Locally advanced head and neck cancer. De-escalation strategy.

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Disclosure
- MSD: trials
- BMS: consultancy fees
- Stichting tegen Kanker: scientific grants

De-escalation strategies in H&N cancer: why?

- H&N squamous cell carcinoma: Higher radiotherapy doses ~ higher locoregional control.
  Concomitant cisplatin in stage III-IV ~ better OS

- Acute toxicity in H&N chemoradiation determines total dose of radiotherapy.
  - 4/5 patients: grade 3-4 oral/pharyngeal mucositis
  - Dysphagia, weight loss, PEG-tube, nephro- and ototoxicity, decline in QOL

- Late toxicity:
  - Determines QOL in survivors
    - Late dysphagia, laryngeal dysfunction and persistent xerostomia
    - Increasing neck fibrosis through years
    - Can lead to treatment-related deaths (e.g. aspiration pneumonia)
    - Long-term ototoxicity and nephrotoxicity

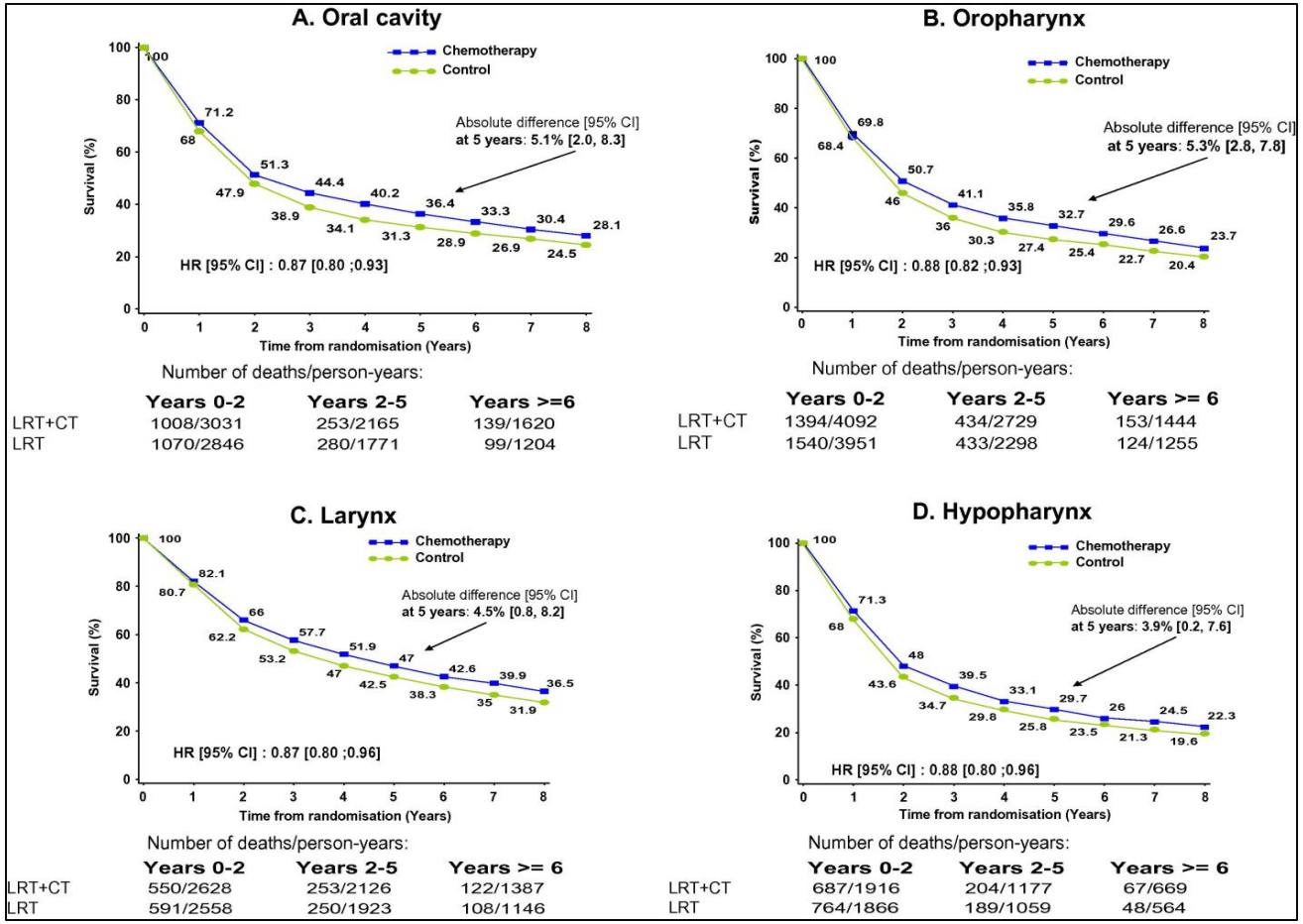
De-escalation strategies in H&N cancer: how?

