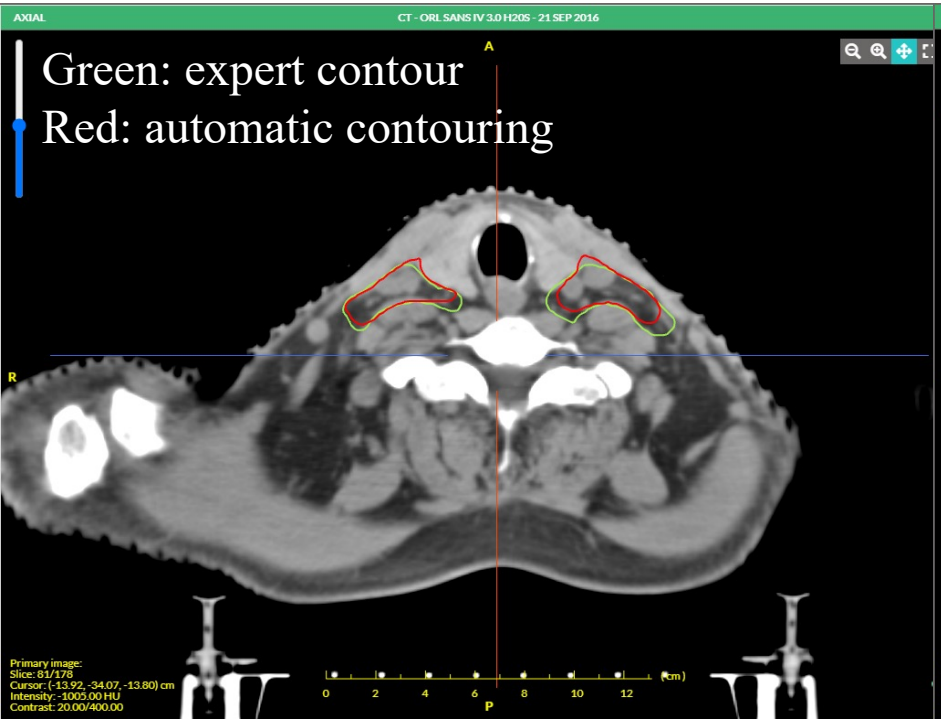
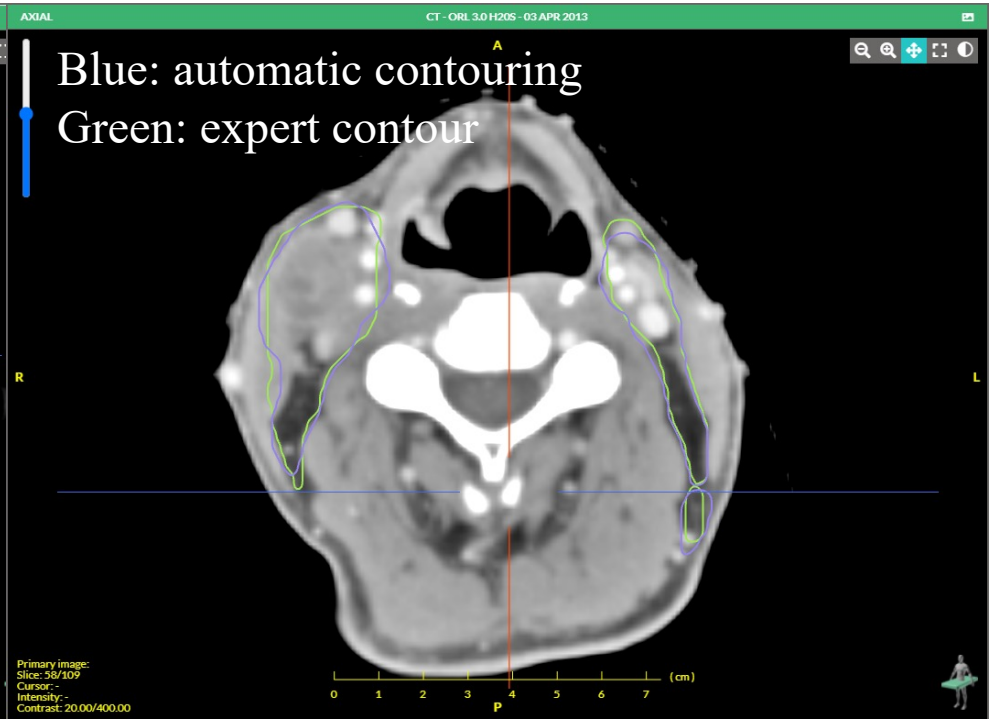
Courtesy of N. Paragios, 2021

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

## Automatic nodal target volume delineation

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

## Integration of clinical examination and imaging

➔ virtual endoscopy and imaging?

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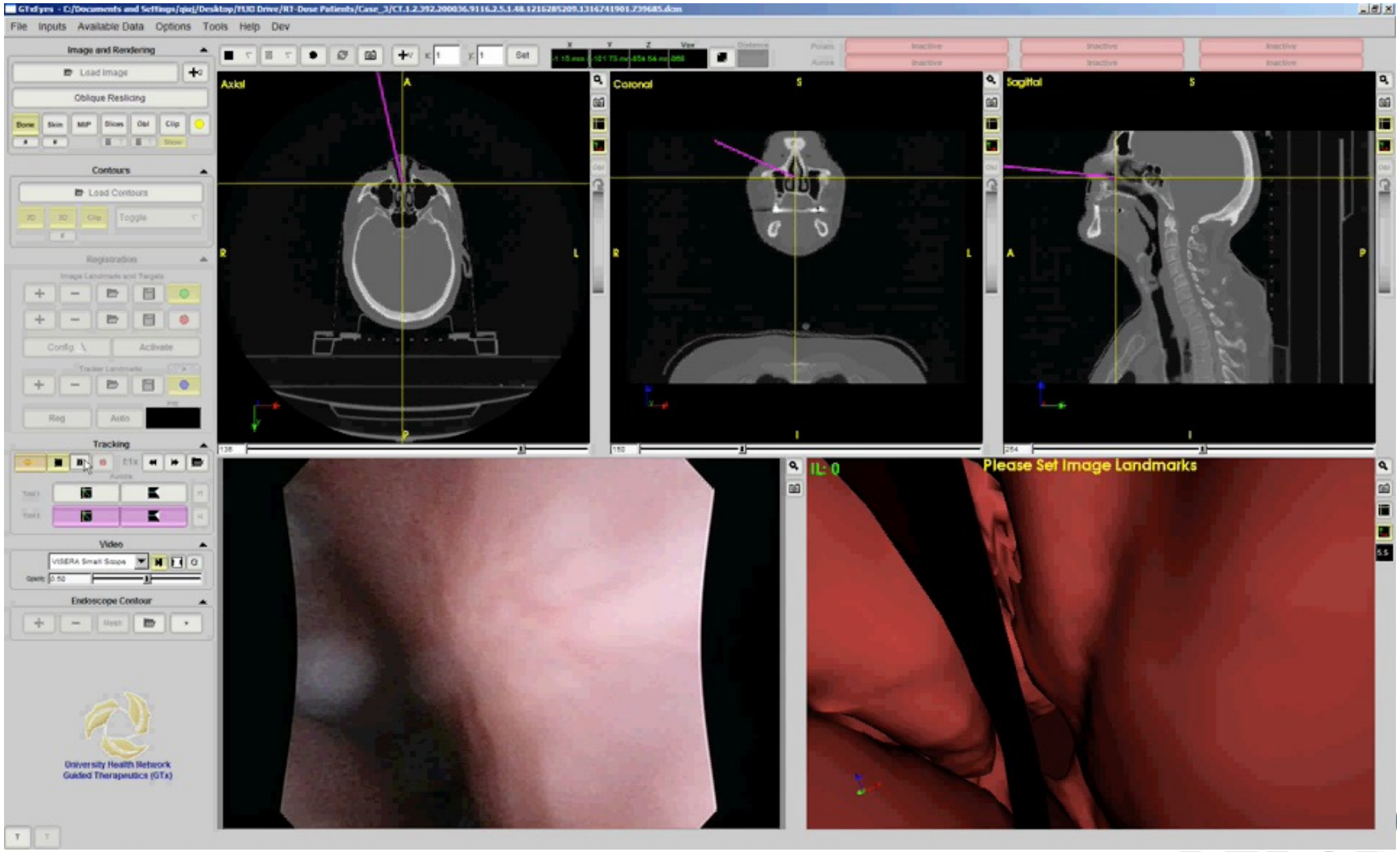
# And in the “foreseeable” future…
# Augmented reality?

