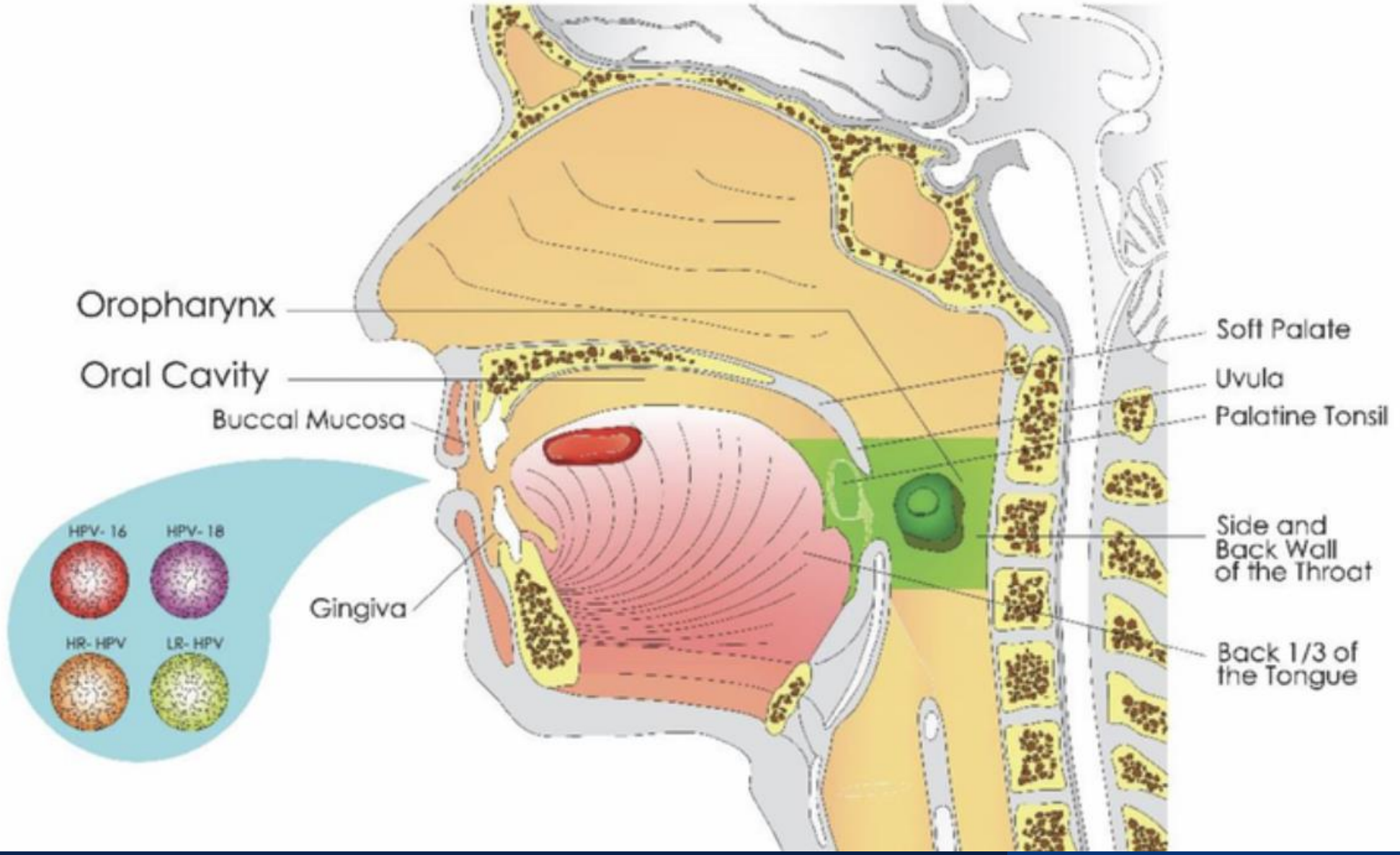
El VPH en el carcinoma de cap i coll: Estat actual

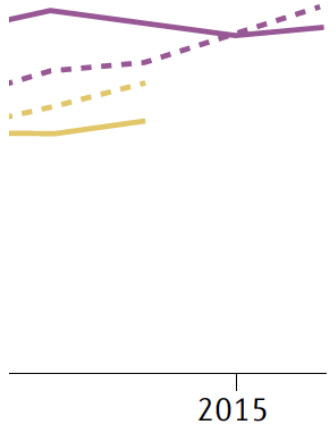
David Virós Porcuna

Vall d'Hebron


Oropharynx
Oral Cavity
Buccal Mucosa
Gingiva
HPV- 16
HPV- 18
HR- HPV
LR- HPV
Soft Palate
Uvula
Palatine Tonsil
Side and
Back Wall
of the Throat
Back 1/3 of
the Tongue

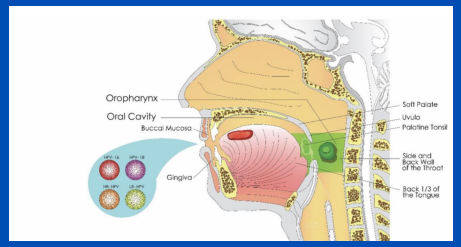
Michael Douglas: I got throat cancer from oral sex

3 June 2013



Vall d'Hebron

Realment és un problema tan prevalent aquí?