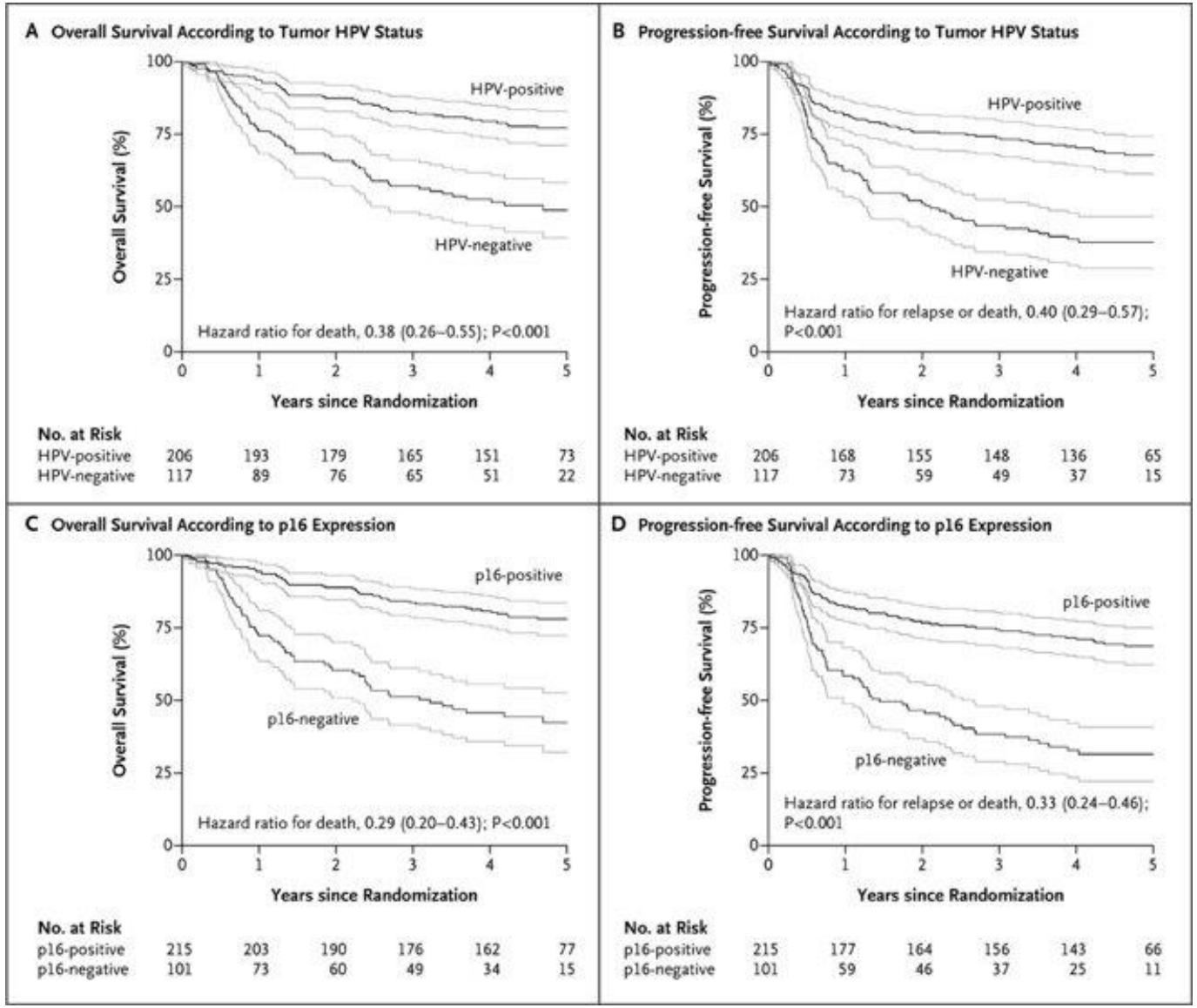
- Systemic de-escalation
  - HPV-related oropharyngeal cancer
  - EBV-related nasopharyngeal cancer
  - Other H&N malignancies
- Radiotherapy de-escalation
  - Prophylactic neck dose
  - Novel technologies
- (Surgical de-escalation)

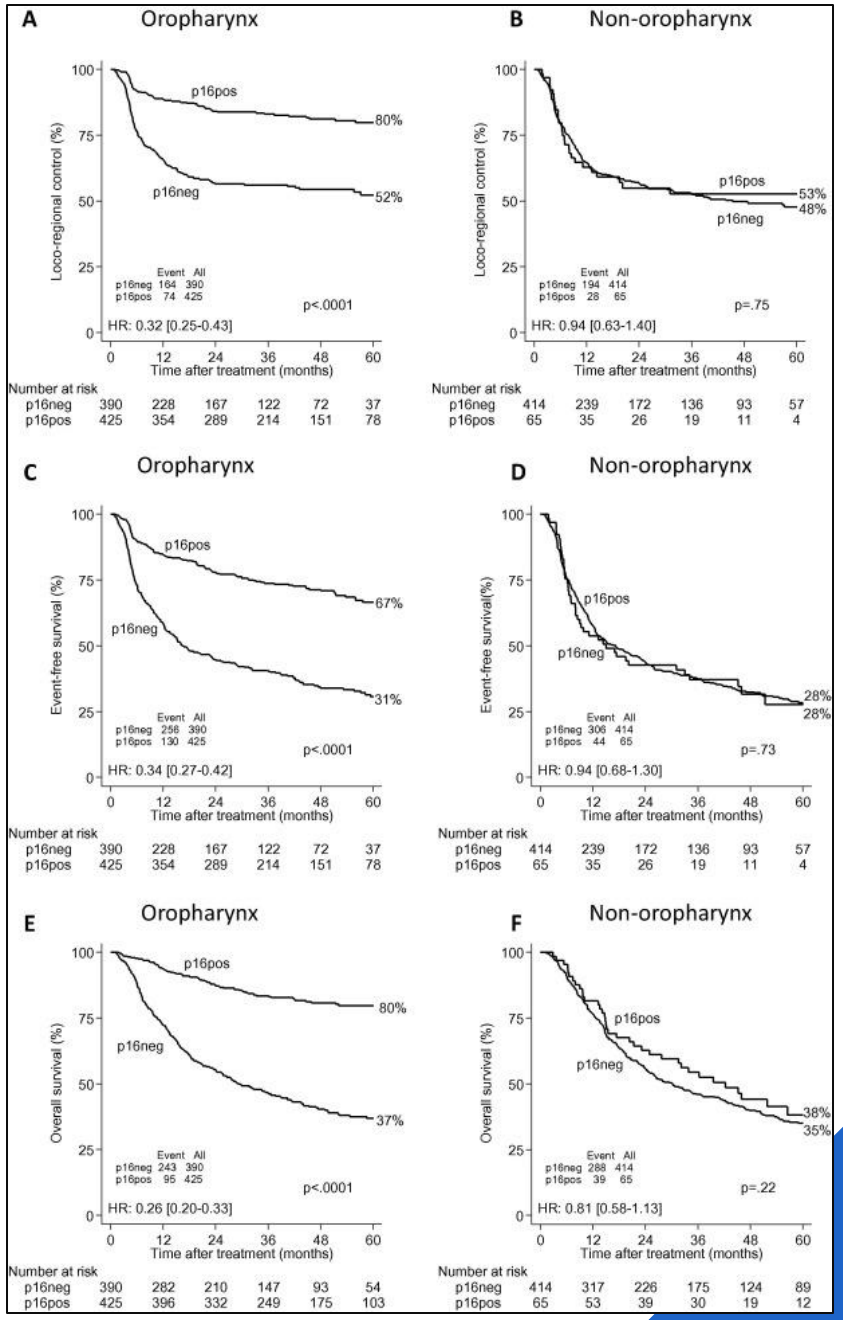
Systemic de-escalation: could it be safe?

