Eugenio Cuadrado Albite
Oncología Médica HCUV

Jornada sobre Cáncer de Cabeza y Cuello

Miércoles,
12 de diciembre de 2018
Hotel Melia Recoletos | Valladolid

Cáncer epidermoide orofaríngeo HPV+: TNM 8º ed. Y opciones de tratamiento

Organiza

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EL Ca de Orofaringe asociado a HPV es una entidad nosológica diferente del no asociado a HPV

- Distinta epidemiología
- Distinta evolución y pronóstico
- Distintos factores de riesgo

Cancer Staging: Key Principles

- Staging should result in similar survival for each subgroup, or *hazard consistency*
- Each subgroup should have a different survival from the one above/below it, or *hazard discrimination*
- Should be relatively equal numbers in each group for better statistical comparisons, aka *balance between groups*
- Stage should give a good approximation of prognosis/survival, aka *high predictive ability*
- With each recommendation for stage change, the data is revisited to make sure that these principles are supported . . .thus this is *an iterative process*.

8th TNM CLASSIFICATION FOR HEAD & NECK CANCER

1.- **NEW STAGE CLASSIFICATIONS (HPV-RELATED OROPHARYNGEAL CANCER)**

2.- **UNKNOWN PRIMARY**

3.- **MODIFICATIONS OF T AND/OR N CATEGORIES**

- OCC (Oral Cavity Cancer) (T)
- Non melanoma skin cancer (NMSC) (T)
- NPC (Nasopharynx) (T and N)
- ENE in N categorization

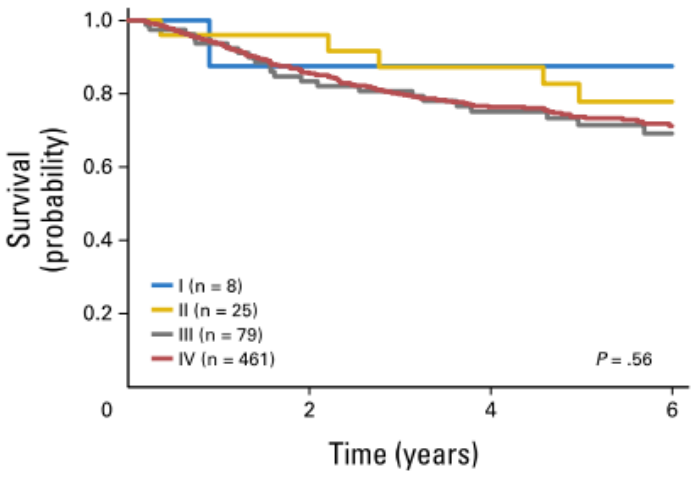
1.- NEW STAGE CLASSIFICATIONS (HPV-RELATED OROPHARYNGEAL CANCER)

- The 7th edition TNM staging of OPC **does not** properly describe **HR-HPV disease** with respect to prognosis or behavior.

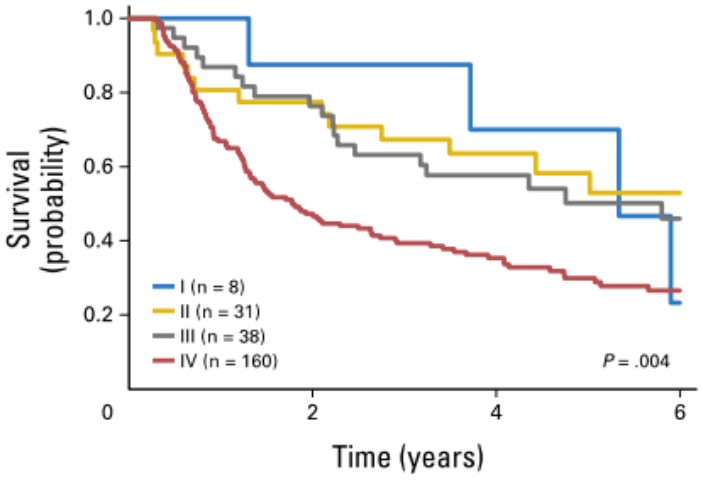
- The 7th edition TNM staging algorithm **lost the ability to differentiate between stages** *(hazard discrimination)*

Overall Survival Based on TNM 7th Edition

HPV-associated OPC



HPV-unrelated OPC



Huang S JCO 2015

HPV-RELATED OROPHARYNGEAL CANCER

- The NCCN Guidelines consider radiation-based or surgically based treatment equally aceptable as 1st line therapy.
- **The data** that led **to the need for a new staging system** and the **data to create and validate the staging systems** were broad based and came from centers treating primarily with radiation or surgically resection.
- The urgency to define staging criteria necessitated use of data from both published and unpublished sources (large data bases for validation).
- **cTNM** & **pTNM**

Oropharynx p16 Positive tumours.

Clinical and Pathologic T category

T CATEGORY	T CRITERIA
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond[b]

Oropharynx p16 Negative tumours.

Clinical and Pathologic T category

T CATEGORY	T CRITERIA
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[b]
T4b	Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

CA CANCER J CLIN 2017;67:122-137

Oropharynx p16 Positive tumours.

Clinical and Pathologic N category

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

Oropharynx p16 Negative tumours.

