HPV-positive Oropharyngeal Cancer: Radiosensitizer Options

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OPC Etiology

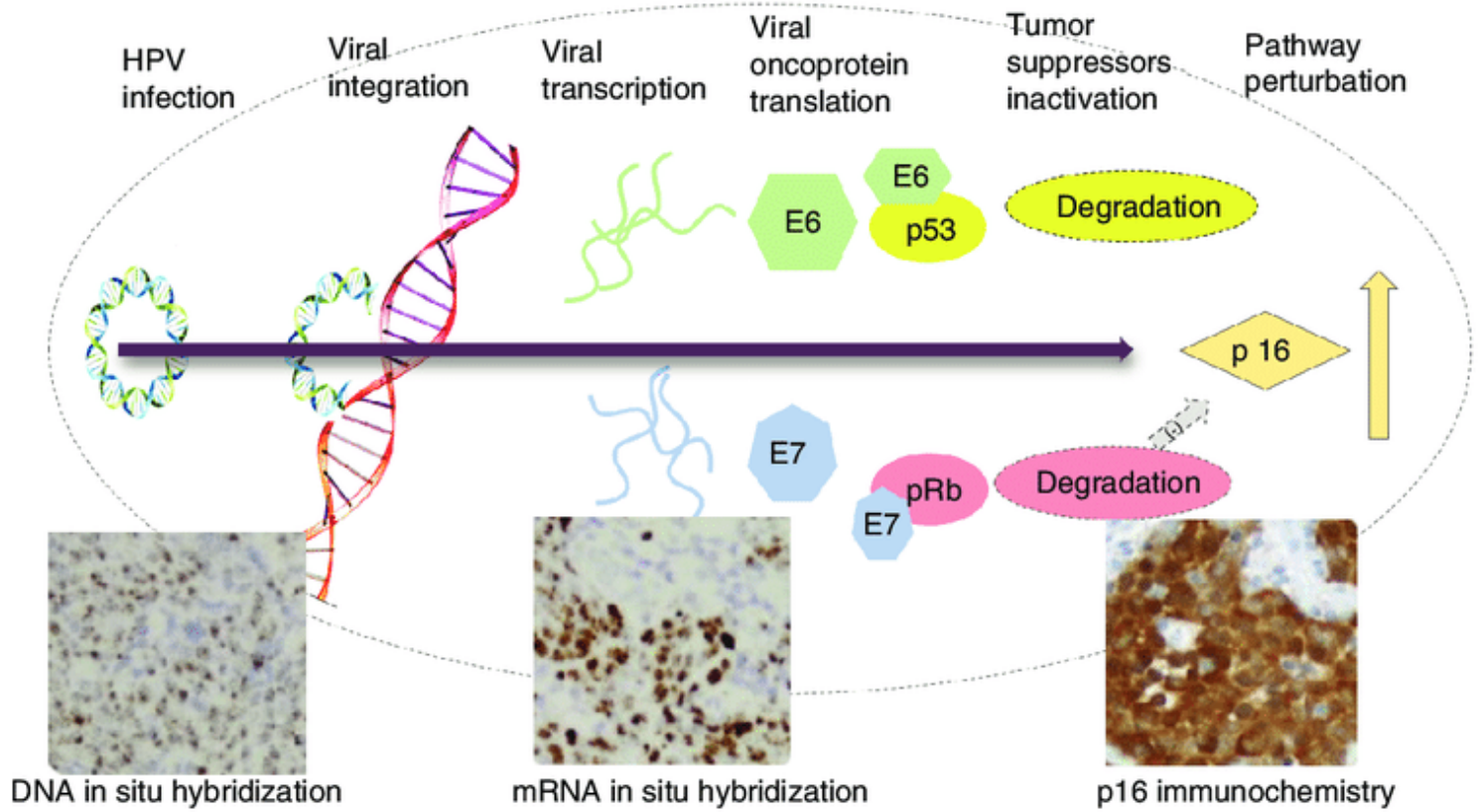
- Smoking/alcohol
- Human papilloma virus (HPV)

- HPV-associated OPC:
  - Epidemic of HPV+ oropharynx cases (70-80%) in US
  - Rapid rise of incidence over past 20 years