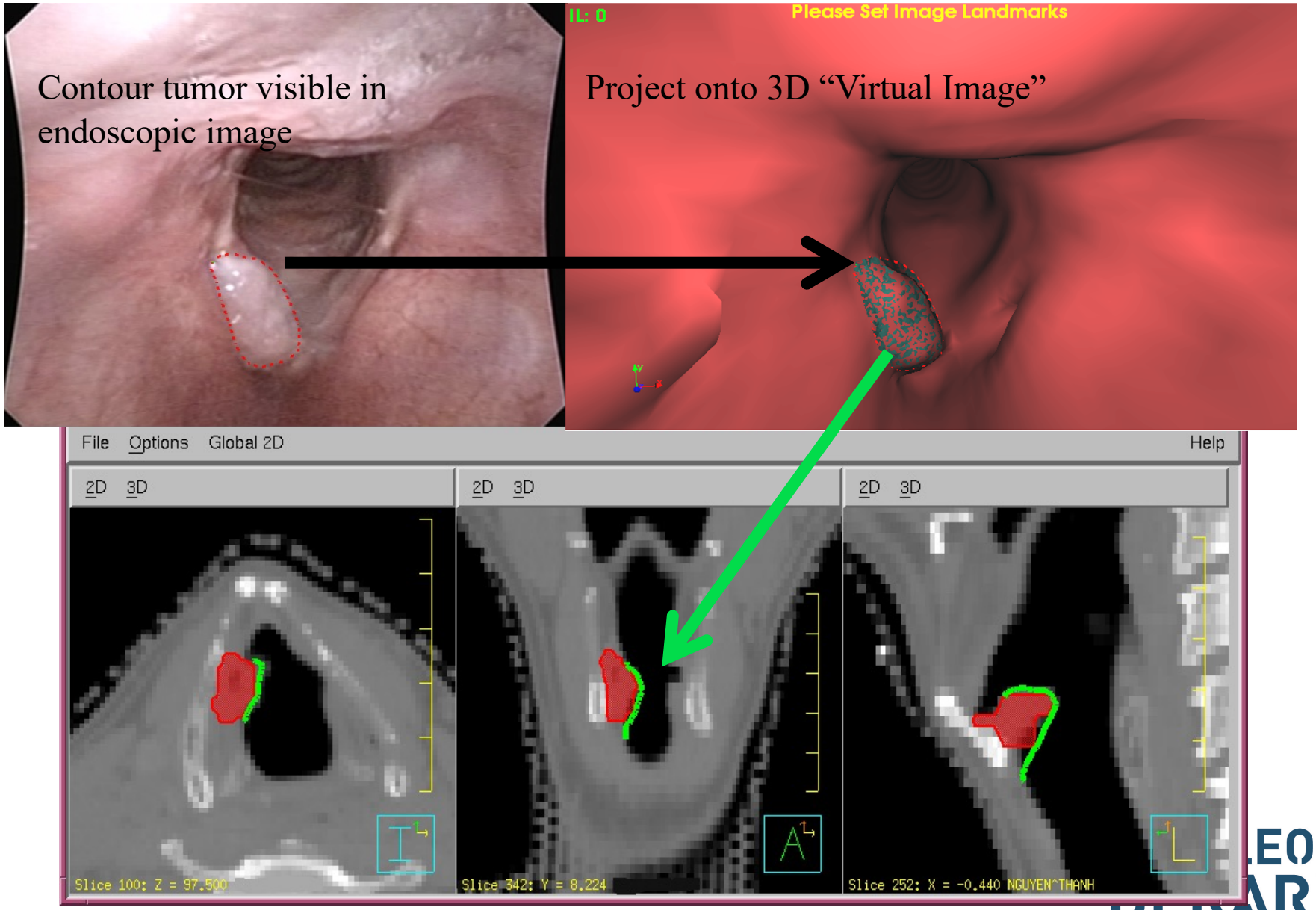





Weersink et al Med. Phys 38 6458, 2011

Weersink, US Patent: 9,138,597

# Endoscopic Contouring






Weersink et al Med. Phys 38 6458, 2011

Weersink, US Patent: 9,138,597

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

Integration of pathological/molecular information

➔ assessment of individualized infiltration risk pattern?