Clinical and Pathologic N category

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

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Anatomic Stage and Prognostic Groups for *Clinical* TNM Grouping of Human Papillomavirus-Associated (p16-Positive) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

T CATEGORY	N CATEGORY			
	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

[a]Any M1 is stage IV.

Anatomic Stage and Prognostic Groups for *Clinical* and *Pathologic* TNM Grouping of Non-Human Papillomavirus-Associated (p16-Negative) Oropharyngeal Cancer, 8th Edition Staging Manual[a]

T CATEGORY	N CATEGORY			
	N0	N1	N2a,b,c	N3a,b
T1	I	III	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVB
T4b	IVB	IVB	IVB	IVB

[a]Any M1 is stage IVC.

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2.-UNKNOWN PRIMARY (CUP)

- Squamous cell carcinoma in lymph nodes arising from an undetected primary cancer is a well recognized clinical entity in the H&N.

- >90% of these T0 (unknown primary) designations reflect viral origin (HPV-OPC and EBV)

- Demonstrating the presence of either EBV or HPV can establish an anatomic site of origin.

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2.-UNKNOWN PRIMARY (CUP)

- **HPV-ISH**, **p16 immunohistochemestry**, and **EBER-ISH** are recommended for all cervical lymph nodes with CUP.

- The specificity of p16 overexpression alone as a surrogate HPV biomarker is limited to OPC.

- If **no primary lesion can be identified**, then **the lymph node may have emanated from any mucosal site**, so there is no rationale to support the T0 designation outside of the virally associated cancers of the OPC and NPC.

2.-UNKNOWN PRIMARY (CUP)

Table 3. The 8th edition N classification for non-viral related head and neck cancer and stage grouping for viral and non-viral unknown primary – cervical nodes

	N category for non-viral CUP and HNC		
N	Clinical N classification	Pathologic N classification	
N1	Single ipsilateral LN, ≤3 cm, no ENE	Single ipsilateral LN, ≤3 cm, no ENE	
N2a	Single ipsilateral LN, 3–6 cm, no ENE	Single ipsilateral LN, ≤3 cm, with ENE[a], single ipsilateral LN, 3–6 cm, no ENE	
N2b	Multiple ipsilateral LNs, ≤6 cm, no ENE	Multiple ipsilateral LNs, ≤6 cm, no ENE	
N2c	Bilateral or contralateral LNs, ≤6 cm, no ENE	Bilateral or contralateral LNs, ≤6 cm, no ENE	
N3a	Any LN >6 cm, no ENE	Any LN >6 cm, no ENE	
N3b	Any LN with clinical ENE[a]	A single LN >3 cm with pathologic ENE[b] Any multiple ipsilateral/bilateral/contralateral LN(s) with ENE	
Stage grouping for viral and non-viral-related CUP			
Stage	HPV+/p16+ CUP	EBV+ CUP	Non-viral related CUP
Stage I	T0_N1_M0	Not applicable	Not applicable
Stage II	T0_N2_M0	T0_N1_M0	Not applicable
Stage III	T0_N3_M0	T0_N2_M0	T0_N1_M0
Stage IV	Clinical: T0_N1–3_M1 Pathological: T0_N1–2_M1	IVA: T0_N3_M0 IVB: T0_N1–3_M1	IVA: T0_N2_M0 IVB: T0_N3_M0 IVC: T0_N1–3_M1

Curr. Treat. Options in Oncol. (2017) 18:40

3.-MODIFICATIONS OF T CATEGORY. OCC (Oral Cavity Cancer)

TABLE 9. T Category for Oral Cavity Cancer, 8th Edition Staging Manual[a]

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) (DOI is depth of invasion and not tumor thickness)
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm *or* tumor >2 cm but ≤4 cm, and ≤10 mm DOI
T3	Tumor >4 cm *or* any tumor >10 mm DOI
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease: (lip) tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose); (oral cavity) tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

[a]Table 9 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]).

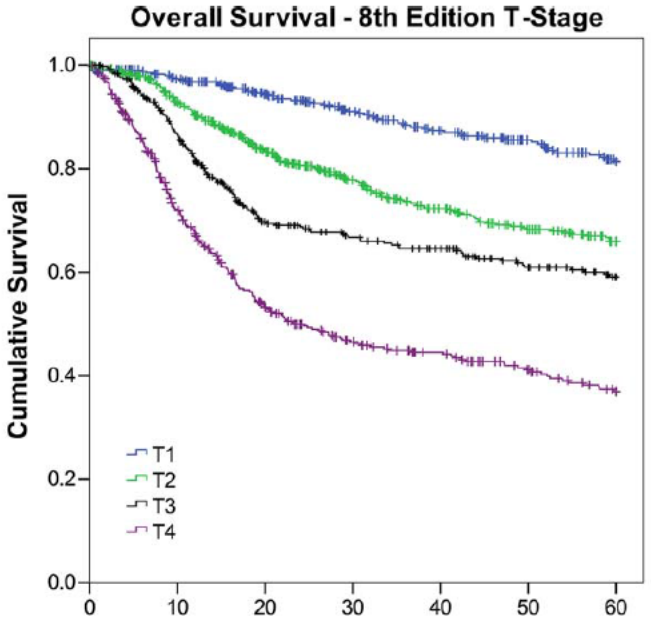

FIGURE 6. Overall Survival Based on New Tumor (T) Criteria Incorporating the Influence of Depth of Invasion in Oral Cavity Cancer (Memorial Sloan Kettering Cancer Center-Princess Margaret Hospital Institutional Data). Cum