- OS benefit: overall 13%!

- Oral cavity: 8.9%
- Oropharynx: 8.1%
- Larynx: 5.4%
- Hypopharynx: 4.0%







ANG ET AL. N ENG J MED 2010; 363: 24-35.
6 / LASSEN ET AL. RADIOTHERR ONCOL 2014; 113: 310-316.

Systemic de-escalation in HPV-associated oropharyngeal cancer. Changing standard of cisplatin.

Outcome.

- **DE-ESCALATE, TROG 12.01 and RTOG 1016**: cisplatin vs. cetuximab as concomitant to RT [1-3]
  - High-risk patients with advanced stage tumors or nodal status
  - DE-ESCALATE and TROG 12.01: toxicity and QOL as primary endpoint
  - RTOG 1016: oncologic outcome as primary endpoint

  - 2-Y OS: 97.5% vs. 89.4% (p = 0.001) [1]
  - 5-Y OS: 84.6% vs. 77.9% (p = 0.001) [2]

  - Difference might be attributed mainly to the portion of patients with ECOG = 1
  - EGFR-targeting in HPV-associated OPC is controversial[3]

1 – MEHANNA ET AL. LANCET 2018; 393: 51-60.
2 – GILLISON ET AL. LANCET 2019; 393: 40-50.
3 - CANCER GENOME ATLAS NETWORK. NATURE 2015; 517: 576-582.

Systemic de-escalation in HPV-associated oropharyngeal cancer. Changing standard of cisplatin.

Toxicity.

- **DE-ESCALATE** and **RTOG 1016**: cisplatin vs. cetuximab as concomitant to RT [1-2]
  - Overall acute and late grade 3-5: equal.
  - Different toxicities:
    - More acute infusion reactions, mucositis and skin rash for cetuximab
    - More nausea, vomiting, anorexia, dehydration and hematological toxicity for cisplatin
    - More ototoxicity and nephrotoxicity for cisplatin in long-term
  - Choose your poison...

1 – MEHANNA ET AL. LANCET 2018; 393: 51-60.
2 – GILLISON ET AL. LANCET 2019; 393: 40-50.

Systemic de-escalation in HPV-associated oropharyngeal cancer. Abandoning cisplatin in low risk patients.

- **NRG HN002**
  - Only non-smokers, T1-2 N1-2b and T3 N0-2b p16+ OPC
  - Weekly cisplatin 40 mg/m² with normofractionation (60 Gy/6 weeks) vs. 60 Gy/5 weeks
  - Hypothesis: in both arms acceptable PFS and MDADI scores

  - MDADI acceptable in both arms
  - 2Y-PFS in IMRT + cisplatin: 90.5% --> ~ 0-hypothesis
  - 2Y-PFS in IMRT: 87.6% --> rejecting 0-hypothesis

  - Concomitant chemoradiation overall better results.

ASTRO 61, SEPTEMBER 2019,

Induction chemotherapy to select patients for further de-escalation.

- **ECOG 1308**
  - Prospective trial of induction cisplatin, paclitaxel and cetuximab
  - RT dose reduction from 69 – 54 Gy in the good responders
  - Swallowing dysfunction reduced
  - Non-smokers without T4: not a single recurrence

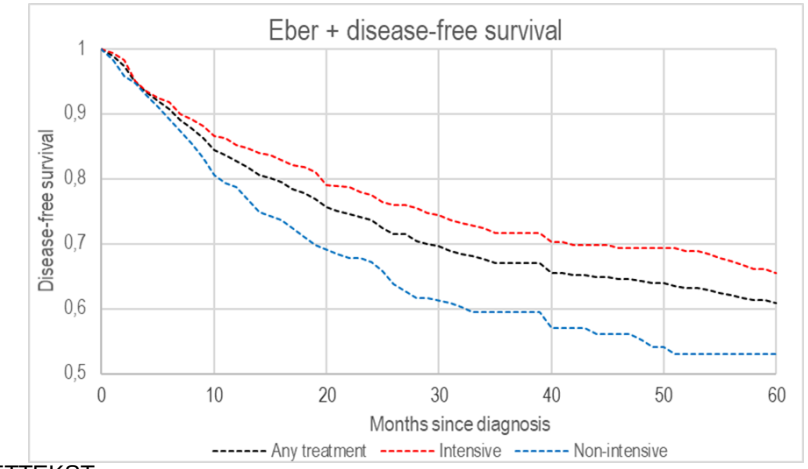
  - **Beware: level I data on concomitant chemoradiation remains the standard**

O'SULLIVAN ET AL. J CLIN ONCOL 2013;31:543-550.

Systemic de-escalation in EBV-associated nasopharyngeal cancer. Abandoning induction/adjuvant chemotherapy.

- EORTC Nasopharyngeal Cancer Portal – P. Bossi – presented 23/10/2020 H&N Group meeting
- Retrospective analysis of 1230 patients in non-endemic setting, 2004-2017
- 85%: non-keratinizing; 82% of tested patients EBER+

	Non-intensive Only chemoradiation	Intensive Chemoradiation + ind/adj chemo	p
HR of OS	1,11	1	0,5
HR of DFS	**1**	**1,37**	**0,005**