Prevalença CEOF VPH + 9-32%
Tendència creixent

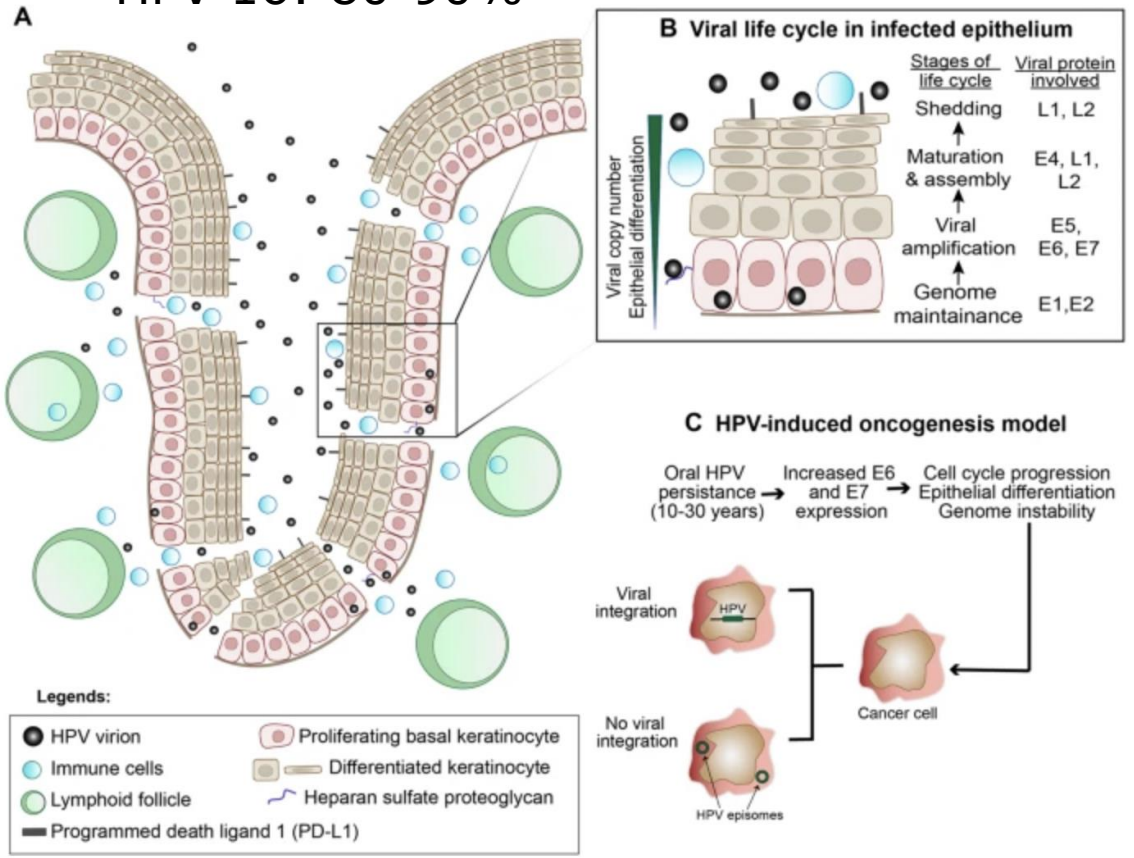
Mena M et al. Nat sci Rep. 2020
Taberna, M. et al. Ann. Oncol. 2017
Castellsagué, X. et al. J.Natl. Cancer Inst. 2016
11. Rodrigo, J. P. et al. Int. J. Cancer 2014

Vall d'Hebron

Que succeeix a causa de la infecció HPV ?

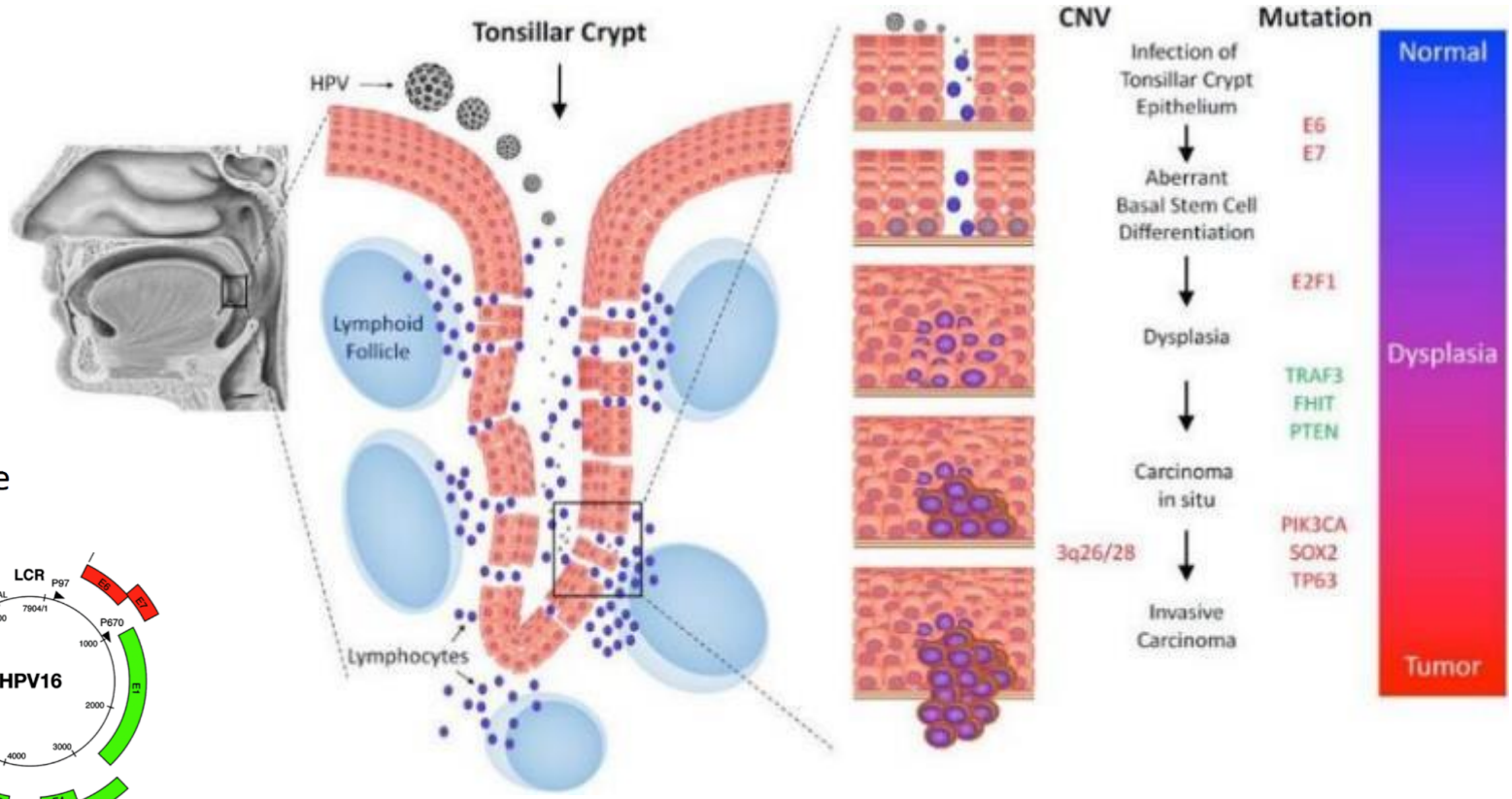
Oncogènesi

HPV 16: 80-90%



Lim, Y.X. et al. *Oncogene* **42**, 2939–2955 (2023).

Oncogènesi



HPV-16 Genome

- Early region
  - E6: inactivates p53
  - E7: inactivates pRb
    - pRb inactivation induces over-expression of p16
- Late region
  - L1, L2: capsid proteins necessary for viral persistence
- Regulatory region
  - Replication/gene expression

Leemans et al. Nature reviews 2018.