Human papillomavirus and OPC

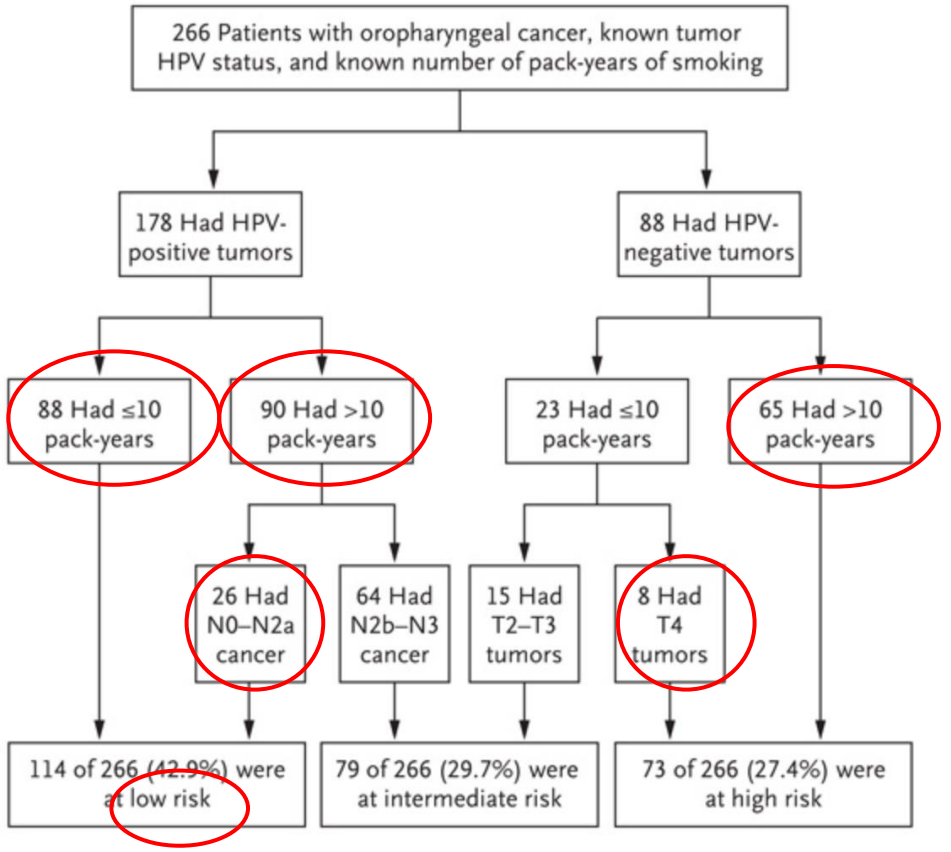
- Circular, double-stranded DNA virus
- In the US, HPV-positive OPC has surpassed cervical cancer as the most common HPV-associated cancer
- Transmission of HPV is thought to occur through direct skin/mucosa-to-skin/mucosa contact, primarily via sexual contact, although nonsexual routes have been described.
- The prevalence of high-risk oral HPV-16 infections: 1.8% in men and 0.3% in women
- *Alphapapillomavirus* genus primarily infect the mucosa: Only 13 HPV genotypes are oncogenic: 51, 56, 66, 18, 39, 45, 59,16, 31, 33, 35, 52, 58
- Approximately 82% of HPV-positive OPC is attributable to HPV-16.
- HPV-16 and HPV-18 together are responsible for 86% of HPV-positive OPCs
- Types 31, 33, 45, 52, and 58 account for 8% of HPV-positive OPCs, and other oncogenic HPV types account for the remaining 6% of HPV-positive OPCs.

