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De-escalatie voor hoofd- halstumoren

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Overview

- Introduction:
  - -Head and neck cancer
  - -Treatment and side effects
  - -De-escalation of the treatment
- De-escalation
  - -RT dose de-escalation
  - -Chemotherapy
  - -Surgery

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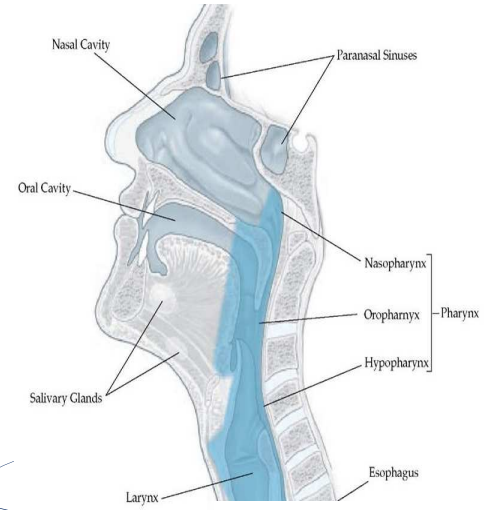
Introduction: head and neck cancer



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Introduction: head and neck cancer

- In Belgium, head and neck cancer is the **4th most** frequent cancer in **males** and the **12th** most frequent in **females**.
- In 2016, there were **2,694** new diagnoses of head and neck cancer in Belgium, 74% were males - M/F: 3/1.
- The most common type of primary head and neck region cancer is **squamous cell carcinoma.**

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Belgian Cancer Registry

Introduction: head and neck cancer

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Introduction: head and neck cancer

- **Risk factors**:

I. **Tabacco** and **alcohol**

II. **HPV** (mostly 16 and 18) in tonsil and base of tongue (oropharynx). **In Flanders: 24.78% of oropharyngeal cancer patients***

*__Van Limbergen E__, Dok R, Laenen A, et al. HPV-related oropharyngeal cancers in Flanders (Belgium): a multicenter study. B-ENT. 2014;10(1):7-14

- HPV related: better prognosis

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Introduction: head and neck cancer

- Treatment of **locoregionally advanced head and neck cancer: radiotherapy +/- chemotherapy; sometimes upfront surgery (oral cavity)**

→ Treatment of the tumor, affected lymph nodes: 70Gy/2Gy

→ Negative/elective lymph nodes, to destroy microscopic disease: 50Gy/2Gy

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Introduction
head and neck cancer; side effects

- Xerostomia
- Mucositis
- Dysphagia, 2nd weight loss
- Erythema
- Neck fibrosis

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Introduction de-escalation

DE-ESCALATION of the treatment

AIM:

Reducing toxicity with similar tumour control

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Overview

- Introduction:
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  - -De-escalation of the treatment

- **De-escalation**
  - **-RT dose de-escalation**
  - **-Chemotherapy**
  - **-Surgery**

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De-escalation (not exhaustive)

- **Radiotherapy**: first results available

I. Belgian DDE I study

II. ECOG 1308

III. Quarterback

- **Chemotherapy**: first results available

I. De-ESCALate HPV trial

II. RTOG 1016

- **Surgery** : results pending

I. ECOG 3311

II. Adept trial

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Radiotherapy: I. DDE Belgian study

Multicentric

Hypothesis:

Dose de-escalation to the elective nodal lymph nodes in head and neck cancer will lead to:

- Decrease in toxicity
- Equal tumor control

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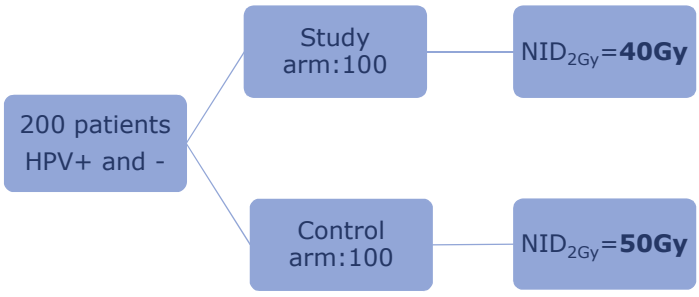
Radiotherapy: I. DDE Belgian study



Primary endpoint: dysphagia at 6 months of follow up

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Radiotherapy: I. DDE Belgian study

- Severe acute skin toxicity: no significant differences.
- Severe acute mucositis: no significant differences.
- Severe acute dysphagia:

Timepoint	40 Gy	50 Gy	p-value
1 month	12,4 %	17,4 %	0,3
2 months	4,8 %	13,3 %	0,06
3 months	**2 %**	**11 %**	**0,03**

Nuyts S, Lambrecht M, Duprez F et al. Reduction of the dose to the elective neck in head and neck squamous cell carcinoma, a randomized clinical trial using intensity modulated radiotherapy (IMRT). Dosimetrical analysis and effect on acute toxicity. Radiother Oncol 2013;109:323-9.