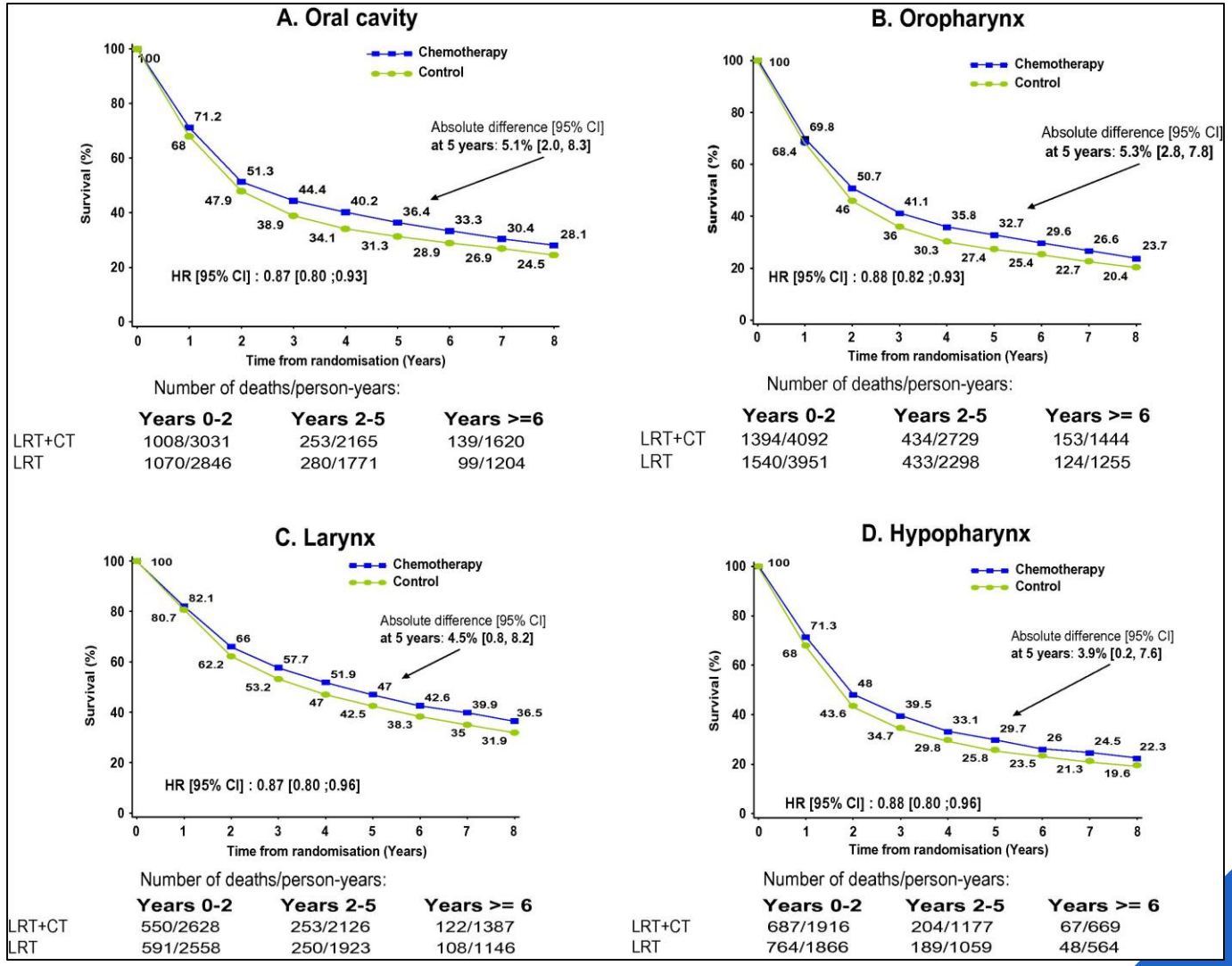
	Non-intensive Only chemoradiation	Intensive Chemoradiation + ind/adj chemo
5-Y-DFS	53%	66%

Figure from P. Bossi
Courtesy of P. Bossi

De-escalation of any other stage III-IV oral cavity/larynx/pharynx?

- Meta-analysis
- 17.000 patients
- Clear OS benefit of cisplatin
- Clear benefit of 70 Gy radiotherapy

- NO possibilities to safely de-escalate dose on macroscopic tumor or de-escalate in concomitant cisplatin



De-escalation in adjuvant radio(chemo)therapy in HPV+ OPC

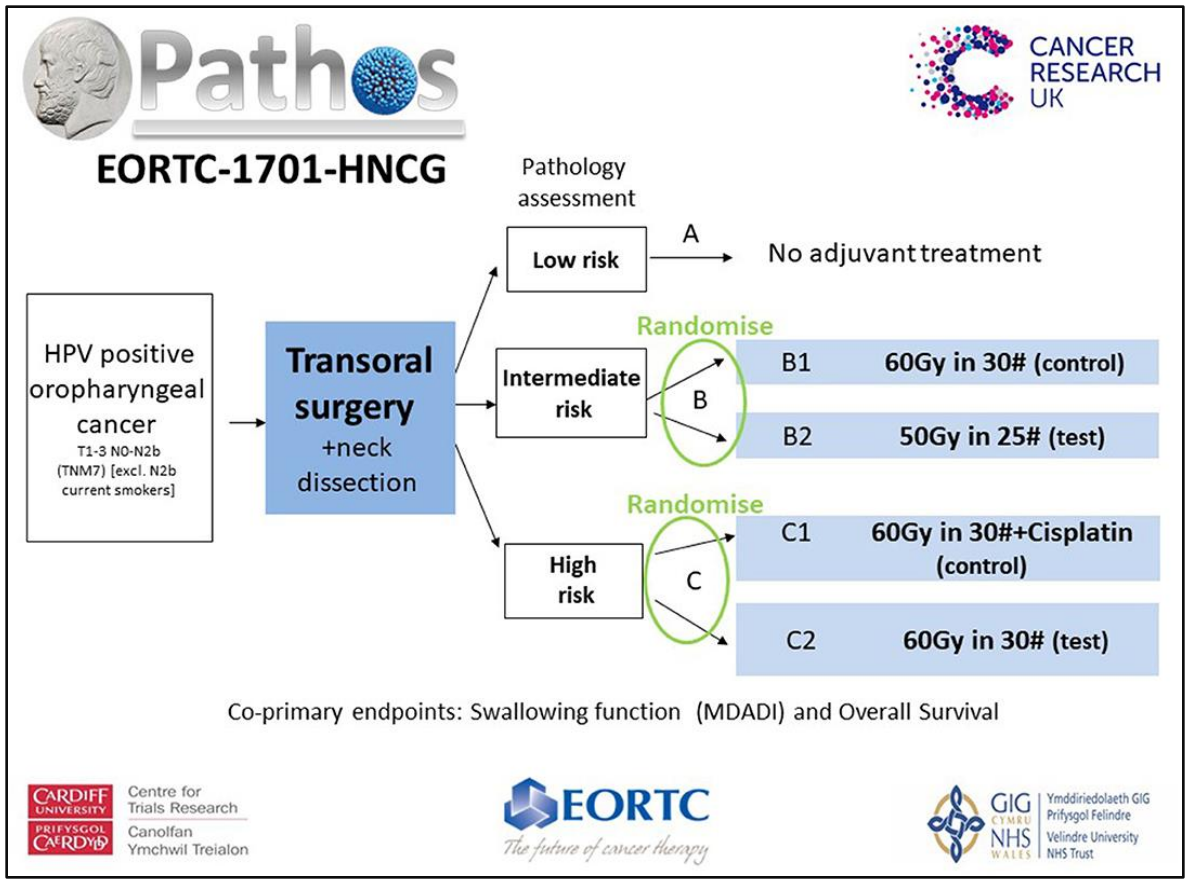
- Omitting local adjuvant radiotherapy in patients with N+ after TORS and neck dissection.
- Retrospective cohort analysis in n = 261.
  - Stage T1-2: n = 202 (of which 92 without planned local CTV)
  - Stage T3-4: n = 59 (of which 12 without planned local CTV)
  - Only 31% chemoradiation (~ ECE)