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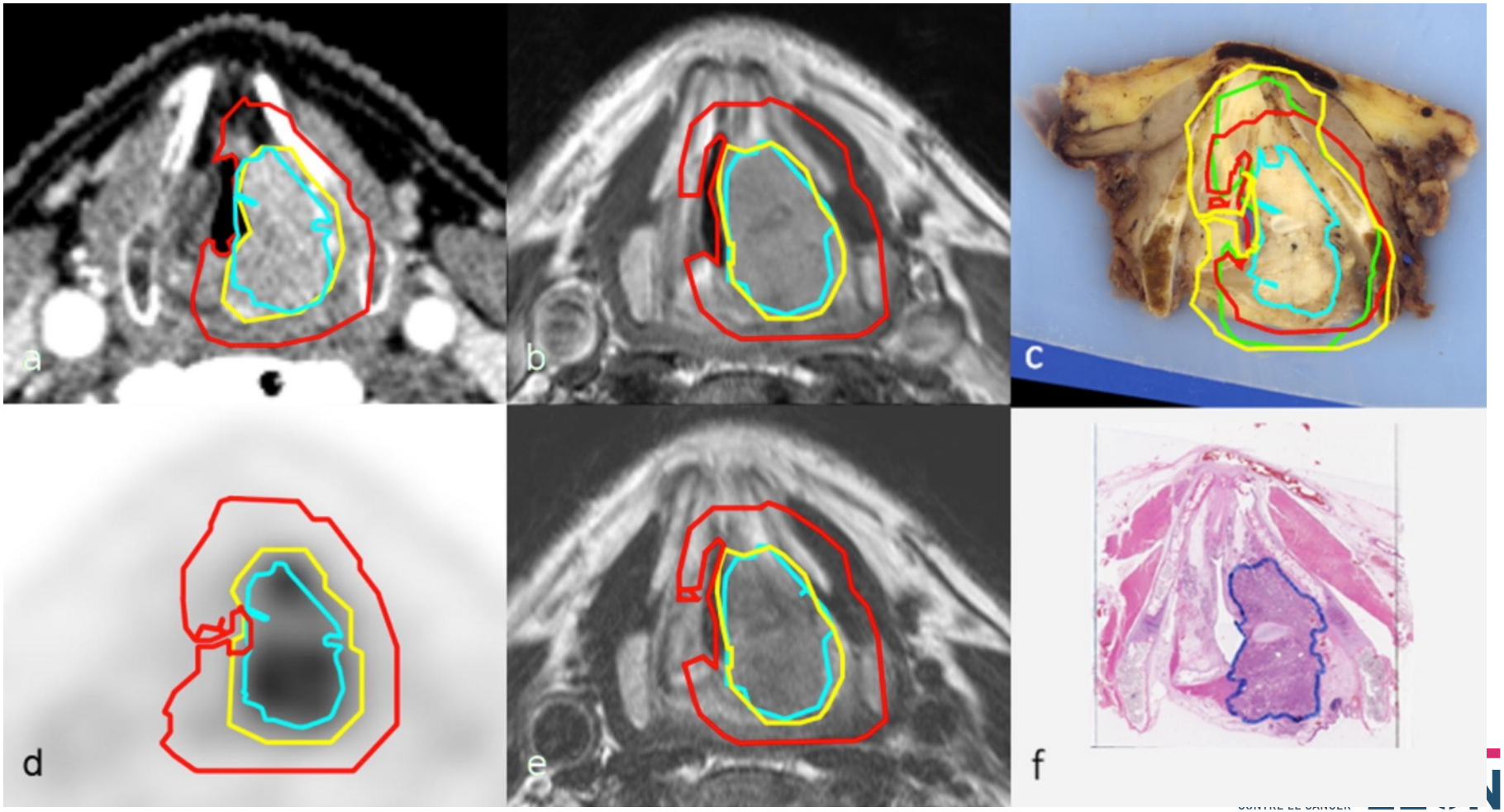
# Primary tumor GTV and CTV

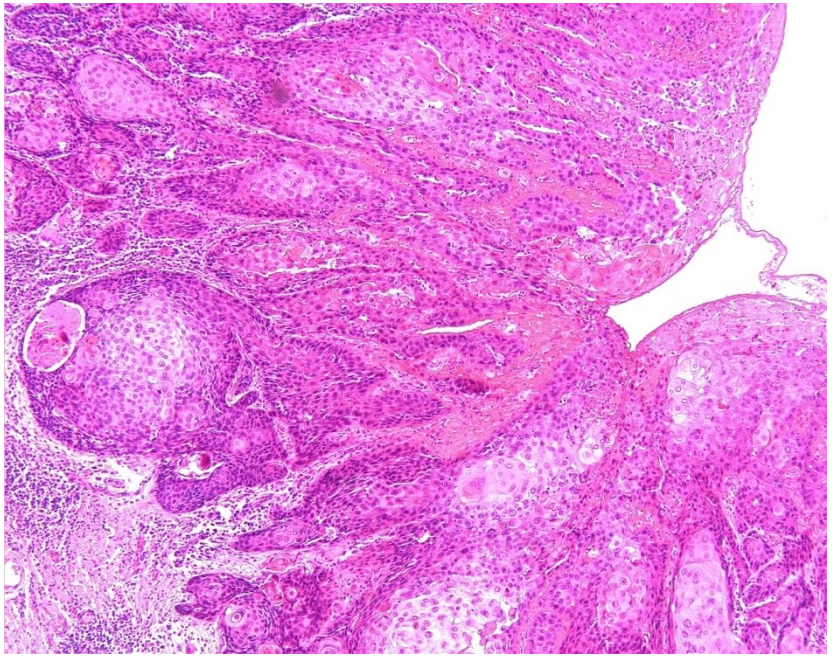
## Imaging-dependent geometrical margins