Vall d'Hebron

Oncogènesi

HPV-16 Genome

- Early region
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  - E7: inactivates pRb
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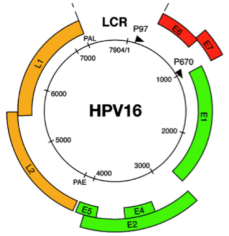
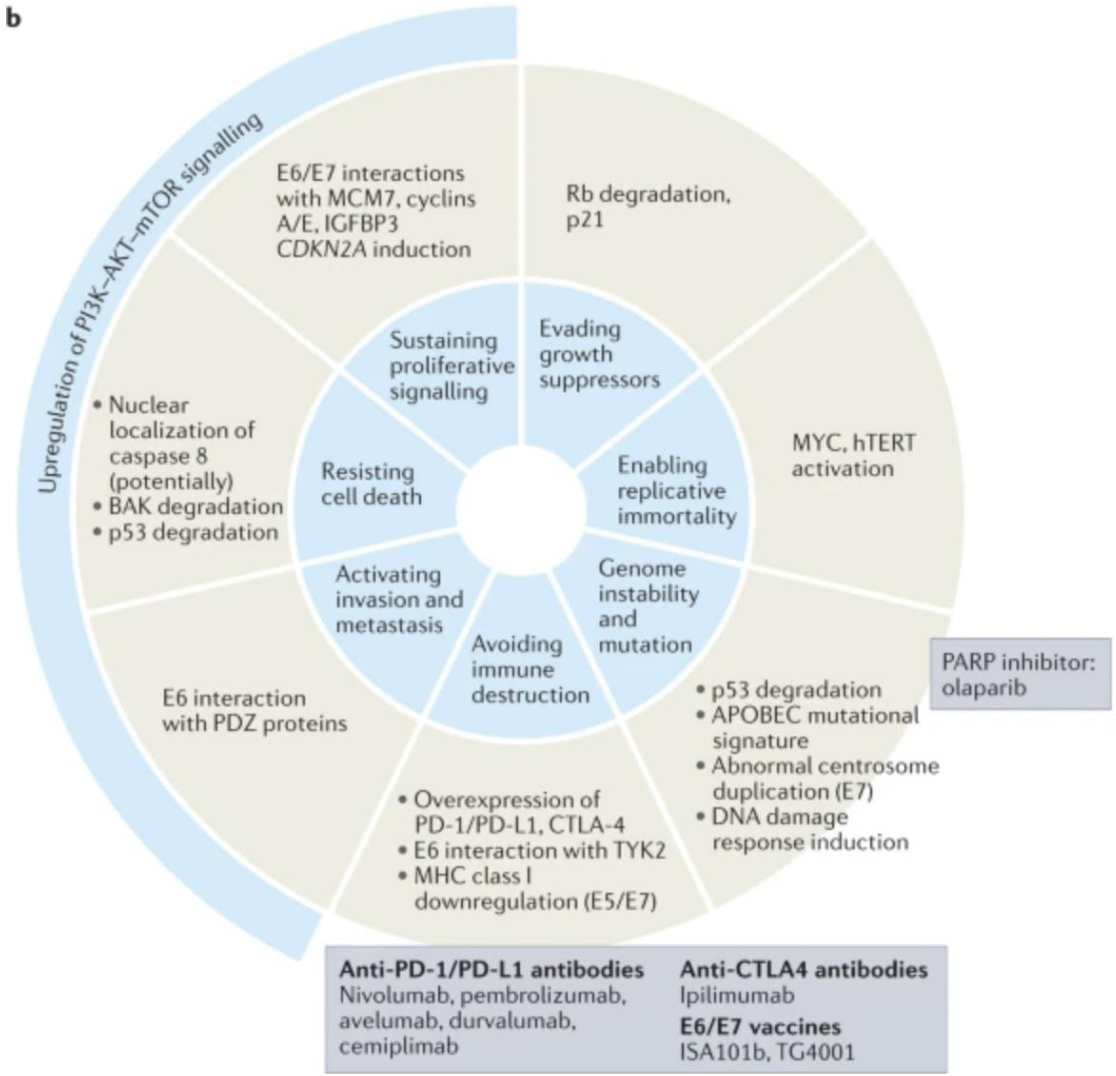
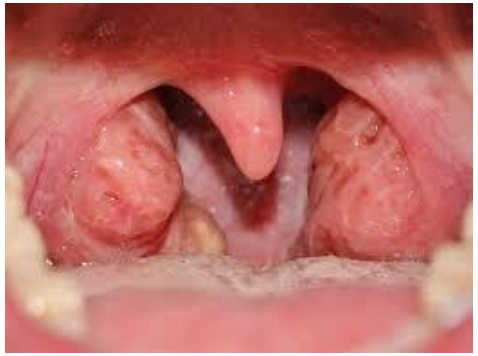
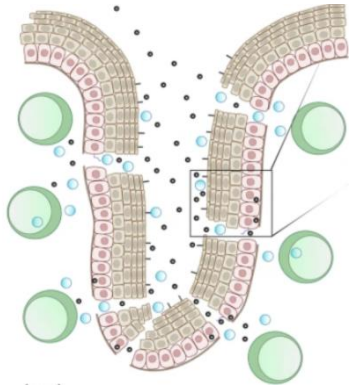


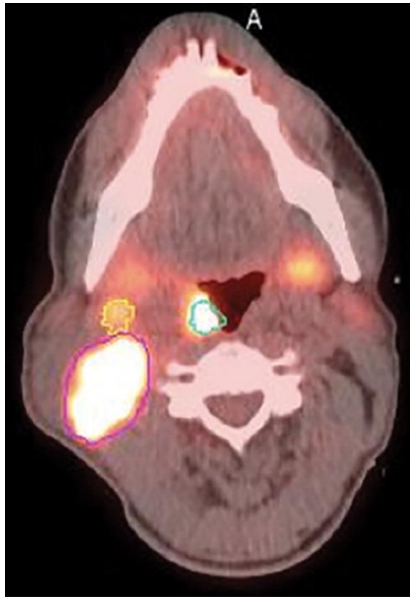


Lim, Y.X. et al. *Oncogene* **42**, 2939–2955 (2023).