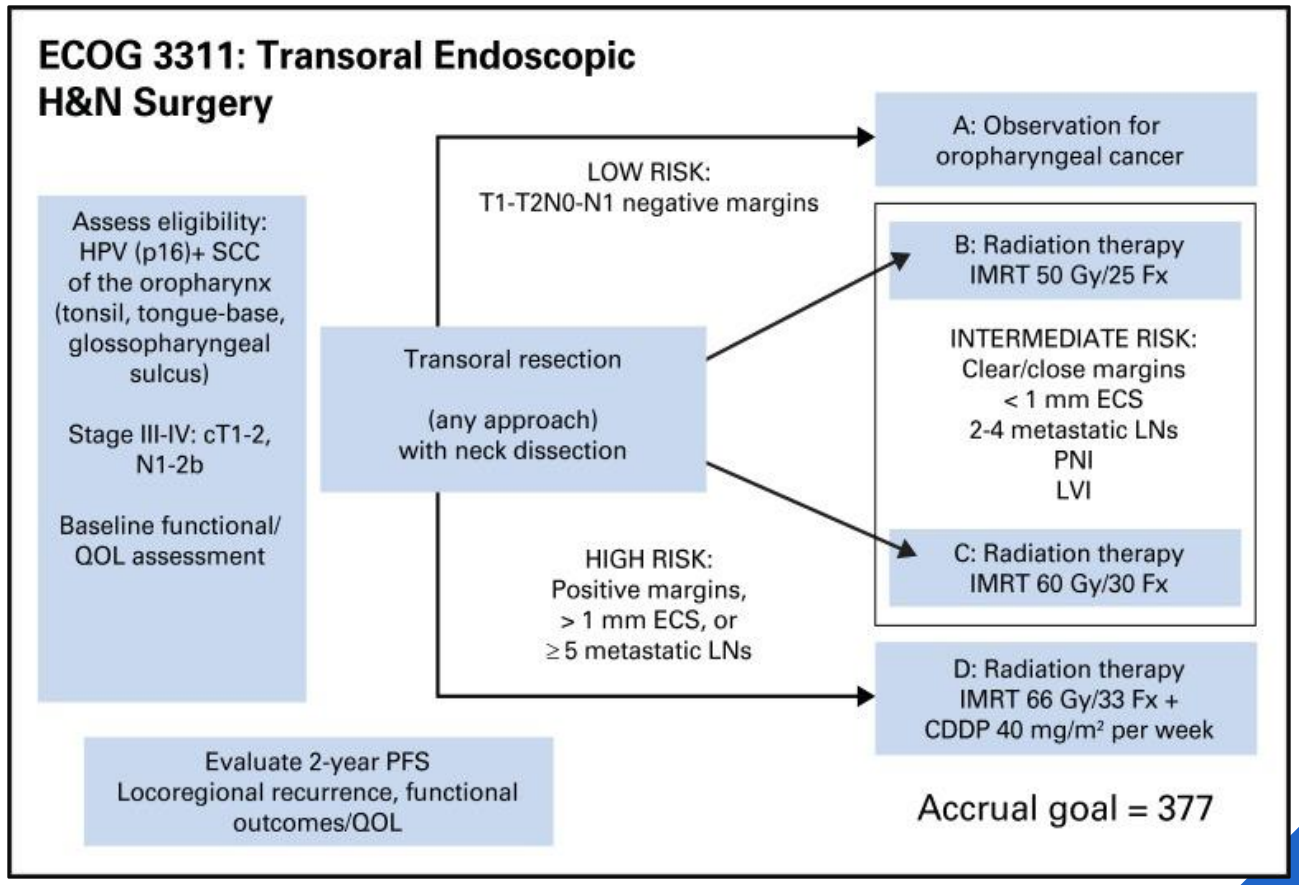
  - T1-2 vs. T3-4 without local RT: 3% vs. 17% recurrence
  - For the T1-2:
    - Number needed to treat = 31 patients to prevent 1 local recurrence
    - Number needed to harm = 3 (1 in 3 had a PEG-tube due to the local RT)

  - For T3-4: for sure local RT
  - For T1-2: better to omit local RT?
  - For all with N+ ECE: adjuvant RT + cisplatin neck remains the standard

  - ADEPT trial: Adjuvant De-escalation for Extracapsular spread P16+, Transoral is recruiting

Accruing trials in de-escalation of post-operative (chemo)radiation





De-escalation using immunotherapy?