Radiotherapy: I. DDE Belgian study

		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	

Using a GEE proportional odds model including treatment, visit and their interaction, the interaction was found not significant (p=0.8332). When dropped from the model, the odds ratio between 40 Gy and 50 Gy for observing a lower grade toxicity was 1.40 (95% confidence interval 0.93 to 2.10, p-value = 0.1088).

Nevens D, Duprez F, Daisne JF, et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol. 2016 Aug 12.

Radiotherapy: I. DDE Belgian study

No statistically significant differences in OS, DFS, LC, MFS, RC following 2 years of follow-up

RECURRENCE	40 Gy ARM	50 Gy ARM
GTV lymph node	6	5
PTV lymph node	1	0
Outside planning volume	2	0
PTV elective	**2**	**1**

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Nevens D, Duprez F, Daisne JF, Dok R, Belmans A, Voordeckers M, Van den Weyngaert D, De Neve W, Nuyts S. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiother Oncol. 2016 Aug 12.

Radiotherapy: I. DDE Belgian study

Late results (submitted):

- 5 years of follow-up: no statistically significant differences regarding OS, LR, RR nor DM between the 40 Gy and 50 Gy arms
- only 2% RR were observed in the PTV elective in both treatment arms
- underpowered to demonstrate non-inferiority undoubtedly and to change the standard of care to 40 Gy
- reducing the dose to the PTV elective appears safe and these results support **further research in de-escalating the dose to the elective neck**

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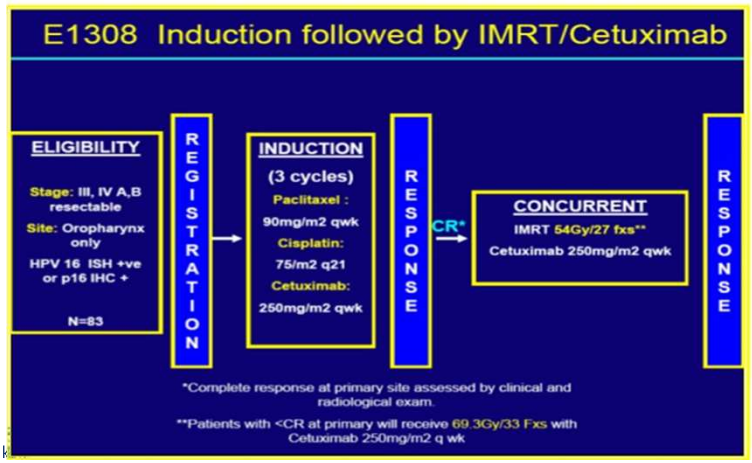
Deschuymer S, Nevens D, Duprez F, et al. Randomised Clinical Trial on Reduction of Radiotherapy Dose to the Elective Neck in Head and Neck Squamous Cell Carcinoma; Update of the Long-Term Tumour Control. Ingediend bij Radiotherapy & Oncology.

Slide 18 14/06/2019

Radiotherapy: II. ECOG 1308

This phase II trial evaluated whether complete clinical response (cCR) to induction chemotherapy (IC) could select patients with HPV-associated OPSCC for reduced radiation dose as a means of sparing late sequelae.



Radiotherapy: II. ECOG 1308

- This study did not meet its own minimum threshold for overall two-year disease-free survival (treshold:PFS at 2 years of 85%; PFS in study 80%)
  - **low risk pt** (low dose of RT) 2y OS 97%
  - **high risk pt** (full dose of RT) 2y OS 87% and 2y PFS 65%
- The results suggest that the low-risk patients could be given less radiotherapy and still achieve excellent survival

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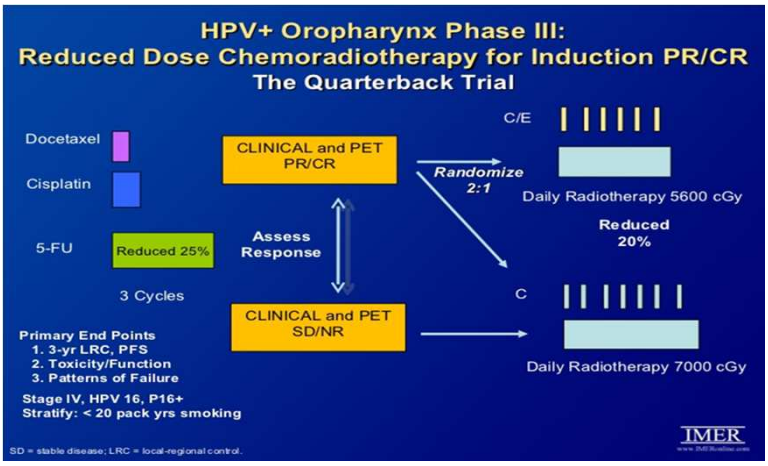
Marur, Li, Cmelak, et al. E1308: Phase II Trial of Induction Chemotherapy Followed by Reduced-Dose Radiation and Weekly Cetuximab in Patients With HPV-Associated Resectable Squamous Cell Carcinoma of the Oropharynx— ECOG-ACRIN Cancer Research Group. JCO 2017.