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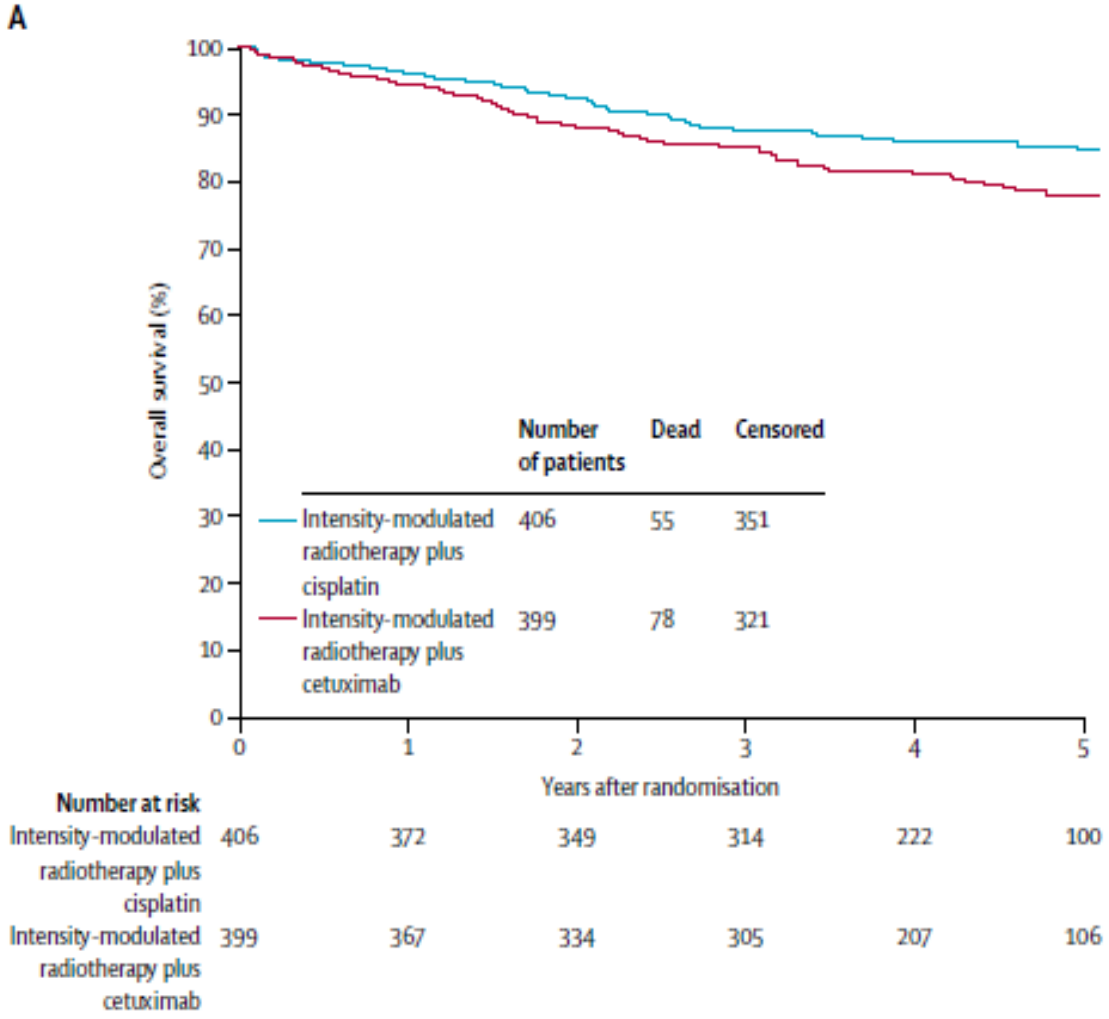
PERO NO TODO ESTÁ TAN CLARO