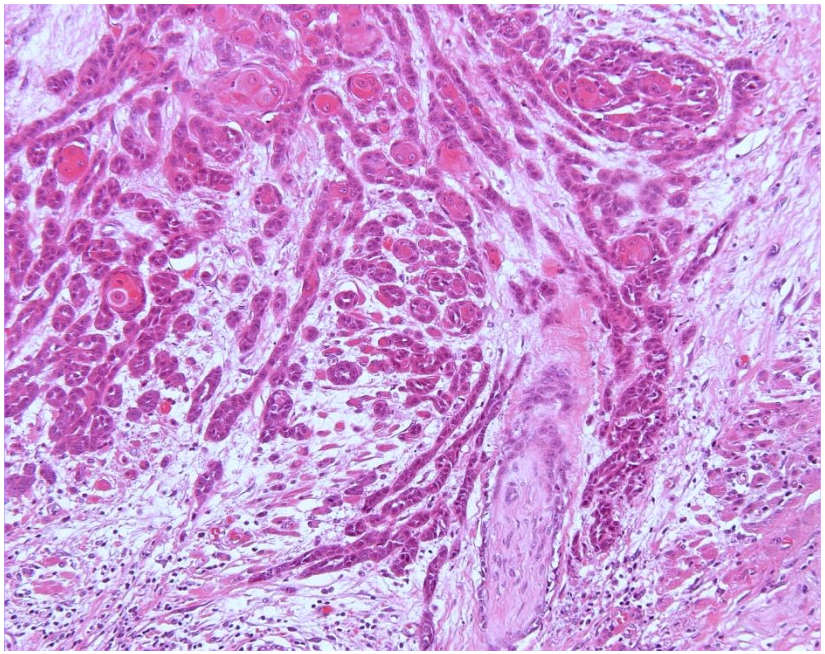



Ligtenberg et al, R&O 2017

# Assessment of individualized infiltration risk pattern?



Cohesive growth



Non-cohesive growth

*Courtesy Elisabeth Bloemena and Ruud Brakenhoff, Amsterdam UMC*

# Radiation Oncology for H&N Cancer in 2025…

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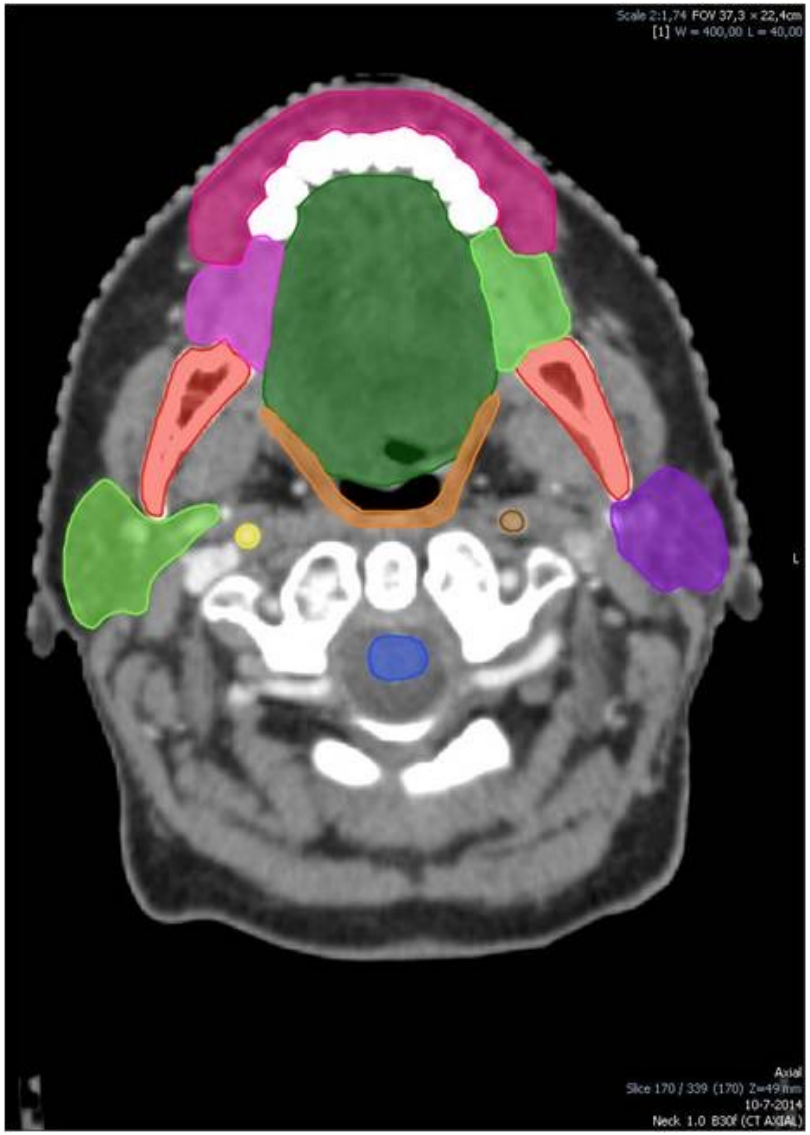
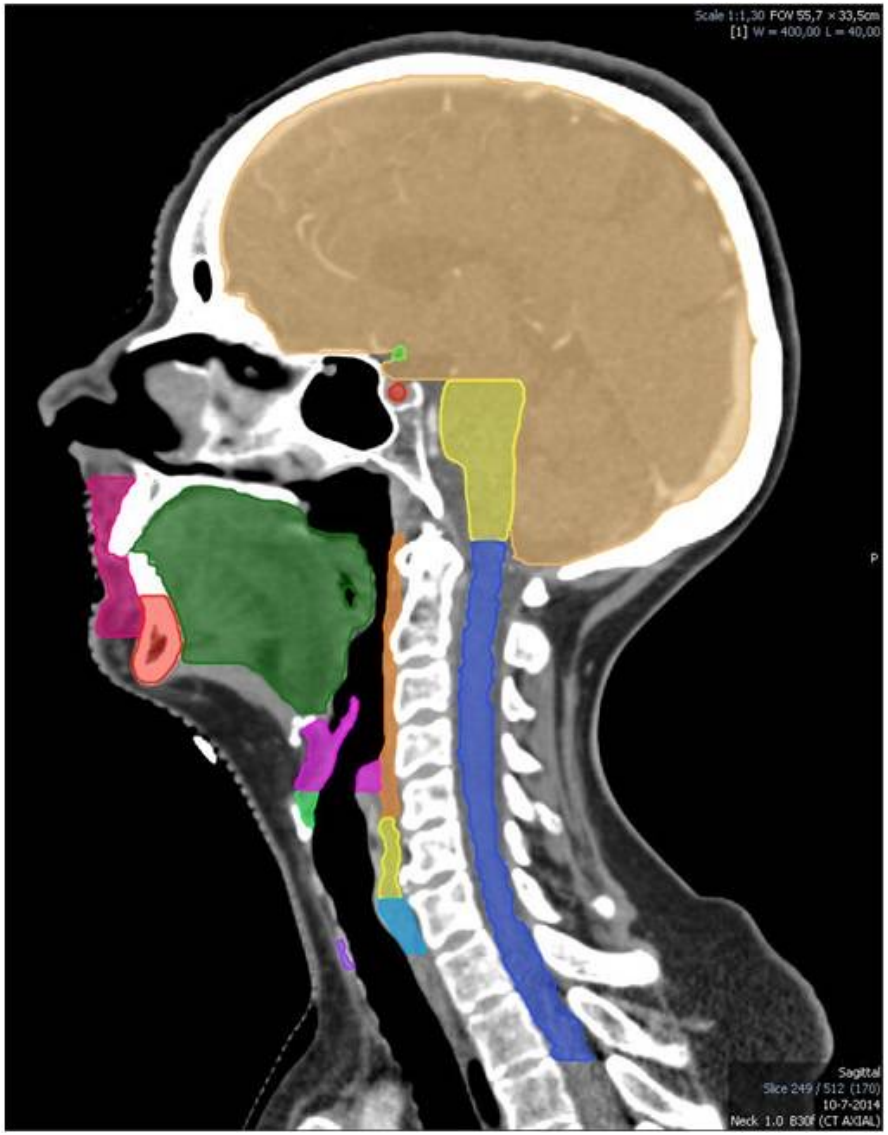
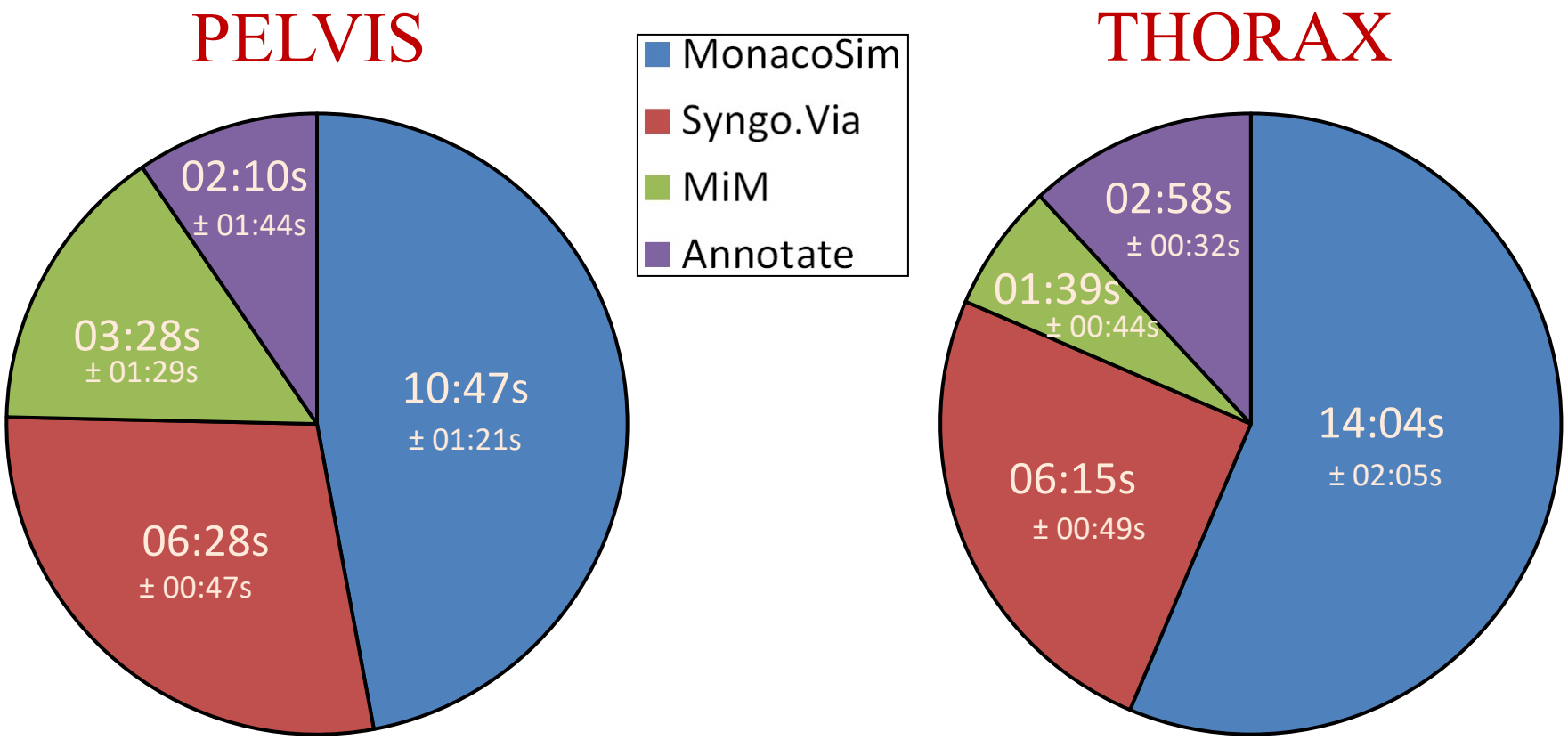
# Atlas of normal tissues