- HPV+ OPC:
  - HPV expresses viral antigens --> better immune recognition and activation to be expected
  - Mainly in base of tongue and tonsils --> lymphoid tissue
- No randomised trials omitting cisplatin in favour of immunotherapy
- Phase I trial in non-cisplatin-fit patients: NCT00349710 – CA209-9TM: nivolumab + RT

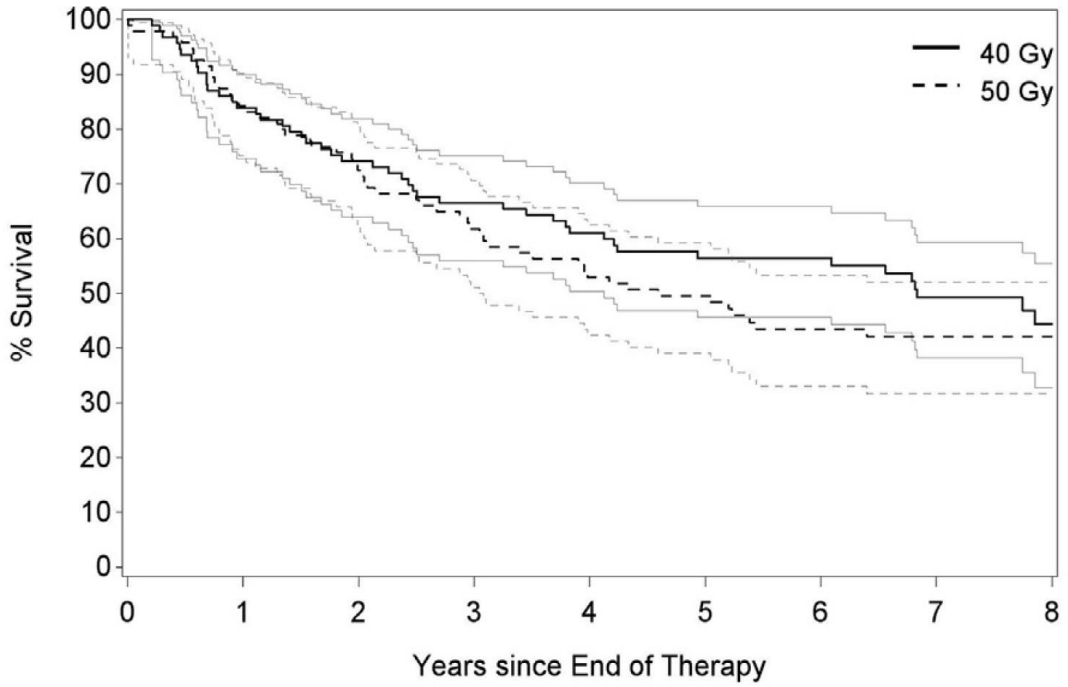
 BLANCHARD ET AL. RADIOTHER ONCOL 2011; 100: 33-40.

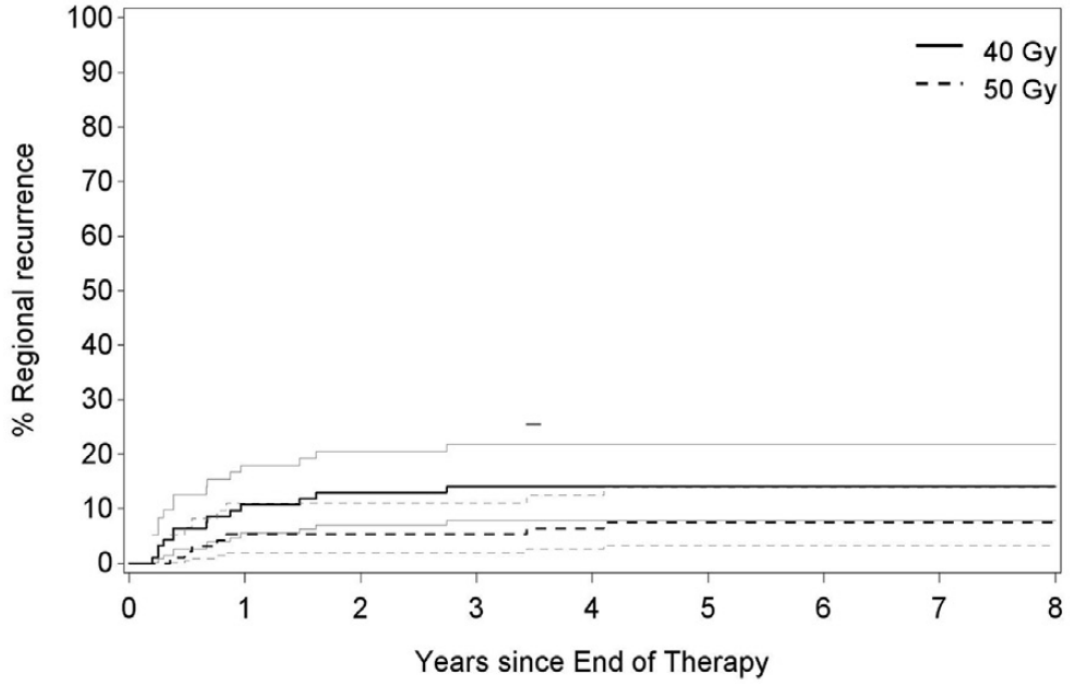
De-escalation of radiotherapy dose?

- Dose to macroscopic tumor cannot be de-escalated without detrimental local control/survival.
- Dose to and volume of prophylactic neck radiotherapy could be de-escalated.

De-escalation of radiotherapy dose?

- Belgian multi-centre de-escalation trials (UZ Leuven, UZ Gent, Institut Bordet, CHU-UCL Namur; 2008-2012).
- 40 Gy vs. 50 Gy prophylactic neck
- Only 2 isolated regional recurrences in prophylactic neck in both arms





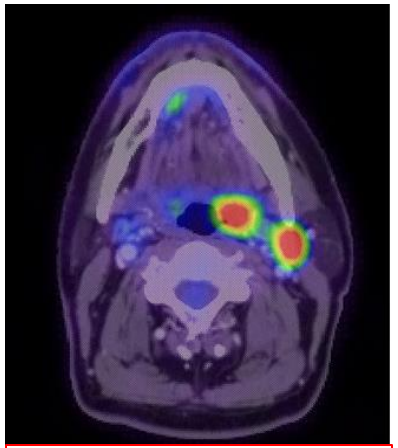
De-escalation of radiotherapy dose?