HPV-associated Carcinogenesis of OPC and Molecular Diagnostic Tests



RTOG 0129

- The 3-year rates of overall survival were :
  - 93.0% (95% CI, 88.3 to 97.7) in the low-risk group
  - 70.8% (95% CI, 60.7 to 80.8) in the intermediate-risk group
  - 46.2% (95% CI, 34.7 to 57.7) in the high-risk group.
- *AJCC cancer staging manual.* 5th ed



N2a* Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, ENE(−)

N2b* Metastasis in multiple ipsilateral lymph nodes, none more that 6 cm in greatest dimension, ENE(−)

Ang K.K. N Engl J Med. 2010 Jul 1;363(1):24-35

HPV-associated OPC

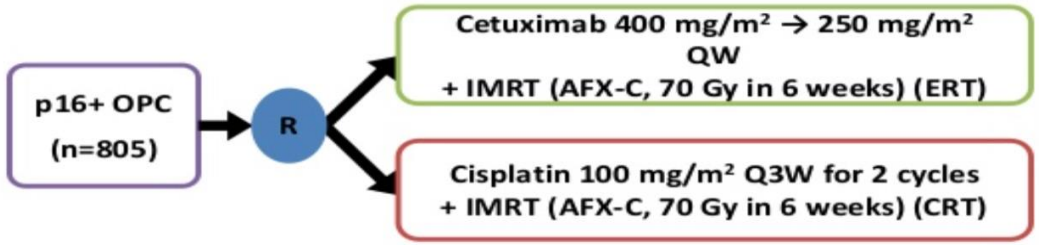
- Although treatments are highly successful in the good prognosis subset of patients with early stage p16+ disease, they are accompanied by significant acute and late toxicity.

- De-intensification of HPV-related HNSCC has been a major focus of recent clinical investigation in order to reduce this toxicity without compromising outcomes.

- Systemic therapy de-escalation – replace cisplatin with cetuximab?

RTOG 1016:
Cis/RT vs Cetuximab/RT in P16+ OPC

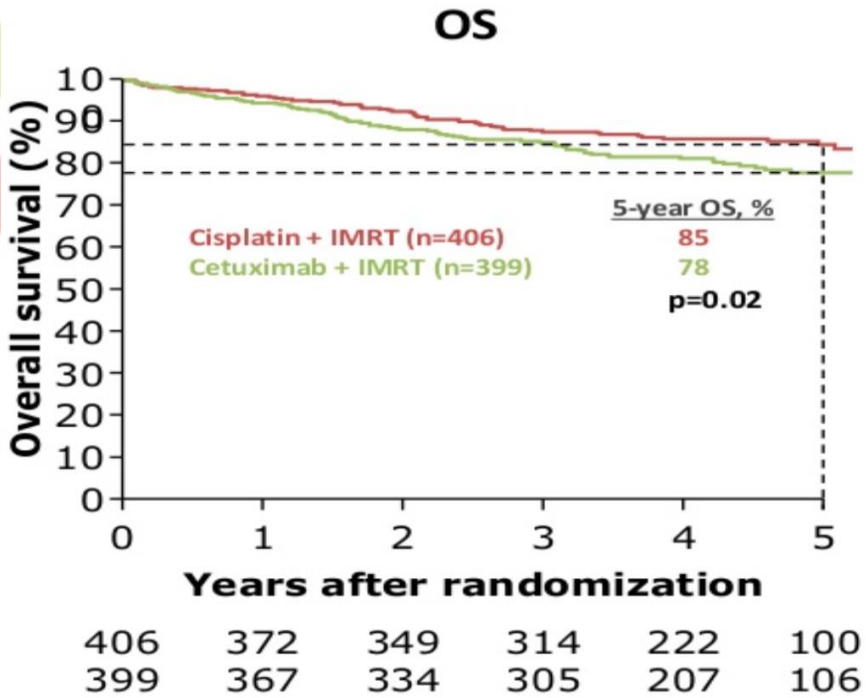
Phase III, open-label, non-inferiority[2]



Primary endpoint:

5-year OS

Efficacy	Cetuximab + RT (n=394)	HD cisplatin + RT (n=398)	p-value
5-year OS, %	78	85	0.02
5-year PFS, %	67	78	<0.001
5-year LRF, %	17	10	<0.001