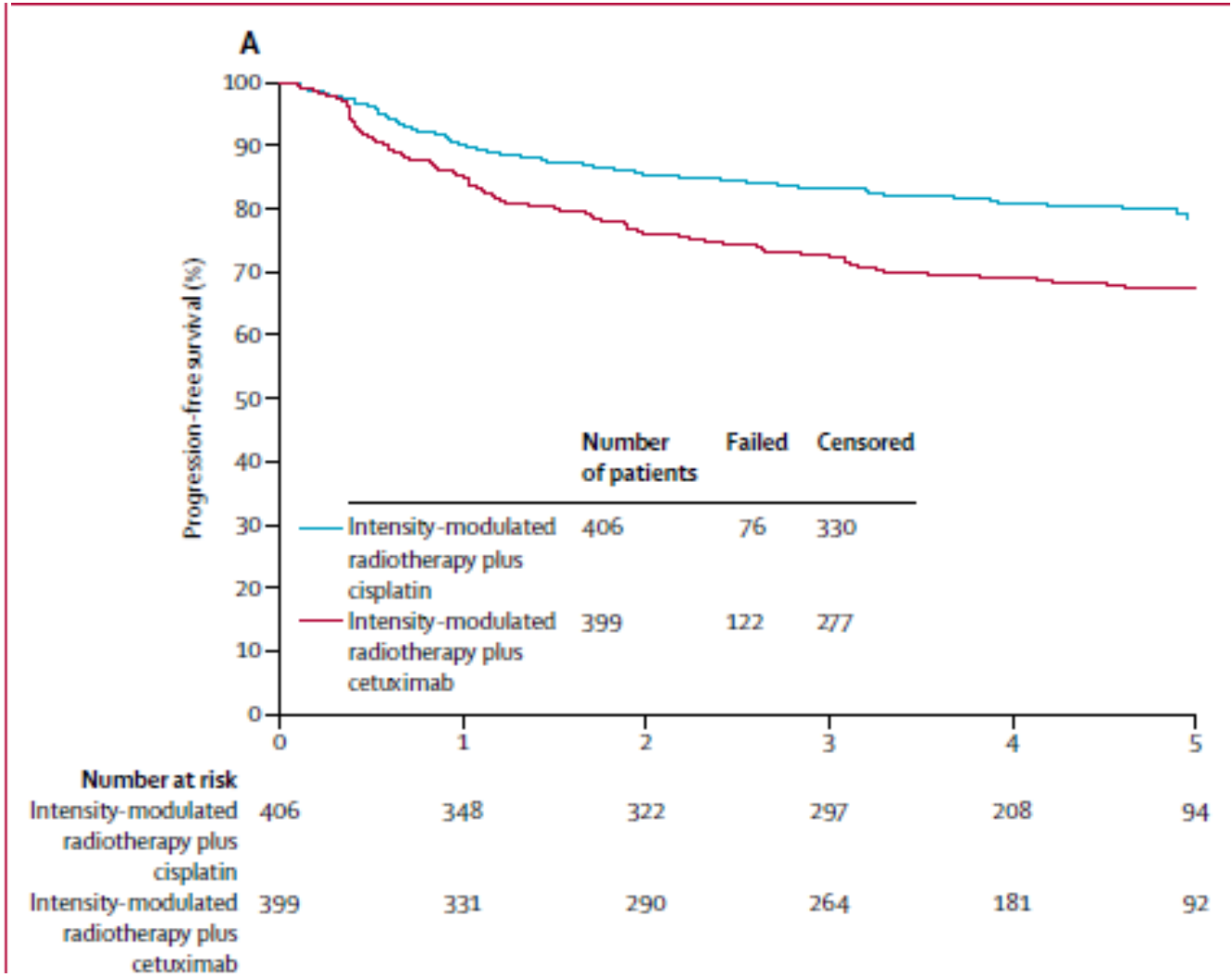
- Entre 2004 y 2014 se ha visto un incremento de la edad media al diagnóstico y un aumento en el porcentaje de pacientes mayores de 70 años, tanto en tumores HPV+ como HPV-. En todos los grupos de edad el pronóstico es mejor para los pacientes con tumores HPV+, pero este beneficio disminuye con la edad. Retting et al. Oral Oncol., 2018 vol.83 pp. 147-153
- "Que tenga un tumor HPV + no significa que no fume y no beba".

Se ha intentado "validar" el nuevo modelo de la 8º edición reclasificando retrospectivamente una base de datos amplia de pacientes HPV +. Para los tumores precoces, funciona bastante bien, pero en los tumores avanzados no discriminaba igual de bien el pronóstico hasta que no se tomaba en cuenta la comorbilidad y el hábito tabáquico. Deschuymer et al. FrontOncol, 2018 Vvol.8 pp. 273

- Parece que en los pacientes tratados exclusivamente con cirugía, la clasificación del estado ganglionar podría no ser adecuada. En un análisis retrospectivo de una serie de estos pacientes, ni el número ni el tamaño de los ganglios afectos predecían la recurrencia. La presencia de invasión extranodal se aproximaba, pero tampoco era significativa. Hobelman et al. Oral –oncol. 2018 vol 82 pp. 138-143

RTOG 1016


A
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Number of patients
Dead
Censored
Intensity-modulated radiotherapy plus cisplatin 406 55 351
Intensity-modulated radiotherapy plus cetuximab 399 78 321
0 1 2 3 4 5
Years after randomisation
Number at risk
Intensity-modulated radiotherapy plus cisplatin 406 372 349 314 222 100
Intensity-modulated radiotherapy plus cetuximab 399 367 334 305 207 106


A
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
Number of patients
Failed
Censored
Intensity-modulated radiotherapy plus cisplatin 406 76 330
Intensity-modulated radiotherapy plus cetuximab 399 122 277
0 1 2 3 4 5
Number at risk
Intensity-modulated radiotherapy plus cisplatin 406 348 322 297 208 94
Intensity-modulated radiotherapy plus cetuximab 399 331 290 264 181 92

B

RTOG 1016

- Es el estudio con la muestra más amplia
- Es el único cuyo objetivo primario es la eficacia, no la toxicidad
- PERO… Incluye pacientes con hábito tabáquico importante, que pueden inclinar los resultados del estudio hacia un resultado peor
- En cualquier caso los resultados son muy robustos