Radiotherapy: III. Quarterback trial



Ongoing…

De-escalation (not exhaustive)

- **Radiotherapy**: results!

I. Belgian DDE I study

II. ECOG 1308

III. Quarterback

- **Chemotherapy**: results!

I. De-ESCALate HPV trial

II. RTOG 1016

- **Surgery** : pending!

I. ECOG 3311

II. Adept trial

Chemotherapy de-escalation: I. De-ESCALate

Design & objectives of De-ESCALate HPV trial

- Oropharyngeal carcinoma HPV+ (p16)
- LOW RISK (Ang) 93% 3-Y OS (Ang NEJM 2010)
- Intermediate stages III-IVa (T3N0-T4N0, T1N1-T4N3)
- T1-2N0 excluded, Tobacco <10 PY

R — Unblinded, randomised controlled trial

- RT + cetuximab
- RT + cisplatin

PRIMARY OUTCOME : SAFETY
Superiority design: >25% reduction severe acute & delayed G3-5 Toxicities over 24 months
SECONDARY OUTCOMES : OS, time to recurrence, QOL (QLQ-C30, QLQ-H&N35)

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Chemotherapy de-escalation: I. De-ESCALate

De-ESCALate HPV trial: Results (N=334)

	RT + Cetuximab (N=168)	RT + cisplatin (N=166)	
Gr 3-5 toxicity (%)* Overall Acute/Delayed	**4.82** 4.35/0.48	**4.81** 4.43/0.41	p=0.98 → did not differ significantly between treatment groups @24 months
All Grade toxicity (%) Overall Acute/Delayed	**30.05** 20.35/9.87	**29.15** 19.96/9.44	p=0.49
2Y OS (%)	**90.0**	**97.5**	**HR 3.96** (1.68-9.37)
2Y recurrence rate (%) Locoregional Distant	**15.4** 10.7 9.5	**5.8** 4.2 3.2	**HR 2.57**(1.30-5.08) → showed significant detriment for survival and tumor control

*Cisplatin caused more serious adverse events (1 vs 0.58 SAE/pt, p=0.001)

→ Cisplatin remains standard of care in HPV + low risk oropharyngeal carcinoma in combination with RT

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Chemotherapy de-escalation: II. RTOG 1016

Trial design

REGISTER

Mandatory p16 testing *

STRATIFY

T Stage
1. T1-2
2. T3-4

N Stage
1. N0-2a
2. N2b-3

Zubrod Performance Status
1. 0
2. 1

Smoking History
1. ≤ 10 pack-years
2. > 10 pack-years

R

Arm 1 (Control):

Accelerated IMRT, 70 Gy/6 weeks
+ high dose DDP (100 mg/m^2) Days 1, 22
(Total: 200 mg/m^2)

Arm 2 (Investigational)

Accelerated IMRT, 70 Gy/6 weeks
+ cetuximab (400 mg/m^2) loading dose
pre-IMRT, then 250 mg/m^2 weekly
during IMRT, + 1 week after IMRT for a
total of 8 doses of cetuximab

*Centralized RTOG lab test

#ASTRO18

Non-inferiority study; Primary endpoint:
To determine whether substitution of cisplatin with cetuximab will result in comparable 5-year overall survival

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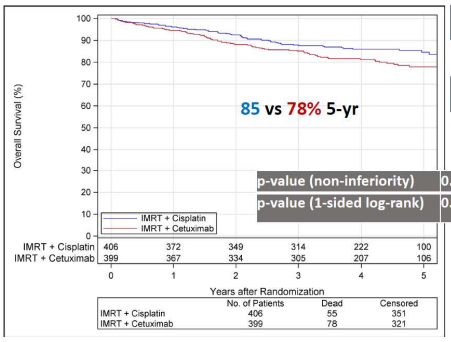
Presented at ASTRO 2018

Chemotherapy de-escalation: II. RTOG 1016

Overall survival



Cisplatin

Cetuximab

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Chemotherapy de-escalation: II. RTOG 10116

Conclusions

- Non-inferiority of cetuximab was NOT demonstrated
  - Cisplatin had better OS, PFS, LRC
  - Acute "Toxicity Burden" 40% worse with cisplatin
  - Late "Toxicity Burden" not significantly different
- RTOG 1016 establishes the first standard of care (no prior phase III trials) in HPV-related oropharynx cancer

  Accelerated IMRT radiation therapy 70Gy/6 weeks + 100mg/m2 Cisplatin x 2
- Outcomes are very good in this population (85% 5 year OS), albeit with moderate to high acute toxicity burden

#ASTRO18

2018 ANNUAL MEETING | HENRY B. GONZALEZ CONVENTION CENTER | SAN ANTONIO

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Chemotherapy de-escalation: I. and II.