Brouwer et al., 2015

# AI for OAR delineation

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# Phase-III randomized trials for HPV$^{+}$ oropharyngeal SCC

## Primary Radiotherapy

| Acronym | Stage | Smoking | Design | Due date |
|---|---|---|---|---|
| De-Escalate | III-IVa | non-smoking<br>smoking<N2b | 70Gy + 3-weekly cddp vs 70 Gy + weekly cetuximab | 2018 |
| NRG HN002 | III-IV | < 10 pack/y | 60 Gy (5w) + weekly cddp vs 60 Gy (5w) | 2018 |
| Quarterback-1 | III-IV | ≥ 20 pack/y | TPFx3 + 70Gy and weekly carbo vs TPFx3 + 56Gy and weekly carbo | 2021 |
| Quarterback-2 | III-IV | ?? | TPFx3 + 56Gy and weekly carbo vs TPFx3 + 50.4Gy and weekly carbo | 2023 |
| RTOG-1016 | III-IV | all pts | 70 Gy + cddp (x2) vs 70 Gy + weekly cetuximab | 2018 |
| TROG-12.01 | III-IV | non-smoking<br>smoking<N2b | 70Gy + weekly cddp vs 70 Gy + weekly cetuximab | 2020 |





ClinicalTrials.gov, November 2021

# Phase-III randomized trials for HPV$^{+}$ oropharyngeal SCC

## Surgery and post-operative radiotherapy

| Acronym | Stage# | Smoking | Design | Due date |
|---|---|---|---|---|
| ADEPT | III-IV | all pts | PORT 60 Gy vs PORT 60 Gy + weekly cddp | 2021 |
| ECOG-3311* | III-IV ≠R1 ≠ECS | < 10 packs/y<br>> 10 packs/y | TOS vs TOS + 50 Gy vs TOS + 60 Gy vs TOS + 60 Gy + chemo | 2023 |
| PATHOS | I-IV | non-smoking<br>smoking<N2b | 1) PORT 60Gy vs PORT 50Gy<br>2) PORT 60Gy + CH vs PORT 60Gy | 2025 |

*randomized phase-II

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ClinicalTrials.gov, May 2021


CANCER RESEARCH UK

HPV positive OPC T1-3 + ipsilateral nodes

[Stage I and some Stage II TNM8]

[current smokers with multiple ipsilateral nodes excluded]

**Transoral surgery** +neck dissection

**Low risk** → A → No adjuvant treatment

**Intermediate risk**

Pathology assessment

Randomise

B

B1 **60Gy in 30# (control)**

B2 **50Gy in 25# (test)**

**High risk**

Randomise

C

C1 **60Gy in 30#+Cisplatin (control)**

C2 **60Gy in 30# (test)**

Group B and C randomisations are independent of each other

Co-primary endpoints: swallowing function (MDADI) at 12months (superiority), Overall Survival (non-inferiority)