B

	Events/ total	Hazard ratio (one-sided 95% CI)	5-year estimate (two-sided 95% CI)		p value
			Intensity-modulated radiotherapy plus cisplatin	Intensity-modulated radiotherapy plus cetuximab	
All patients	133/805		84·6 (80·6–88·6)	77·9 (73·4–82·5)	
Age (years)					
≤65	110/689		84·9 (80·6–89·3)	79·0 (74·3–83·7)	0·9948
>65	23/116		82·9 (73·2–92·6)	70·4 (55·4–85·5)	
Zubrod performance status					
0	81/595		84·6 (79·8–89·4)	84·0 (79·4–88·6)	0·0149
1	52/210		84·9 (78·0–91·7)	58·1 (46·5–69·7)	
Smoking history					
≤10 pack-years	73/502		86·9 (82·4–91·3)	80·5 (74·9–86·1)	0·5745
>10 pack-years	60/303		80·9 (73·2–88·6)	73·5 (65·7–81·3)	
T stage					
T1–2	55/500		89·5 (85·4–93·7)	84·4 (79·0–89·8)	0·5104
T3–4	78/305		76·2 (68·0–84·3)	66·8 (58·8–74·8)	
AJCC 7th edition N category					
N0–2a	20/194		92·4 (87·0–97·8)	84·6 (76·5–92·8)	0·5616
N2b–3	113/611		82·1 (77·2–87·0)	75·6 (70·2–81·0)	
AJCC 8th edition N category					
N0–1	75/611		88·8 (84·6–92·9)	82·6 (77·7–87·5)	0·8311
N2–3	58/194		71·3 (61·6–81·1)	63·4 (53·4–73·4)	
AJCC 8th edition stage					
I	36/407		92·4 (88·4–96·5)	85·9 (80·0–91·7)	0·8253
II	58/278		81·0 (74·2–87·8)	74·3 (66·7–81·9)	0·9730
III	39/120		66·1 (50·7–81·6)	57·5 (43·5–71·5)	
Risk group per RTOG 0129[1]					
Low	81/573		88·1 (84·1–92·0)	80·4 (75·2–85·5)	0·6981
Intermediate	52/232		76·4 (67·0–85·8)	71·4 (61·9–80·8)	

De-ESCALaTE: Study design

Phase III, open-label

Low-risk HPV+ OPC (N=334)

→ **R**

Cisplatin 100 mg/m² Q3W + RT (70 Gy in 35F over 7 weeks)

(minimum follow-up: 24 months)

Cetuximab 400 mg/m² → 250 mg/m² QW + RT (70 Gy in 35F over 7 weeks)

(minimum follow-up: 24 months)

Inclusion criteria

- p16+
- Low-risk on Ang classification
- T3N0–T4N0, and T1N1–T4N3
- ECOG PS 0–2
- Clinical MDT decision to treat with primary curative cisplatin + RT
- Adequate cardiovascular, hematological, renal and hepatic function

Exclusion criteria

- Intermediate or high-risk on Ang classification

Primary endpoints: Severe acute and late grade 3–5 toxicity

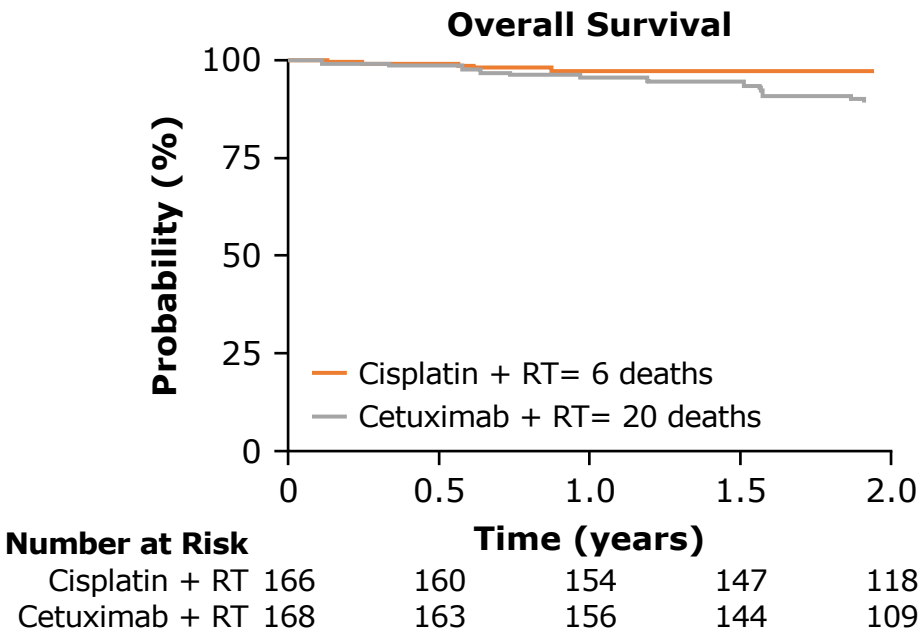
Secondary endpoints: Number of acute severe AEs, number of late severe AEs, QoL, swallowing, cost-effectiveness, OS and recurrence

Mehanna H, et al. ESMO 2018 (Abstract No. LBA9_PR).