Gillison ML et al Lancet 2019; 393: 40 - 50

RTOG 1016: Acute & Late Toxicity

T-score—the mean number of grade 3–4 acute adverse events per patient

Safety endpoint	HD cisplatin + RT (n=398)	Cetuximab + RT (n=394)	p-value
Acute toxicity burden (mean raw T-score)	3.19	2.35	<0.001
Grade 3–4 overall acute toxicity, %	81.7	77.4	0.16
Late toxicity burden (mean raw A-score)	0.38	0.27	0.12
Grade 3–4 overall late toxicity, %	20.4	16.5	0.19

- Grade 3–4 anemia, hearing impairment (acute and late), nausea, vomiting, neutropenia, leukopenia, and acute kidney injury were significantly worse with HD cisplatin + RT than cetuximab + RT*
- There were significantly fewer cases of grade 3–4 radiation dermatitis and acneiform rash with HD cisplatin + RT than with cetuximab + RT*

Gillison ML et al Lancet 2019; 393: 40 - 50

RTOG 1016: Conclusion

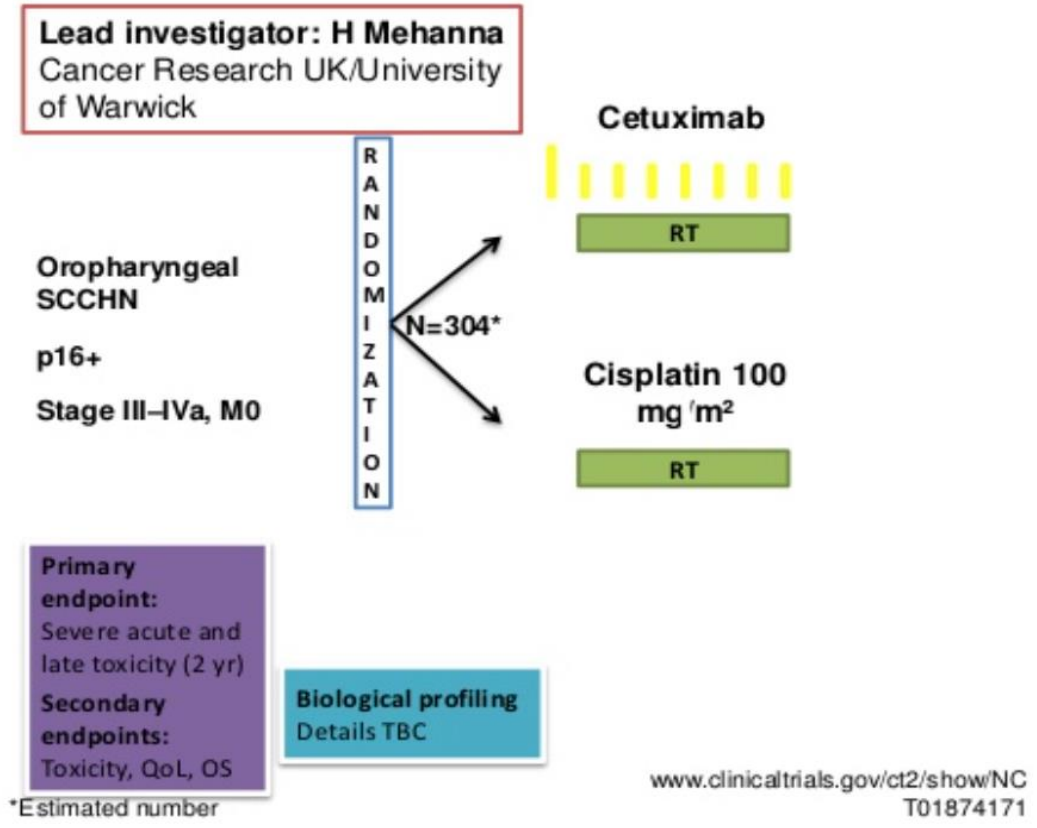
- Cetuximab/RT led to inferior overall survival when compared with cisplatin/RT for HPV-positive oropharyngeal carcinoma

- The overall burden of acute toxicity was greater for patients treated with cisplatin than with cetuximab, as reflected by T-scores.