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Courtesy of M. Evans

# Radiation Oncology for H&N Cancer in 2025…

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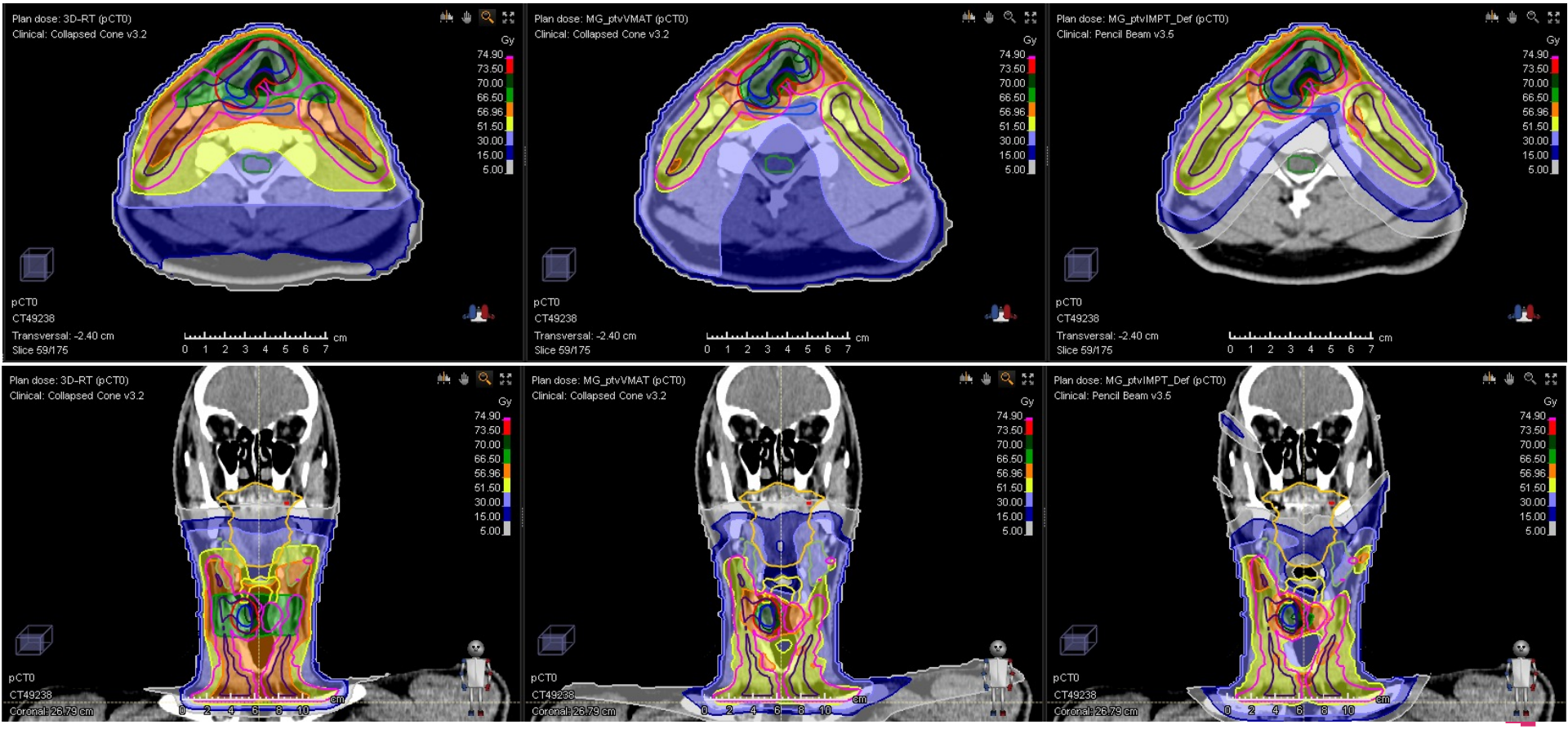
# Revisiting Radiation Dose Delivery