De-ESCALaTE: Patients with HPV+ OPC benefit from excellent survival outcomes with cisplatin + RT

	HD CRT (n=166)	Cetuximab + RT (n=168)
2-year OS, %*	97.5	89.4
	HR 4.99 (95% CI 1.70–14.67), p=0.001	
2-year recurrence, %	6.0	16.1
	HR 3.39 (95% CI 1.61–7.19), p=0.0007	
Loco-regional recurrence, %	3	12
	p=0.003	
Distant recurrence, %	3	9
	p=0.009	

*Regarding OS, the number needed to treat for harm was 12: if 12 patients were treated with cetuximab, one would be harmed



HR, hazard ratio.

Mehanna H, et al. ESMO 2018 (Abstract No. LBA9_PR).

	HD CRT (n=166)	Cetuximab + RT (n=168)
All-grade AEs, events per patient	29.15 (95% CI 27.33–30.97)	30.05 (95% CI 28.26–31.85)
	p=0.49	
Severe (grade 3–5) AEs, events per patient	4.81 (95% CI 4.23–5.40)	4.82 (95% CI 4.22–5.43)
	p=0.98	
Serious AEs, events per patient	1.00	0.58
	p=0.001	

Compliance

- Cisplatin: 84% of patients received ≥200 mg/m^2 cisplatin
- Cetuximab: 79% of patients received 8 doses of cetuximab
- RT: Overall, 96% of patients received 70 Gy+ and 4% received 65–70 Gy (8% had modifications)

QoL

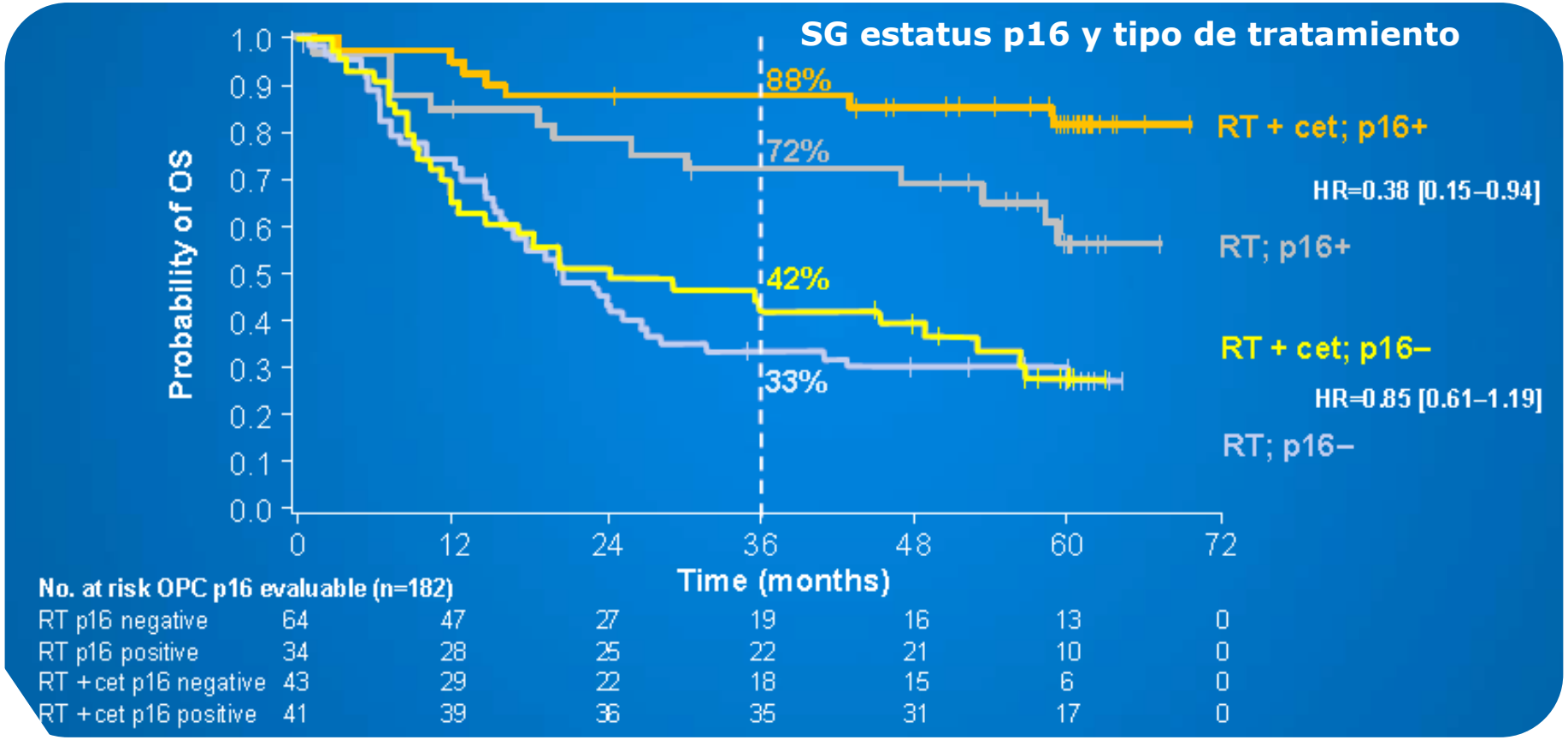
- There was no difference in QoL and swallowing between arms

HD, high-dose; QoL, Quality of life

Mehanna H, et al. ESMO 2018 (Abstract No. LBA9_PR).