Gillison ML et al Lancet 2019; 393: 40 - 50

De-ESCALate HPV:
Cis/RT vs. Cetuximab/RT in P16+ OPC

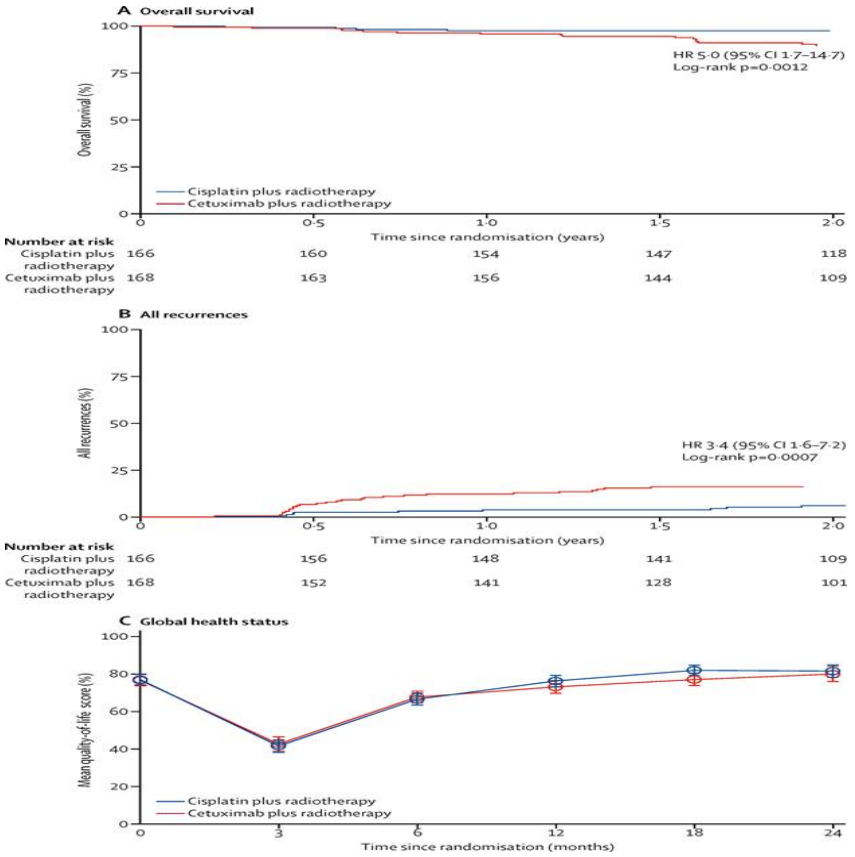
- Low Risk disease:
  - P16 positive, non-smoker or < 10 pack-years.
- The primary outcome: overall severe (grade 3–5) toxicity events at 24 months from the end of treatment



Mehanna H, et al Lancet 2019; 393:51-60

De-ESCALate HPV: Toxicity & Efficacy

		Cisplatin plus radiotherapy (95% CI)	Cetuximab plus radiotherapy (95% CI)	p value
Primary outcome				
Overall				
	Grade 3–5	4.81 (4.23–5.40)	4.82 (4.22–5.43)	0.98
	All grades	29.15 (27.33–30.97)	30.05 (28.26–31.85)	0.49
Secondary outcomes				
Acute short-term toxicities				
	Grade 3–5	4.43 (3.88–4.97)	4.35 (3.84–4.86)	0.84
	All grades	19.96 (18.81–21.12)	20.35 (19.18–21.52)	0.64
Severe late toxicities				
	Grade 3–5	0.41 (0.29–0.54)	0.48 (0.30–0.67)	0.53
	All grades	9.44 (8.53–10.34)	9.87 (9.02–10.72)	0.49



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De-ESCALate HPV: Conclusion

- Overall (acute and late) severe (grade 3–5) or all grade toxicity did not differ significantly between treatment groups at 24 months
- Significant better 2-year overall survival (97.5% *vs* 89.4%, hazard ratio 5.0 [95% CI 1.7–14.7]; p=0.001) and 2-year recurrence (6.0% *vs* 16.1%, 3.4 [1.6–7.2]; p=0.0007) were observed with cisplatin 100 mg/m^2

Mehanna H, et al Lancet 2019; 393:51-60

References

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Mehanna H, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomized controlled phase 3 trial. Lancet Oncology 2019; 393:51-60