## T3-N0-M0 glottic Squamous Cell Carcinoma




6 MV X-rays, 3D-CRT | 6 MV X-rays, IMRT | 230 MV protons, IMPT

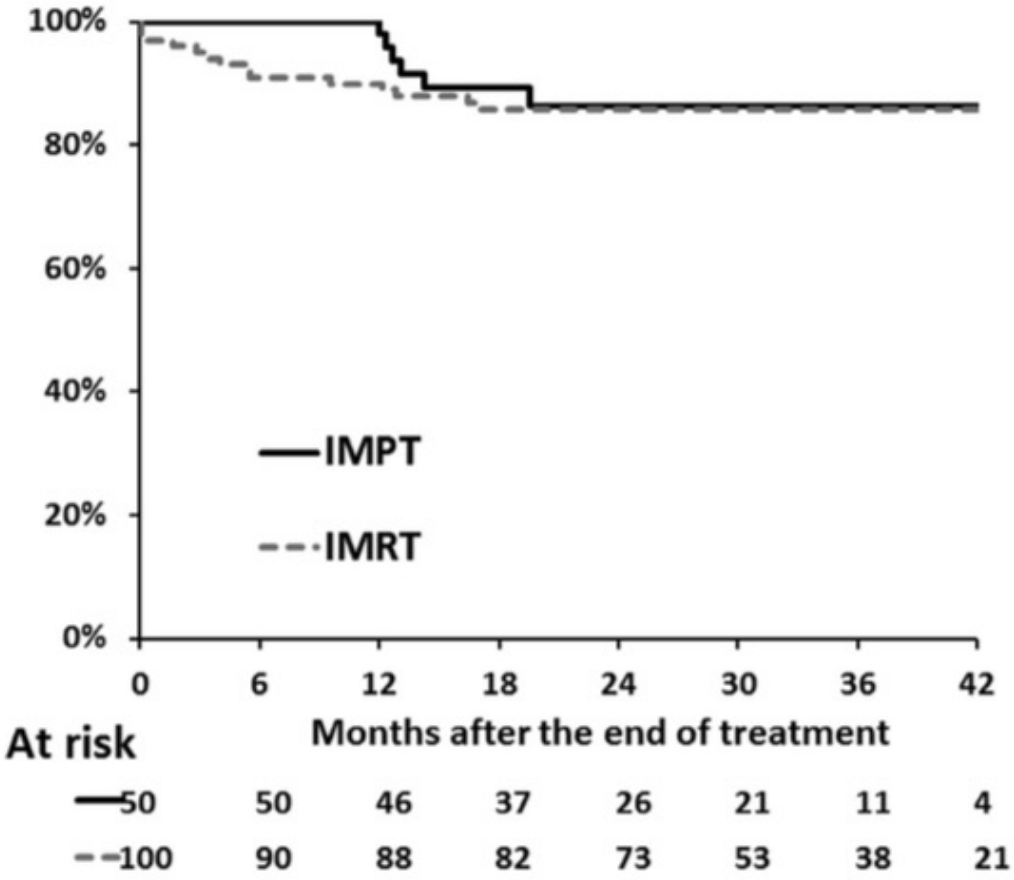
BERARD



Courtesy of Langendijk, 2016

# Protontherapy for primary H&N SCC

## Progression-free survival: IMRT (n= 100) > < IMPT (n= 50)
## Stage I-IV, oropharynx SCC, 87% p16+

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Blanchard et al, R&O, 2016

# Protontherapy for primary H&N SCC

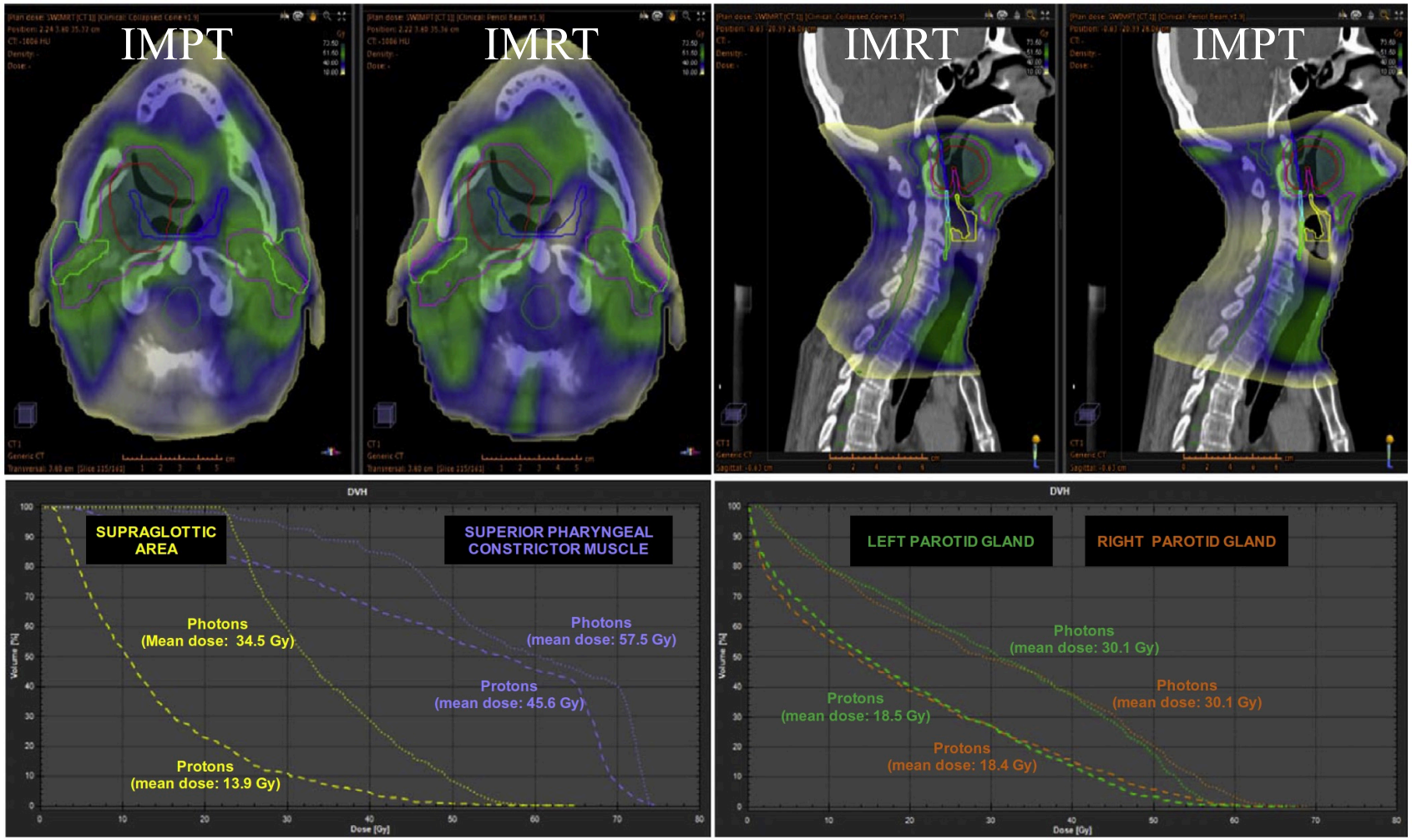
## Comparative toxicity data: IMRT (n= 100) > < IMPT (n= 50)

| Endpoint | During RT | | | | 3-months post RT | | | | 1 year post RT | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IMPT *n* (%) | IMRT *n* (%) | OR (95% CI) | *p* | IMPT *n* (%) | IMRT *n* (%) | OR (95% CI) | *p* | IMPT *n* (%) | IMRT *n* (%) | OR (95% CI) | *p* |
| G-tube presence | 12 (24) | 38 (38) | 0.53 (0.24–1.15) | 0.11 | 6 (12) | 23 (23) | 0.43 (0.16–1.17) | 0.10 | 1 (2) | 7 (7.8) | 0.16 (0.02–1.37) | 0.09 |
| Weight loss > 20% compared to baseline | – | – | – | – | 4 (8.3) | 13 (13.5) | 0.64 (0.19–2.11) | 0.46 | 3 (6.7) | 17 (19.3) | 0.28 (0.08–1.05) | 0.06 |
| G-tube OR weight loss > 20% | – | – | – | – | 9 (18) | 34 (34) | 0.44 (0.19–1.0) | 0.05 | 4 (8) | 22 (24.7) | 0.23 (0.07–0.73) | 0.01 |
| Patient rated xerostomia grade 2–3 | – | – | – | – | 21 (42) | 60 (61.2) | 0.38 (0.18–0.79) | 0.009 | 21 (42) | 42 (47.2) | 0.63 (0.30–1.33) | 0.23 |
| Patient rated fatigue grade 2–3 | 39 (78) | 84 (86.6) | 0.49 (0.20–1.23) | 0.13 | 20 (40.8) | 34 (36.2) | 1.1 (0.53–2.27) | 0.80 | 7 (14.6) | 17 (22.1) | 0.5 (0.18–1.36) | 0.17 |
| Emergency room visit | 16 (32) | 32 (32) | 0.95 (0.45–2.0) | 0.89 | – | – | – | – | – | – | – | – |
| Unscheduled hospitalization | 10 (20) | 21 (21) | 0.92 (0.39–2.2) | 0.84 | – | – | – | – | – | – | – | – |