Actualizaciones

Estatus HPV – Abstract presentado en ESMO 2014



Mayor SG en pacientes con **p16 positivo tratados con Cetuximab + RT**

Bonner JA et al. ESMO 2014 abstract #5866

OTRAS ESTRATEGIAS PENDIENTES DE RESULTADOS

- Reducir la dosis de RT
- Utilizar QT de inducción para discriminar que pacientes pueden ir a tratamientos menos tóxicos
- Elegir a estos pacientes para técnicas quirúrgicas más conservadoras

Baseline Characteristics

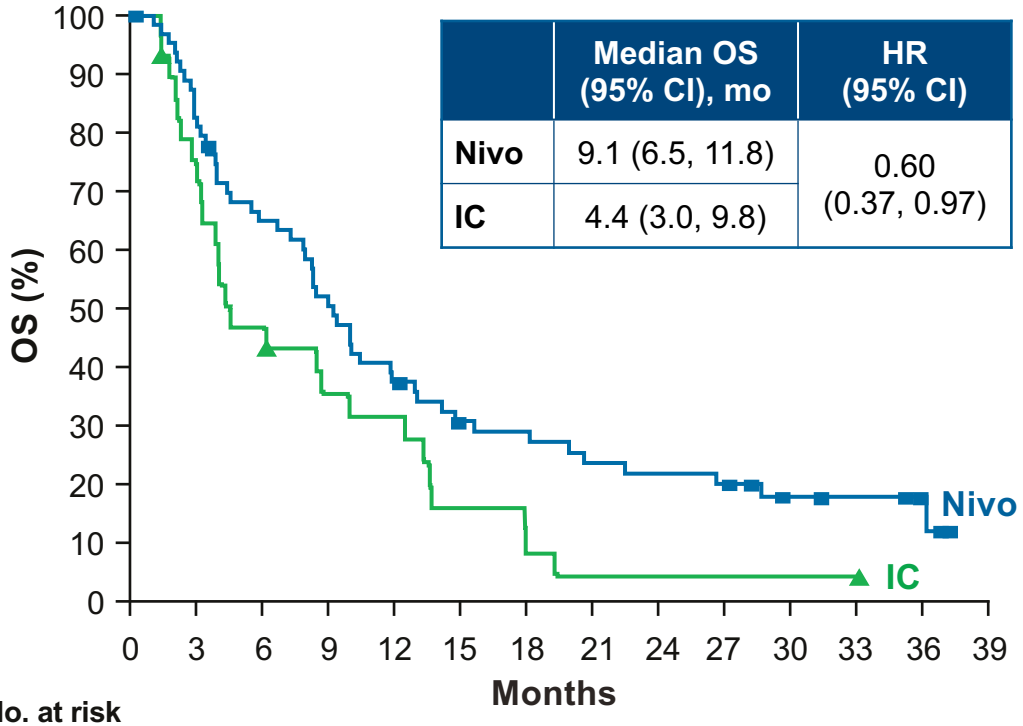
Patients, n (%)	Nivolumab (n = 240)	IC (n = 121)
Tumor PD-L1 expression[a]		
≥1% (PD-L1 expressors)	96 (40.0)	63 (52.1)
<1% (PD-L1 non-expressors)	76 (31.7)	40 (33.1)
Not quantifiable[b]	68 (28.3)	18 (14.9)
HPV status[c]		
Positive	64 (26.7)	29 (24.0)
Negative	56 (23.3)	37 (30.6)
Unknown/not reported	120 (50.0)	55 (45.5)

[a]PD-L1 status was determined using the Dako PD-L1 IHC 28-8 pharmDx test
[b]Tumor not present, sample not provided, or sample could not be processed
[c]HPV status was assessed using p16 immunohistochemical testing; required only for patients with OPC

OS by HPV Status[a]

- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC

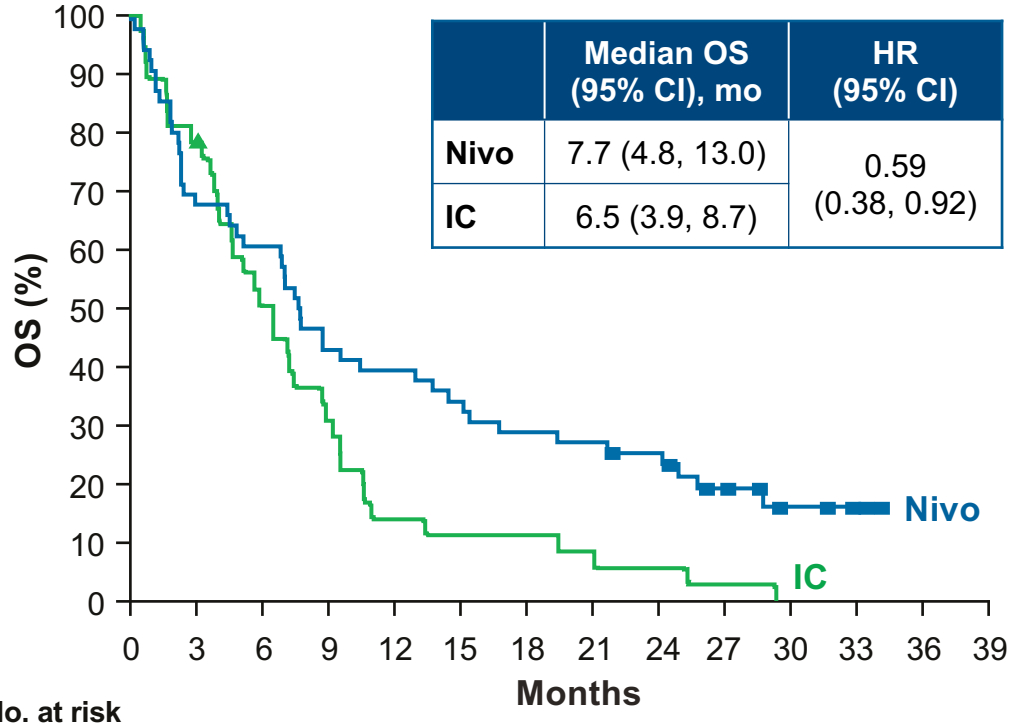
HPV-Positive



	Median OS (95% CI), mo	HR (95% CI)
Nivo	9.1 (6.5, 11.8)	0.60 (0.37, 0.97)
IC	4.4 (3.0, 9.8)	

No. at risk														
Nivo	64	50	40	31	23	17	16	13	12	11	7	6	3	0
IC	29	20	13	9	8	4	2	1	1	1	1	1	0	0

HPV-Negative

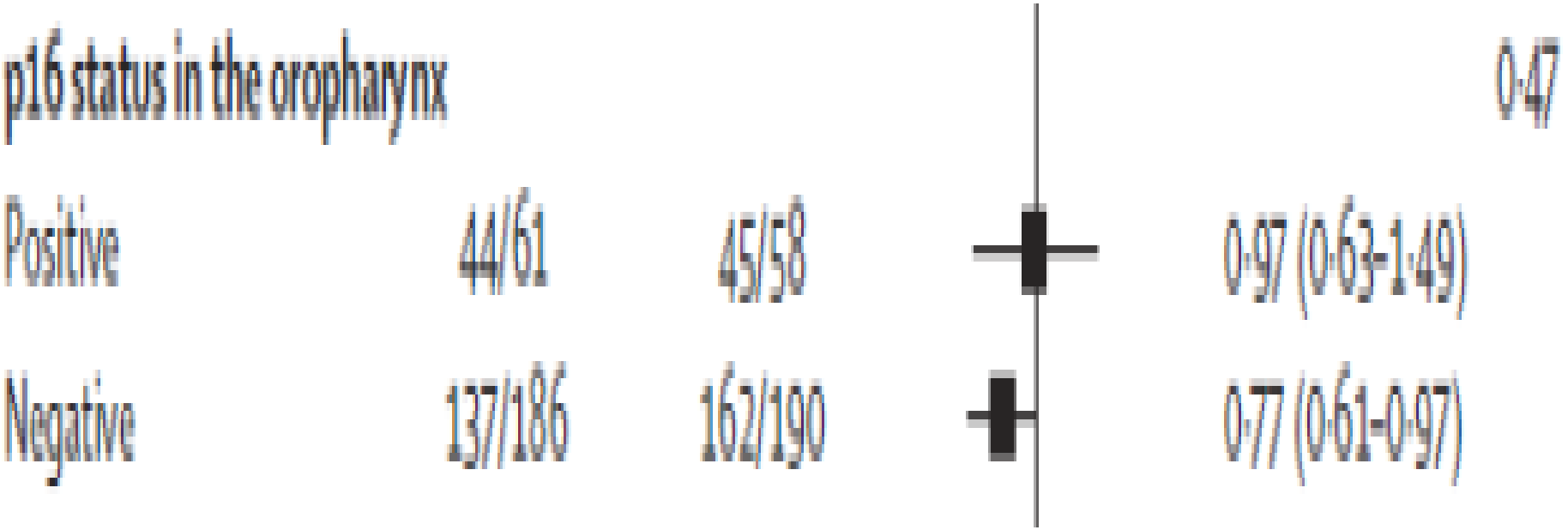


	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (4.8, 13.0)	0.59 (0.38, 0.92)
IC	6.5 (3.9, 8.7)	

No. at risk														
Nivo	56	38	34	24	22	19	16	15	13	8	4	2	0	0
IC	37	28	18	11	5	4	4	3	2	1	0	0	0	0

[a]HPV testing was required only for patients with OPC; symbols represent censored observations

KEYNOTE-040


p16 status in the oropharynx
0·47
Positive
44/61
45/58
0·97 (0·63–1·49)
Negative
137/186
162/190
0·77 (0·61–0·97)

CONCLUSIONES

- La nueva clasificación TNM discrimina mejor la evolución de los pacientes con COFHPV+ que su predecesora
- Aunque los pacientes con COFHPV+ tienen mejor pronóstico que aquellos con COFHPV-, a día de hoy no tenemos evidencia para prescribir regímenes de tratamiento específico
- La QRT con cisplatino se ha mostrado más efectiva que con Cetuximab. Está mantiene su papel como alternativa para pacientes que no pueden tolerar cisplatino

MUCHAS GRACIAS Y FELIZ NAVIDAD