Oncogènesi





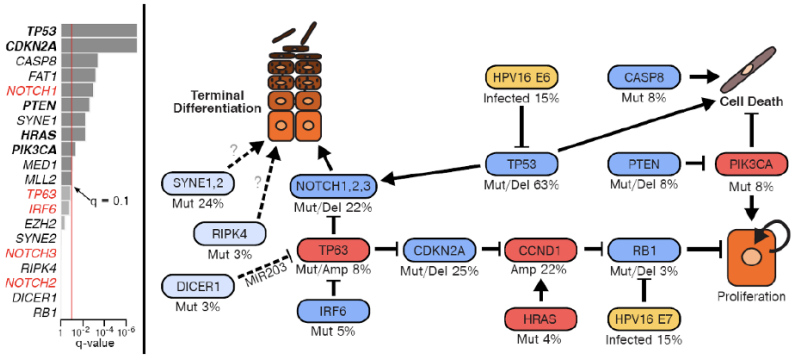


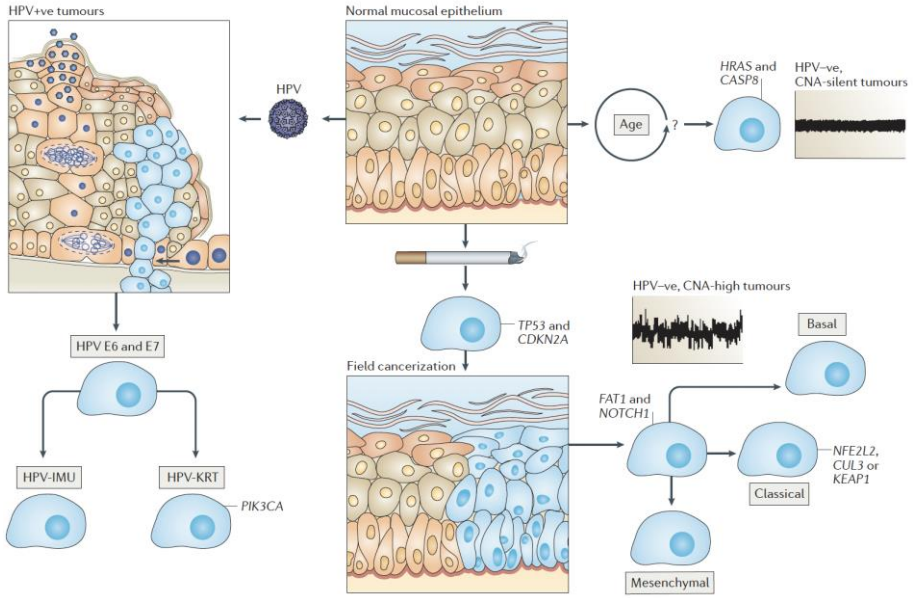
Important tropisme ganglionar

COD → T0

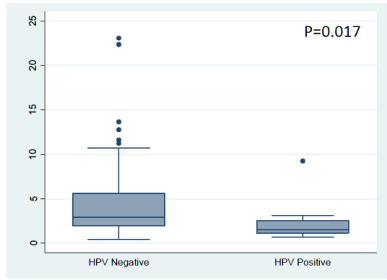
Oncogènesi

Gens reguladors diferenciació escamosa

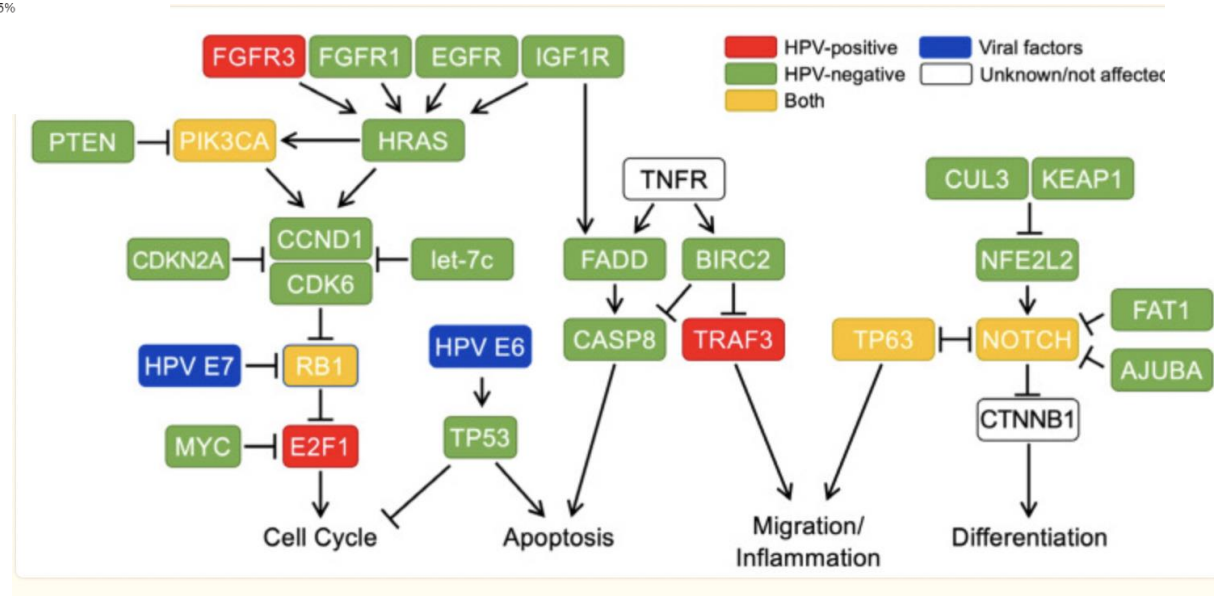




Taxa Mutacional HPV + vs HPV –

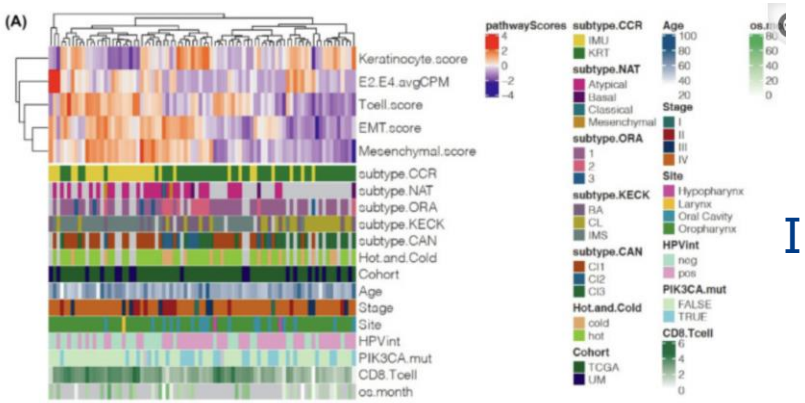


Mutation Rates per MB		
	HPV Negative	HPV Positive
Mean	4.54	2.38
Median	2.98	1.50



Menor taxa mutacional i disregulacions mol.leculars en CEOF VPH +

Oncogènesi



Tres subtipus mol.leculars HNSCC HPV+

I- Baixa integració – Alta diferenciació mesenquimal

II- Altament queratinitzat- basaloide – Alt contingut estromal

Diferències en pronòstic

Relació amb integració VPH – a > -- Pitjor pronòstic (II)

III- Altament queratinitzat – Alt contingut estromal – Rta immunitària suprimida

Vall d'Hebron

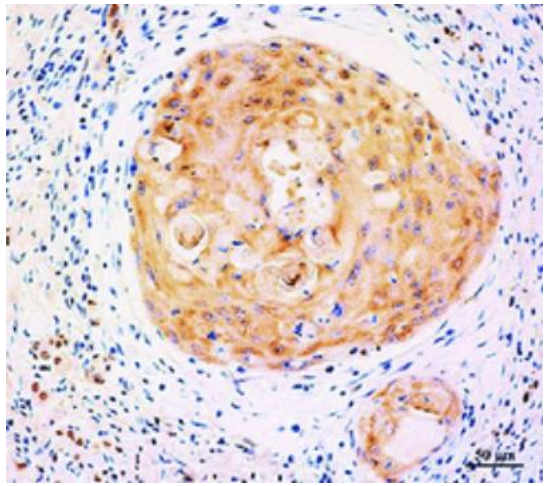
Qin T. et Cancers (Basel). 2021 May 31;13(11):2721

Com el diagnostiquem ?