Blanchard et al, R&O, 2016

# Protontherapy indications: in silico studies

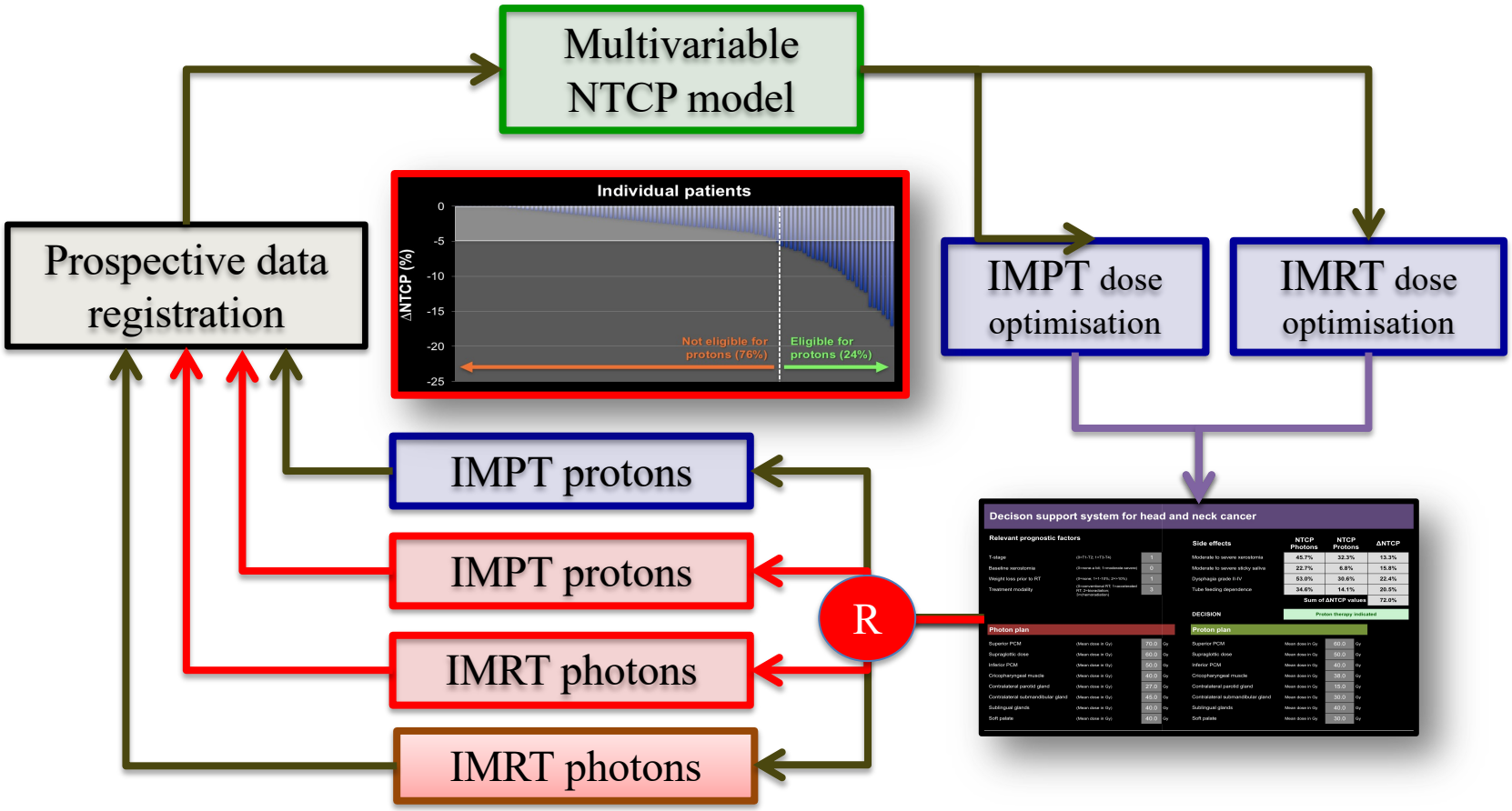





Courtesy of Langendijk, 2016

# The "Biomarkers" of protontherapy

## The model-based approach

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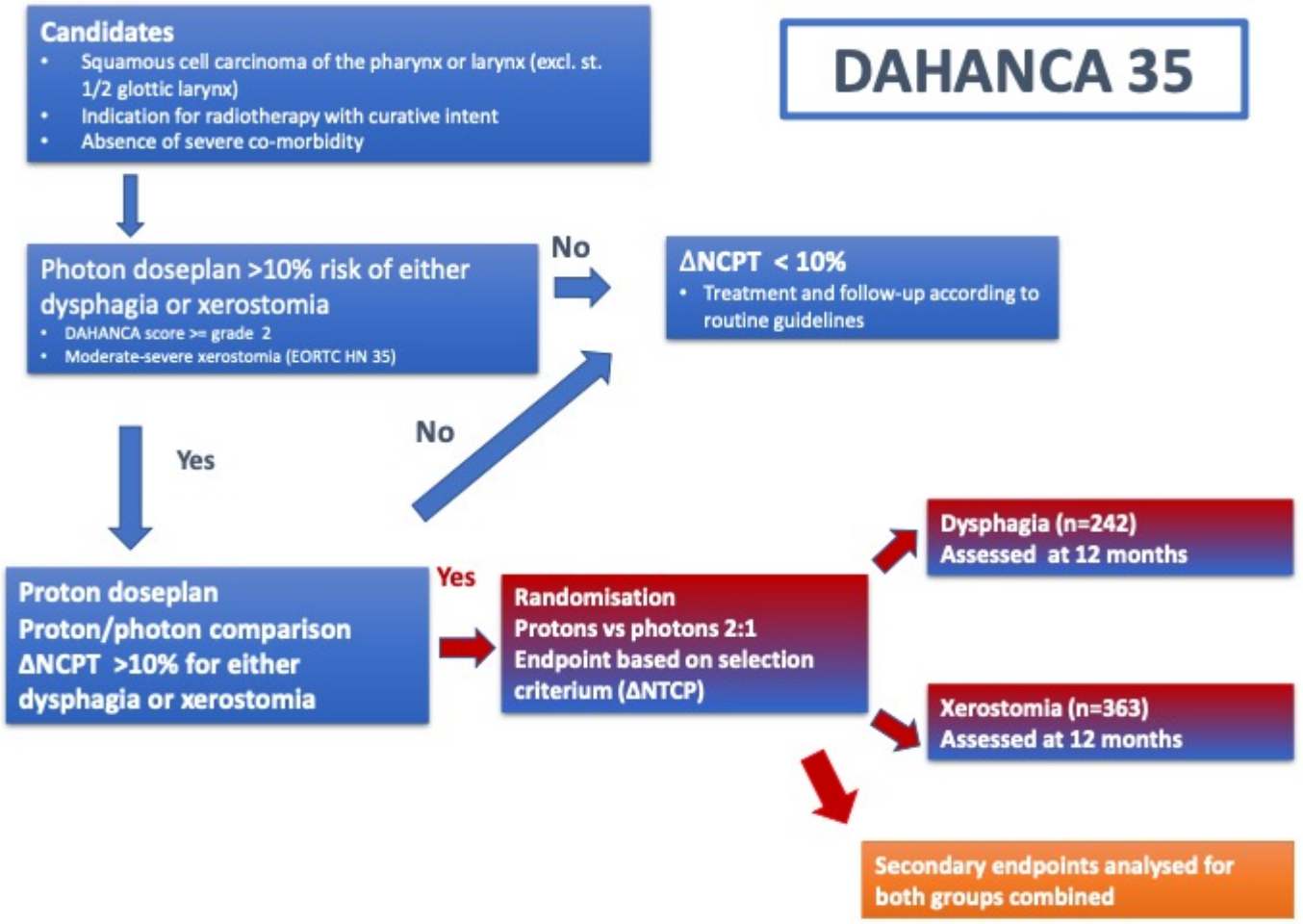
Courtesy of Langendijk, 2016

# DAHANCA 35: a multicentric randomized trial of proton versus photon radiotherapy for the treatment of head and neck squamous cell carcinoma.






Courtesy of J. Friborg, 2021

# Radiation Oncology for H&N Cancer in 2025…

## Role of the Radiation Oncologist…?

- Clinical component
- Treatment strategy
- Multi-disciplinarity
- R&D and concept validation

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Experience is simply the name we give to our mistakes.

Oscar Wilde

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