Despite several specific characteristics, the results from De-ESCALate HPV and RTOG 1016 studies are very consistent

	De-ESCALate HPV	RTOG 1016
Primary objective	Safety (toxicity reduction)	Survival (maintain overall survival)
Design	Superiority	Non-inferiority
Population	N=334 patients Low risk* (100%)	N=987 patients Low (71%) & intermediate risk* (29%)
HPV tests used	p16 & HPV DNA	p16
Median follow up	25.9 months	4.5 years

*Ang, NEJM 2010

- **Concomitant cisplatin and radiotherapy should remain the standard of care for patients with low-risk HPV-positive oropharyngeal cancer (De-ESCALate)**
- **Cetuximab should not be substituted for cisplatin for patients with HPV-positive oropharyngeal cancer who are platinum eligible (RTOG 1016)**

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Presented at ICHNO 2019

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De-escalation (not exhaustive)

- **Radiotherapy**: results!

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III. Quarterback

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- **Surgery** : pending!

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II. Adept trial

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Surgery + chemoRT

Geiger et al. Curr. Treat. Options in Oncol. (2019) 20:20 DOI 10.1007/s11864-019-0620-y

HPV+, TO(R)S

Table 1. Current deintensification studies involving surgery/adjuvant therapy

Trial	Patient population (AJCC 7th Edition)	Treatment	Primary outcome measures	Deintensification trategy
ORATOR2 NCT03210103	T1-2, N0-2, p16-positive or HPV-positive	Deintensified primary RT ± chemotherapy vs. TOS and neck dissection (plus RT if required); randomized 1:1 ratio	2-year PFS	Upfront surgery
ECOG 3311 NCT01898494	Resectable stage III–IVB HPV-OPC	TORS then risk-adapted postoperative therapy (observation/50 vs. 60 Gy/66 Gy with weekly cisplatin)	2-year PFS, accrual rate, risk distribution, and surgical events (bleeding, positive margin rate)	Reduction of adjuvant RT
SIRS Trial NCT02072148	Resectable T1N0-2B, T2N0-2B, p16-positive	TORS then risk-adapted postoperative therapy (imaging surveillance/50 Gy/50 Gy with weekly cisplatin/56 Gy with weekly cisplatin)	DFS, LRC	Reduction of adjuvant RT
PATHOS NCT02215265	Resectable T1-3, N0-2b HPV-OPC	TOS then risk-adapted postoperative therapy (observation/50 vs. 60 Gy/60 Gy ± weekly cisplatin	Swallowing outcome, QOL, toxicity, OS, DFS	Reduction of adjuvant RT; omission of adjuvant chemotherapy
ADEPT NCT01687413	Resectable, p16-positive, stage III, IV, + ECE	TOS then 60 Gy ± weekly cisplatin	DFS, LRC	Omission of adjuvant chemotherapy
University of Pennsylvania NCT02159703	Resectable, p16-positive, T1-2, N2a-c	TORS then forgo adjuvant RT to primary bed if no PNI in primary and surgical margins ≥ 2 mm	LCR, QOL, toxicity	Omission of adjuvant RT to primary bed
Mayo Clinic NCT02736786	Resectable T1-2, N1-3 OPC	TOS then mucosal sparing PBT if negative margin and no PNI/LVI in primary	LCR, QOL, toxicity	Omission of adjuvant RT to primary bed and the use of PBT

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De-escalation, conclusions

- Many trials

-Cetuximab trials: disappointing results

-Radiotherapy trials: needs further research

-Surgery trials: ongoing

- **Currently no practice changing trials** (also not for HPV+!)

→De-escalation only in the setting of clinical trials

- Will hopefully lead to **more patient-tailored treatments** in the future, with reduction of the side-effects as a result

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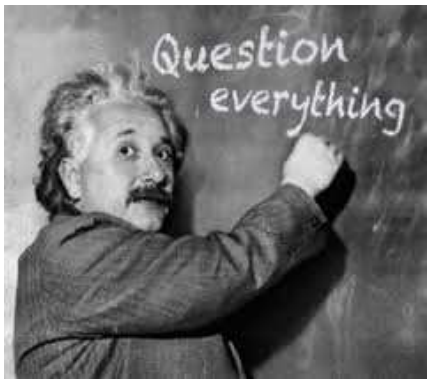

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