Diagnòstic

Patologia:

- Biòpsia
- Citologia



P16 IHQ positiva

PCR - HPV – DNA Positivitat

Problemes:

T0 No tumor local. Citologia baix percentatge dx definitiu HPV

No screening

Control posterior??

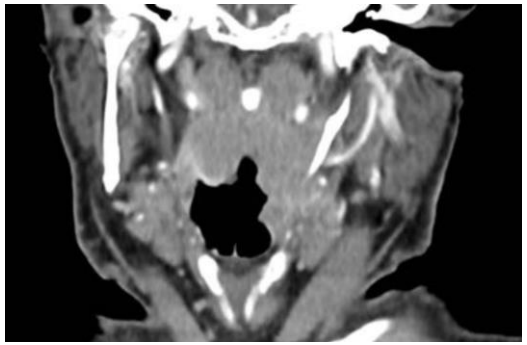
Mena et al. Oral Oncology. 2018.

Diagnòstic

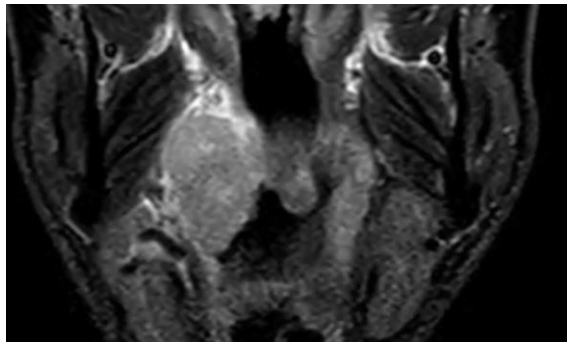
T0 No tumor local. Citologia baix percentatge dx definitiu HPV

T Orofaringe

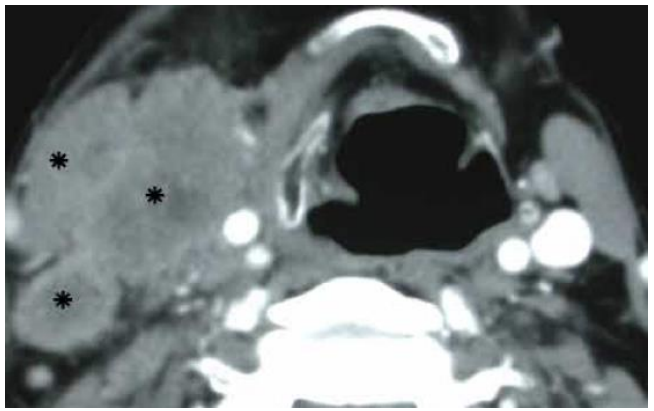
HPV-

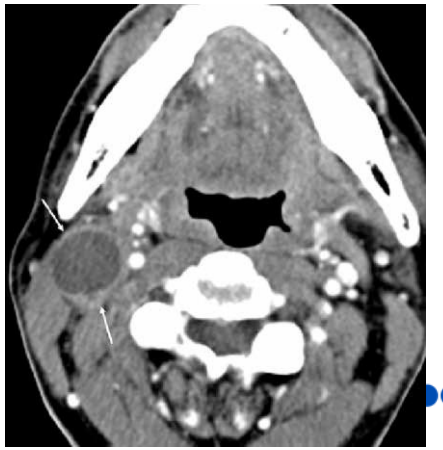


HPV +



N Orofaringe





Vall d'Hebron

Diagnòstic

T0 No tumor local. Citologia baix percentatge dx definitiu HPV

Radiòmica -Machine learning

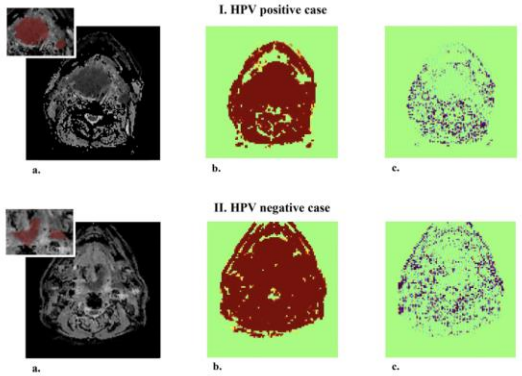


Figure 2. Example of the original apparent diffusion coefficient (ADC) map and its 3D wavelet-transformed image for each human papillomavirus (HPV)-positive and HPV-negative case. (**a**) Original ADC map. (**b**) 3D wavelet-transformed image of 'LLL'. (**c**) 3D wavelet-transformed image of 'HLH'.

Sequence	No. of selected features	AUC					
		Logistic regression	*P* value	Random forest	*P* value	XG boost	*P* value
ADC	166	0.72 ± 0.11	.016	0.76 ± 0.11	.456	0.69 ± 0.11	.240
T1WI	160	0.42 ± 0.15	< .001	0.45 ± 0.13	< .001	0.43 ± 0.17	< .001
T2WI	156	0.47 ± 0.13	< .001	0.52 ± 0.13	< .001	0.50 ± 0.12	< .001
CE-T1WI	165	0.55 ± 0.12	< .001	0.54 ± 0.13	< .001	0.59 ± 0.15	< .001
ADC + T1WI	190	0.69 ± 0.12	< .001	0.74 ± 0.11	.165	0.71 ± 0.11	.393
ADC + T2WI	196	0.72 ± 0.11	.020	0.73 ± 0.11	.141	0.69 ± 0.11	.113
ADC + CE-T1WI	193	0.76 ± 0.11	.357	0.76 ± 0.12	.495	0.71 ± 0.14	.481
T1WI + T2WI	185	0.48 ± 0.15	< .001	0.46 ± 0.13	< .001	0.44 ± 0.16	< .001
T1WI + CE-T1WI	200	0.56 ± 0.13	< .001	0.56 ± 0.14	< .001	0.51 ± 0.14	< .001
T2WI + CE-T1WI	191	0.52 ± 0.13	< .001	0.54 ± 0.14	< .001	0.51 ± 0.14	< .001
ADC + T1WI + T2WI	210	0.69 ± 0.14	.003	0.73 ± 0.11	.167	0.69 ± 0.12	.229
ADC + T1WI + CE-T1WI	211	0.76 ± 0.11	.316	0.74 ± 0.11	.186	0.71 ± 0.12	.482
ADC + T2WI + CE-T1WI	212	0.75 ± 0.11	.173	0.74 ± 0.11	.181	0.70 ± 0.12	.373
T1WI + T2WI + CE-T1WI	213	0.53 ± 0.15	< .001	0.54 ± 0.15	< .001	0.50 ± 0.14	< .001
All	221	0.77 ± 0.12	*Ref*	0.76 ± 0.12	*Ref*	0.71 ± 0.12	*Ref*

Table 3. Classification accuracies between various combinations of sequences. Average results ± standard deviations are reported. *AUC* area under the curve, *ADC* apparent diffusion coefficient, *T1WI* T1-weighted imaging, *T2WI* fat-suppressed T2-weighted imaging, *CE-T1WI* fat-suppressed contrast-enhanced T1-weighted imaging.