- Acute toxicity
  - No differences during therapy
  - Dysphagia grade 3-4 at 3 months: 2% vs. 11% ($p = 0.03$)

- Late toxicity
  - Xerostomia Grade 1-2 at 6 months: 55% vs. 63% ($p = 0.01$)
  - Xerostomia Grade 1-2 at 18 months: 37% vs. 49% ($p = 0.03$)

- QOL
  - Less trouble with social eating, less speach problems and less senses problems ($p < 0.01$; $p = 0.03$ and $p = 0.02$)
  - Altogether marginal effects, less then expected.

De-escalation of radiotherapy dose and volume?

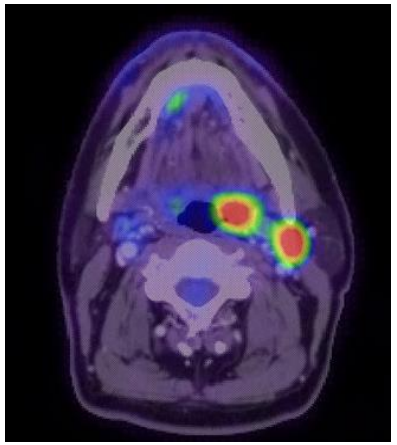


Week 1-2
Based on pre-RT PET-CT

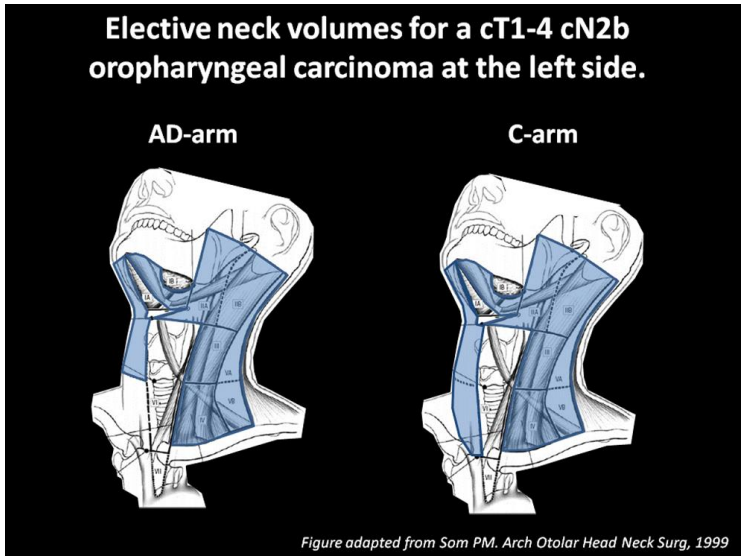
Week 3-4
Based on per-RT CT

Week 5-6
Based on per-RT CT

vs.



Week 1-6
Based on pre-RT PET-CT



De-escalation of radiotherapy dose and volume?

- Equal acute and late toxicity.
- Equal disease control

- Underpowered?
- Anticipated benefit of adaptive radiotherapy with only 2 adaptations overestimated
- Volumes of reduction in the neck very modest in most patients due to mostly advanced stage disease

- Comparable results in a very likewise study (Sher et al., 2020): no isolated regional recurrence in n = 72

ICHNO 2015, DUPREZ ET AL.
/ESTRO 2016, SCHATTEMAN ET AL.
SHER ET AL. INT J RADIAT ONCOL BIOL PHYS 2020, AVAILABLE ON-LINE.

Other harm-minimisation strategies in radiotherapy?

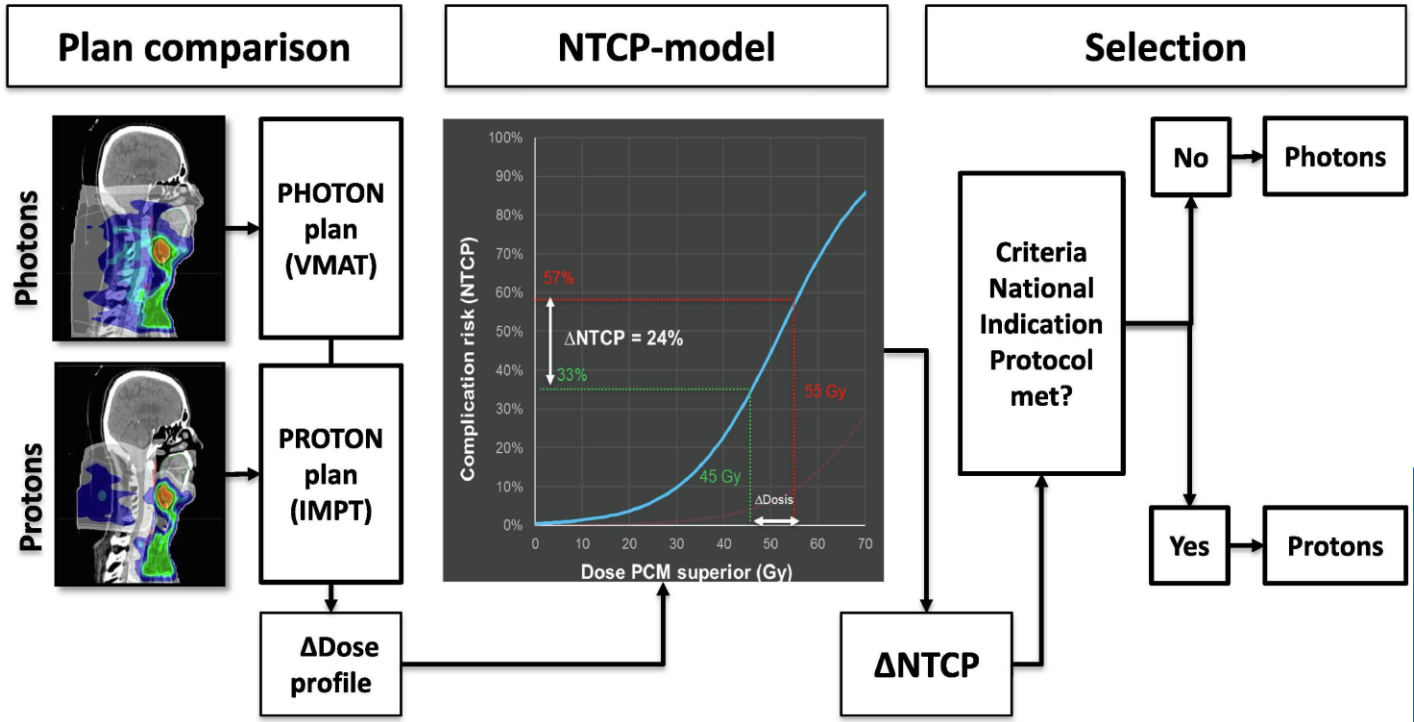
- IMRT is now a standard
- Dysphagia-optimised radiotherapy (currently DARS-trial)
- Novel evolutions in sculpting the dose around the target and dose minimisation in OARs:
  - VMAT – rotational IMRT