Capacitat per discriminar HPV + vs HPV -

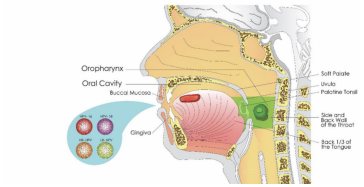
Sohn et al. Laryngoscope 2021.
Sym Y. et al. Eur Radiol. 2024

Vall d'Hebron

Diagnòstic

No screening

Enjuague bucal o raspatllat



Positiu: Estudi Possible SCCOF HPV+

Negatiu: Stop

Detectar ADN o ARN del VPH en la saliva

Sensitivity and Specificity of Oral HPV Detection for HPV-Positive Head and Neck Cancer

Cancer type	Oral HPV type	Oral HPV detection method	Sensitivity (95% CI)	Specificity (95% CI)
HNSCC	Any Oncogenic	Rinse or Swab	72% (45–89%)	92% (82–97%)
HNSCC	Any Oncogenic	Rinse Only	77% (61–87%)	95% (70–99%)
HNSCC	HPV16 Only	Rinse or Swab	68% (27–92%)	95% (83–99%)
OPSCC	Any Oncogenic	Rinse or Swab	55% (25–82%)	94% (85–98%)

Bona especificitat però moderada sensibilitat

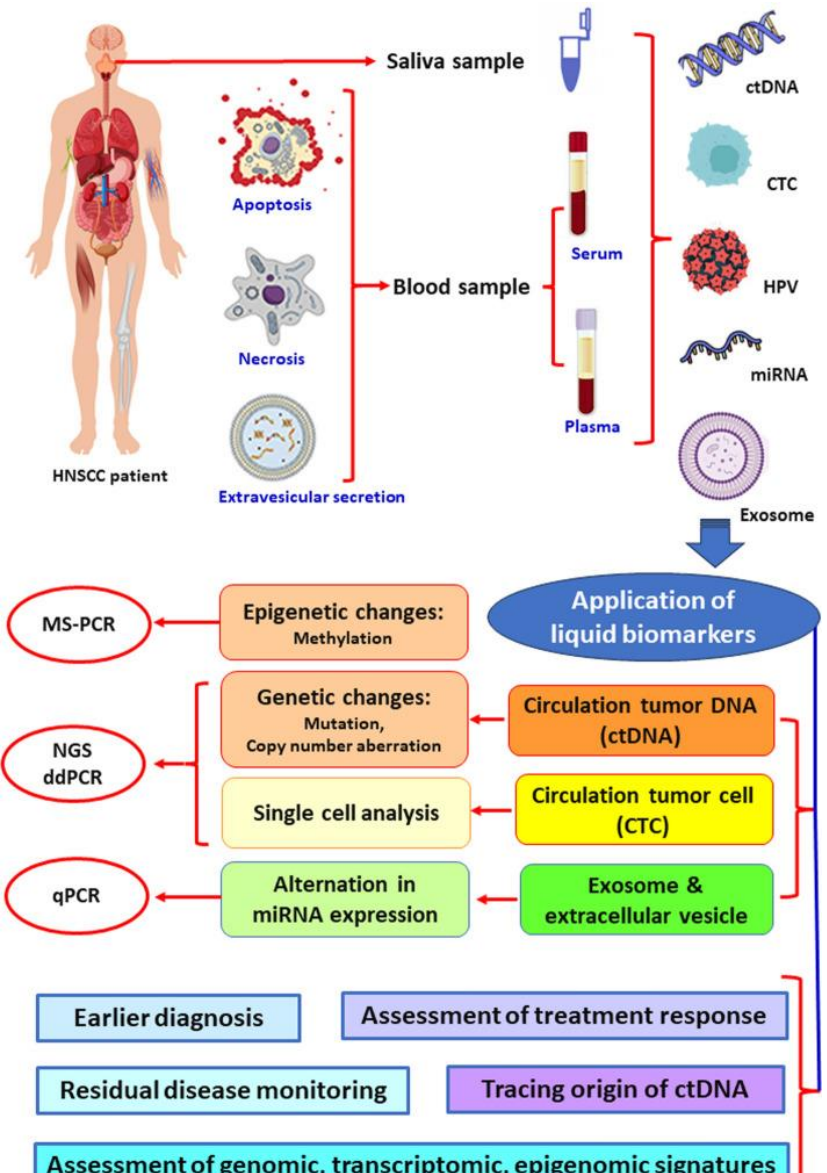
Falsos positius població sana

Gipson et al Oral Oncol 2018

Vall d'Hebron

Diagnòstic

Control posterior??



Biopsia líquida

Ct HPV 16

Valor diagnòstic inicial

- No relacionat malaltia local
- Relacionat malaltia nodal
- Relacionat amb valors PET.TC

Seguiment post tractament

Proposta seguiment:

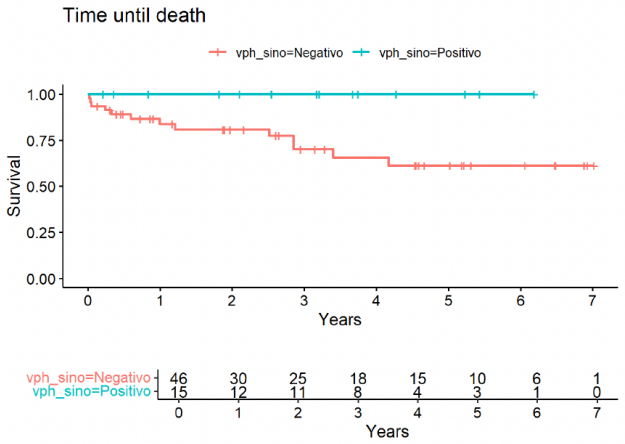
Biòpsia líquida + PET.TC

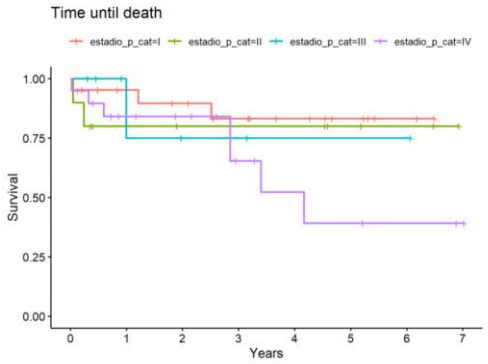
Kentnowski M. et al. Sci. Rep. 2023
Tanaka et al. Int J. Cancer 2021
Ghiyasimoghaddam N et al. Discov Oncol. 2024

Com el tractem ?

Premises

Important Factor pronòstic





Tipus de pacient

Toxicitats TTM

- Inicials
- Tardanes

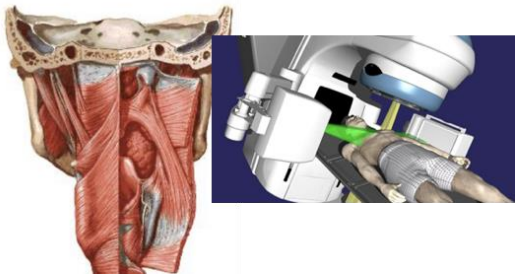
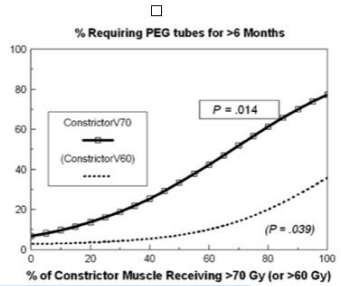


Table 3. Types of Late Toxicity Events Seen by Trial

Variable	91-11	97-03	99-14	Total
Feeding tube dependence > 2 years post-radiation therapy	—*	29*		29
RTOG late toxicity criteria, grade 3+				
Pharyngeal dysfunction	16	28	19	63
Laryngeal dysfunction	22	6	0	28
Death	11	9	2	22
Other (eg, infection, fistula)	3	0	1	4
Any	38†	40†	21†	99†
No severe late toxicity event (controls)	50	62	19	13

Abbreviation: RTOG, Radiation Therapy Oncology Group.
*Feeding tube data were not collected at all in RTOG study 91-11.
†Numbers do not always add up along columns, due to some patients having more than one toxicity event.