FUTURE DEVELOPMENTS AND PROMISING STUDIES:

- Proton therapy – model based approached in The Netherlands
- (Daily) adaptive IMRT – e.g. via MR-based LINACs
- Use of sentinel techniques to selectively detect elective nodal regions

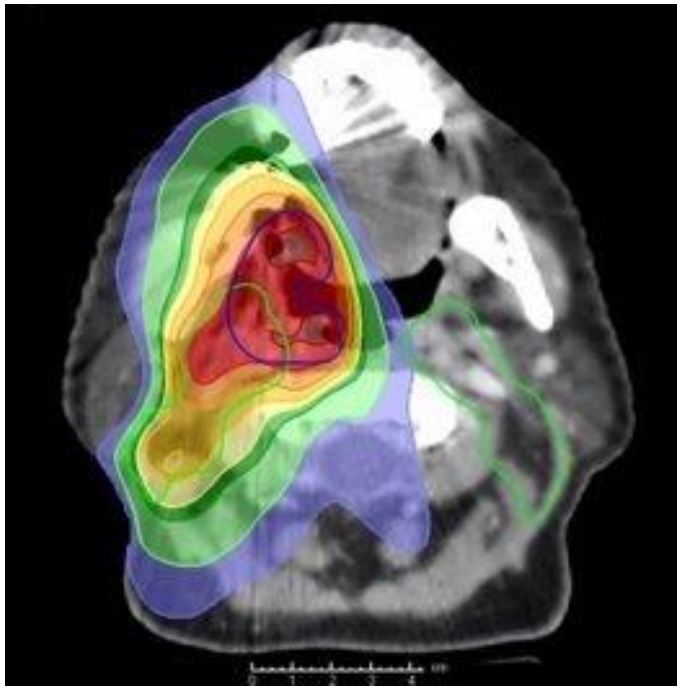
Model-based selection of radiotherapy modality

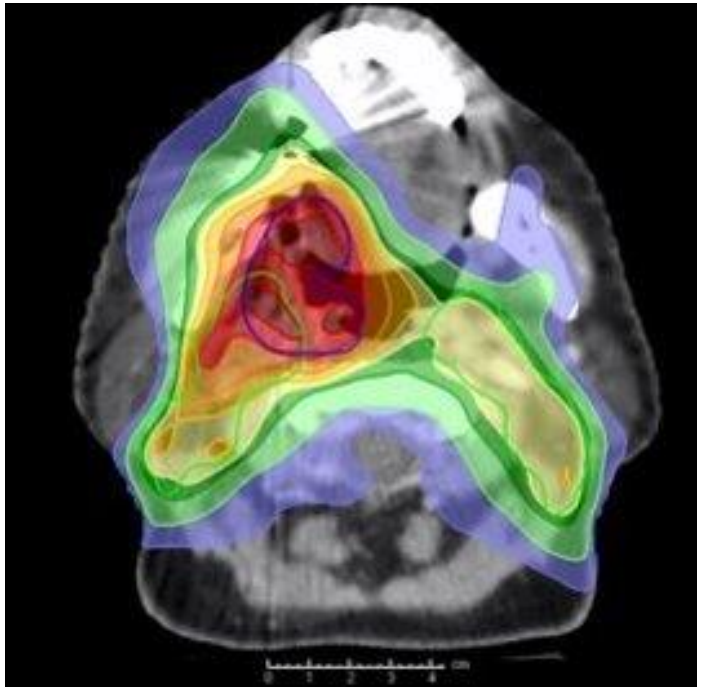
- The Netherlands, national platform
- How to select who will profit most from (expensive) proton therapy vs. classical photon therapy?
- Model-based selection, using NTCP for dysphagia (normal tissue complication probability)
- All OPC patients are planned in the "home" hospital --> replanned with proton therapy
- If incremental gain with less NTCP sufficient: referral for proton therapy
  - 1/3 patients referred for proton
  - Mostly:
    - advanced stage disease
    - pharyngeal tumors



Upcoming trial in Belgium

- **SEMIRAHN**
  - Prospective randomised trial
  - Sentinel node detection in ipsilateral tumors
    - Ipsilateral drainage: only ipsilateral radiotherapy
    - Contralateral drainage: whole level RT vs. only nodal RT





What do patients prefer?

- Primary concern = survival
  - 1/3 is not willing to risk any drop in survival probability
  - 1/3 is only willing to have less toxic treatment if < 5% reduction in survival probability
- No de-intensification outside routine clinic
- Patients need to be well informed about any deviation of standard practice

 BROTHERSTON DC ET AL. HEAD NECK 2013; 35: 151-159.

De-escalation for H&N squamous cell carcinoma: CONCLUSIONS

- Combined radiotherapy to an equivalent of 70 Gy with cisplatin remains the standard for locoregionally advanced HPV+ OPC.
- Combined radiotherapy to an equivalent dose of 70 Gy with cisplatin remains the standard for non HPV-related OPC, as well as oral cavity, laryngeal and hypopharyngeal carcinoma.
- Omiting induction or adjuvant chemotherapy for NON-EBV-related NPC could probably safely be done.

- Radiotherapy de-escalation of dose in prophylactic neck: in research context.
- Novel radiotherapy techniques such as proton therapy and other optimization techniques in photon therapy will be examined in the future.

- De-escalation: only in research arena.

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