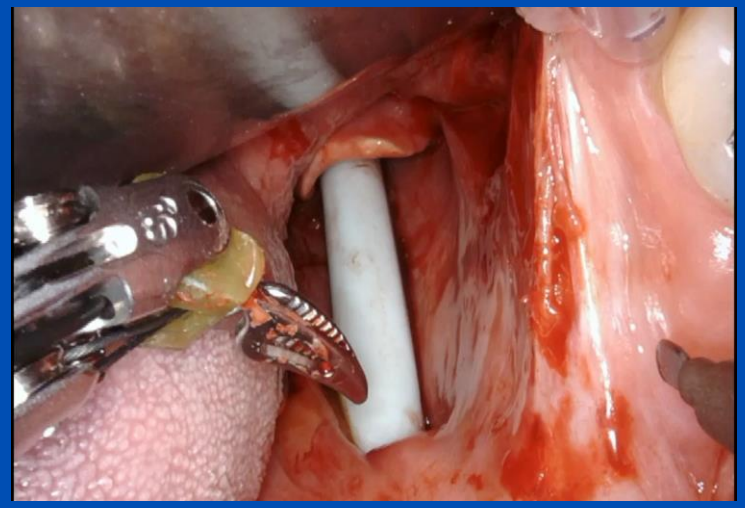


Evolució en les estratègies de tractament

Vall d'Hebron

Estratègia Actual

Estadis I-II

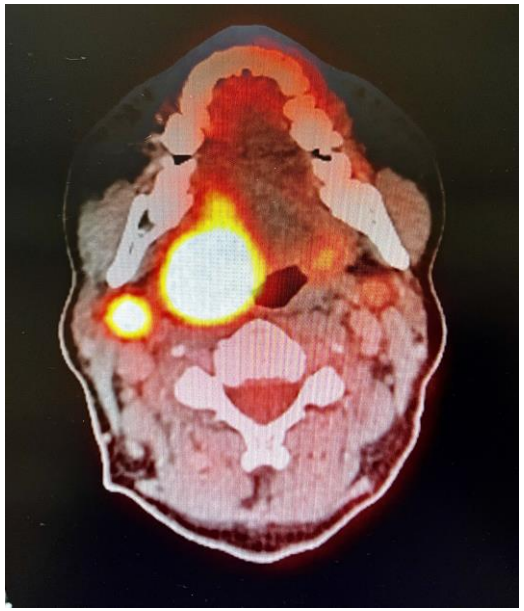


	TORS	Vs	IMRT
HPV -	81-92%		70-80%
HPV +	77-89%		45-65%

Toxicitat Lleu. MDADI 80-90%

QOL

Estadis III-IV



	QTRT	QTind-QTRT
HPV -	50-60%	
HPV +	70%	

Toxicitat severa grau IV 20-40 %

Vall d'Hebron

QOL

Estratègies desescalada

Reducció Dosi Radiació

Cetuximab vs. Cisplati

QT de Inducció Reduint Dosi Radiació

Inmunoterapia en diferents règims

Vall d'Hebron

QOL Estratègies desescalada

	Trial	Phase	Regimen	Outcome
Decreased Total Radiation Dose	Chera et al (2015)	II	Weekly Cisplatin (30 mg/m^2) for 6 doses + IMRT (60 Gy in 30 Fx over 6 weeks)	Pathologic CR was 86% with less toxicity profile overall
	NRG HN002	II	Weekly Cisplatin (40 mg/m^2) + IMRT (60 Gy in 30 Fx over 6 weeks) vs IMRT alone (60 Gy in 30 Fx over 5 weeks)	Met criteria for 2-year PFS>85%, MDADI index
Cetuximab vs Cisplatin	RTOG 1016	III	Weekly Cetuximab (400 mg/m^2 load with 250 mg/m^2 for 7 doses) + RT (70 Gy in 35 Fx over 6 weeks) vs Cisplatin (100 mg/m^2 for 2 doses on days 1 and 22) + RT (70 Gy in 35 Fx over 6 weeks)	5-year OS 77.9% (cetuximab) vs 84.6% (cisplatin). Cetuximab arm showed worsening 5-year PFS and locoregional failure with similar late to moderate toxicity profiles
	De-ESCALaTE	III	Weekly Cetuximab (400 mg/m^2 load with 250 mg/m^2 for 7 doses) + RT (70 Gy in 35 Fx over 6 weeks) vs Cisplatin (100 mg/m^2 on days 1, 22, and 43) + RT (70 Gy in 35 Fx over 6 weeks)	All-grade toxicity was similar in both arms, but there was worsening 2-year OS and recurrence rate in the cetuximab arm
	ARTSCAN III	III	Weekly Cetuximab (400 mg/m^2 load with 250 mg/m^2 for 7 doses) + RT (70 Gy in 35 Fx over 6 weeks) vs Weekly Cisplatin (40 mg/m^2) + RT (70 Gy in 35 Fx over 6 weeks)	3-year OS was not significant but favored cisplatin arm. Significant worsening 3-year locoregional control with cetuximab
Induction Chemotherapy with Reduced Dose Chemoradiation	E1308	II	3 cycles of induction Cisplatin (75 mg/m^2) Day 1 + Paclitaxel (90 mg/m^2) Day 1, 8, and Cetuximab (400 mg/m^2 load with 250 mg/m^2) weekly every 21 days followed by either high dose or reduced-dose radiation (69 Gy in 33 Fx vs 54 Gy in 27 Fx) depending on response with weekly Cetuximab (250 mg/m^2)	2-year PFS and OS were 80% and 94% respectively with less grade 3 mucositis and dysphagia
	Quarterback	III	3 cycles of induction Cisplatin (100 mg/m^2) Day 1 + Docetaxel (75 mg/m^2) Day 1, 5-FU (750 mg/m^2) Days 1-4 every 21 days followed by either standard dose or reduced-dose radiation (70 Gy in 35 Fx vs 56 Gy in 28 Fx) depending on response with weekly Carboplatin (AUC 1.5)	3-year PFS and OS >80% seen in both standard and reduced dose RT groups
Immunotherapy	KEYNOTE-012	Ib	Pembrolizumab 10 mg/kg every 2 weeks for 24 months or until progression or unacceptable toxic effects	ORR ~22%, Grade 3/4 AEs occurred in ~13% of patients
	JAVELIN Head and Neck 100	III	Lead-in dose with either Avelumab (10 mg/kg) or placebo followed by Avelumab (10 mg/kg) every 2 weeks + Cisplatin (100 mg/m^2) every 3 weeks + IMRT (70 Gy in 35 Fx over 7 weeks vs chemoradiotherapy alone.	No improvement to PFS, OS, or ORR although no significant worsening toxicity with Avelumab
	NRG-HN004	II	Randomized 2:1 to RT (70 Gy in 35 Fx over 7 weeks) plus either: (arm A) durvalumab (1500 mg) every 4 weeks starting 2 weeks before RT for 7 cycles or (arm B) cetuximab (400 mg/m^2) 1 week prior to RT then (250 mg/m^2) weekly for 8 cycles	Durvalumab arm showed no improvement to 2-year PFS or OS and showed worsening locoregional failure
	NRG-HN005 (ongoing)	II/III	Arm I: Cisplatin on days 1 and 22 + IMRT/IGRT (6 Fx per week) over 6 weeks Arm II: Cisplatin on days 1 and 22 + IMRT/IGRT (5 Fx per week) over 6 weeks Arm III: Nivolumab every 2 weeks up to 6 cycles + IMRT/IGRT (6 Fx per week) over 5 weeks	Seeking to evaluate non-inferiority with PFS when compared to cisplatin + RT as well as superior QOL measured by MDADI

Wu et al. Cancers 2024.

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Problemes per ressoldre diferents a QOL

Diferents genotips diferents comportaments? 16 vs altres diferent pronòstic?

Constantino et al Laryngoscope 2024

Subtipus molecular

Qin T. et al. Cancers (Basel). 2021

M1 a distancia

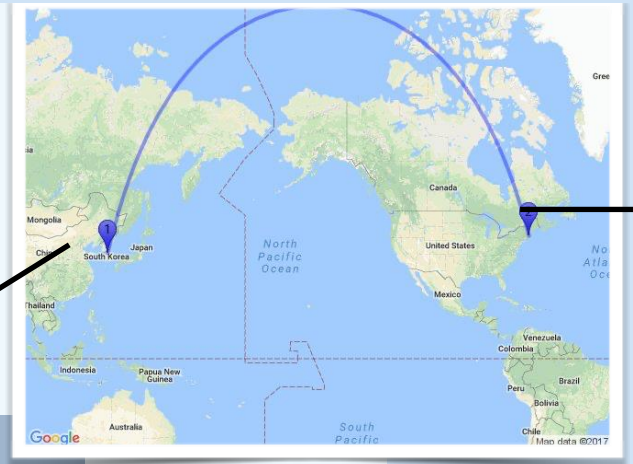
Weiss JM et al. , Cancer. 2018

Associació fumador a HPV empitjora el pronòstic. fet clàssic a tenir en compte en el nostre medi.

Ang KK et al. N Engl J Med. 2010

Altres posibles estratègies ?

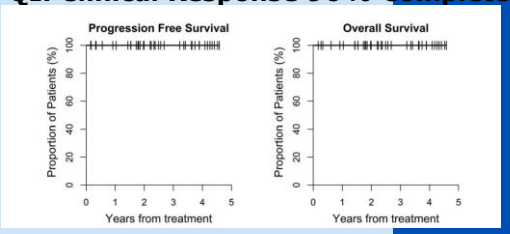
QT inducció a TORS en CE OF Localment avançat



n=40 SCC OF Estadio III-IV HPV+

QI (CarbP-Lapatinib) + TORS + Complementario

QI: Clinical Response 96% Complete 40%



QOL: 96% preserved
MDADI 83 a 82 1 año post TTM

Weiss JM et al. , Cancer. 2018

n=31 SCC OF Estadio III-IV
P16 + : 21

QI (CisP-TS1) + TORS + Complementario

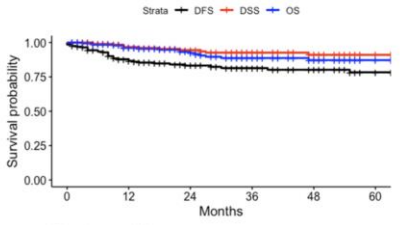
QI: Partial response 90.3% Complete 9.7%
Márgenes Libres: 71%

SV 5 a: 80% p16+: 90% p16-: 70%

FOSS: 86%

Park YM et al. Ann Surg Oncol. 2017.

n=198 SCC OF Estadio III-IV
QI (CisP-TS1) + TORS + Complementario



Constantino A, et al. Eur J Surg Oncol. 2023

n=261 SCC OF Estadio III-IV HPV+

QTRT vs QI (CisP-T) + TORS + Complementario

QI: RC T 72%. RC N. 57%
Margenes libres: 96.3%

SV 5a
QI: 96.1% (90.8-100 IC 95%) vs **QRT 67.6%** (50.7-84.5 IC 95%)
(P=0.01)

Sadeghi N, et al. Head & Neck. 2020

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Consideracions Finals

Carcinoma en creixement fins resultat de profilaxis vacunal

Oncogènesi diferenciada dels carcinomes escamosos HPV –

Bon pronòstic amb excepcions – Influència subtipus mol.lecular?

Línies futur:

- Diagnòstic diferents subtipus
- Diagnòstic no invasiu (Imatge - biopsia líquida)
- Estratègies de tractament (TTM actual no difereix VPH -)
- Screening?

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Moltes gràcies

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