Lo infrecuente en el carcinoma epidermoide: variantes histopatológicas, localizaciones especiales y situaciones avanzadas

Onofre Sanmartin Jimenez

SERVICIO DE DERMATOLOGIA

FUNDACION INSTITUTO VALENCIANO DE ONCOLOGIA

Carcinoma epidermoide cutáneo. Epidemiologia

- Incremento progresivo de la incidencia del CEC
  - 38’16 casos/100 000 habitantes/ año en España

    (Actas Dermosifiliogr. 2016;107:318)

- Buen pronóstico global: Tasas de Respuesta completa > 90%
  - Mortalidad relacionada con el tumor < 3%.

    (Actas Dermosifiliogr 2013;104:367)
  - 374 + 250 = 624 muertes/año en España

    (ISCIII. Causas de muerte por cancer 2014)

- Tasas de enfermedad metastásica del CEC: 2-5%

  (Lancet Oncol 2008; 9: 713)

- Supervivencia a los 5 años en caso de afectación nodal : 23-66%

  (Head Neck 2012; 34:1524)

REVIEW ARTICLE PRIMARY CARE

Cutaneous Squamous-Cell Carcinoma

Murad Alam, M.D., and Désirée Ratner, M.D.

March 29, 2001
N Engl J Med 2001; 344:975-983
DOI: 10.1056/NEJM200103293441306

CARCINOMA EPIDERMOIDE DE ALTO RIESGO

Aquellos tumores que en el momento del diagnóstico tienen un riesgo aumentado de originar recurrencia, metástasis o muerte relacionada con la enfermedad como consecuencia de factores intrínsecos al tumor

TABLE 2. RISK FACTORS FOR RECURRENCE AND METASTASIS OF CUTANEOUS SQUAMOUS-CELL CARCINOMA.

VARIABLE	APPROXIMATE RELATIVE RISK*	
	RECURRENCE	METASTASIS
Clinical features		
Rapid growth	—	—
Size >2 cm	2	2
Site		
Lip	2	3
Ear	2	3
Immunosuppression	—	2
History of radiation treatment	—	—
History of treatment for squamous-cell carcinoma	3	4
Histologic features		
Tumor depth >4 mm or to Clark level IV or V†	2	5
Poorly differentiated appearance	2	3
Infiltrative deep or peripheral margins	—	—
Spindle-cell features	—	—
Acantholytic features	—	—
Perineural invasion	5	5

*A relative risk of 1 is defined as the likelihood of recurrence or metastasis of a small primary squamous-cell carcinoma. Dashes indicate an association with increased risk, but one for which there are insufficient data to estimate the relative risk.

†Clark level IV indicates a lesion that involves the reticular dermis, and level V indicates invasion into subcutaneous fat.

Pobre evolución tras metástasis nodales

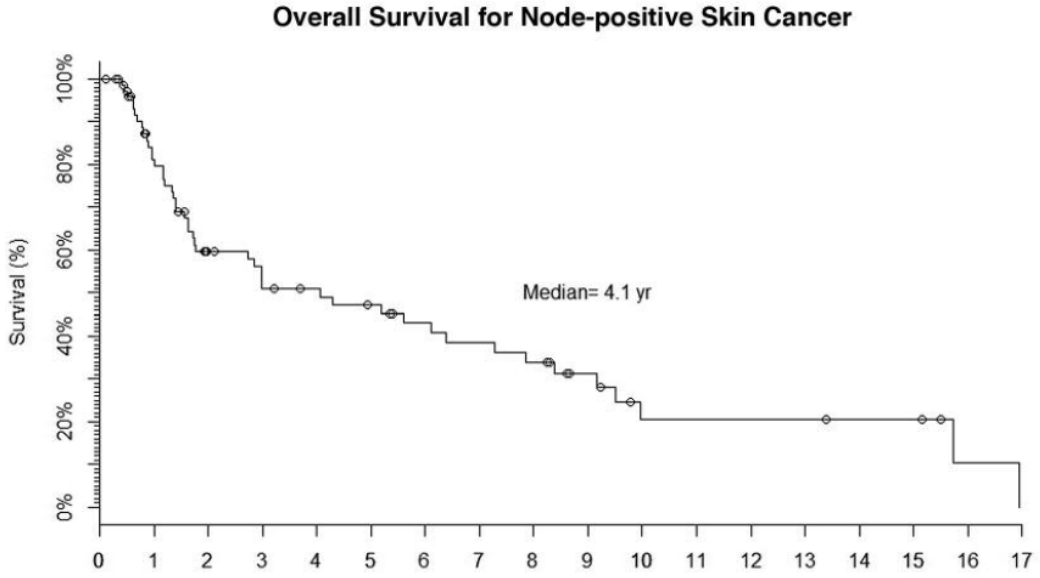
- Estudio retrospectivo 76 pacientes con CECAR N+ a cuello o parótida
- Tratado con CIR + RT adyuvante
- **OS a los 2 años.: 60%**
- Recurrencias a los 2 años: 40%
- Intervalo libre de enfermedad claramente inferior en inmunodeprimidos ILE (28% vs. 55%; p=0.003) y recurrencias (61% vs. 34%; p=0.04)
- Extensión extracapsular e inmnosupresión asociada son los factores más importantes en la supervivencia

ANTICANCER RESEARCH *38*: 5825-5830 (2018)
doi:10.21873/anticanres.12923

Suboptimal Outcomes in Cutaneous Squamous Cell Cancer of the Head and Neck with Nodal Metastases

VAMSI VARRA[1], NEIL M. WOODY[1], CHANDANA REDDY[1], NIKHIL P. JOSHI[1], JESSICA GEIGER[2], DAVID J. ADELSTEIN[2], BRIAN B. BURKEY[3], JOSEPH SCHARPF[3], BRANDON PRENDES[3], ERIC D. LAMARRE[3], ROBERT LORENZ[3], BRIAN GASTMAN[4], BINDU V. MANYAM[1] and SHLOMO A. KOYFMAN[1]

Departments of [1]Radiation Oncology, [2]Solid Tumor Oncology, [3]Otolaryngology and [4]Plastic Surgery, Cleveland Clinic, Cleveland, OH, U.S.A.



Carcinoma escamoso cutáneo

ESTADIFICACION ALTO RIESGO

Nuevo sistema de estadificación de la AJCC para el carcinoma epidermoide cutáneo (cabeza y cuello)

Criterios T del AJCC 2018 en CEC (solo tumores de cabeza y cuello)	
T1	Tumor < 2 cm en su mayor dimensión
T2	Tumor 2 cm - 4 cm en su mayor dimensión
T3	Tumor > 4 cm Tumor con erosión ósea Tumor con invasión perineural Tumor con invasión profunda
T4	Tumor invasión de hueso cortical o médula ósea Tumor con invasión de la base del cráneo Tumor con invasión de foramen de la base del cráneo
T4a	Tumor con invasión de hueso cortical / médula ósea
T4b	Tumor con invasión de la base del cráneo y / o afectación del foramen de la base del cráneo

AJCC Cancer Staging System, 8th Edition: UPDATE

*** La invasión profunda se define como invasión más allá de la grasa subcutánea o > 6 mm (medida desde la capa granular de la epidermis normal adyacente hasta la base del tumor); La invasión perineural para la clasificación T3 se define como células tumorales dentro de la vaina nerviosa de un nervio situado más profundo que la dermis o que mide 0,1 mm o más de calibre, o presentando una afectación clínica o radiográfica de los nervios nombrados sin invasión o transgresión de la base del cráneo.**

2018

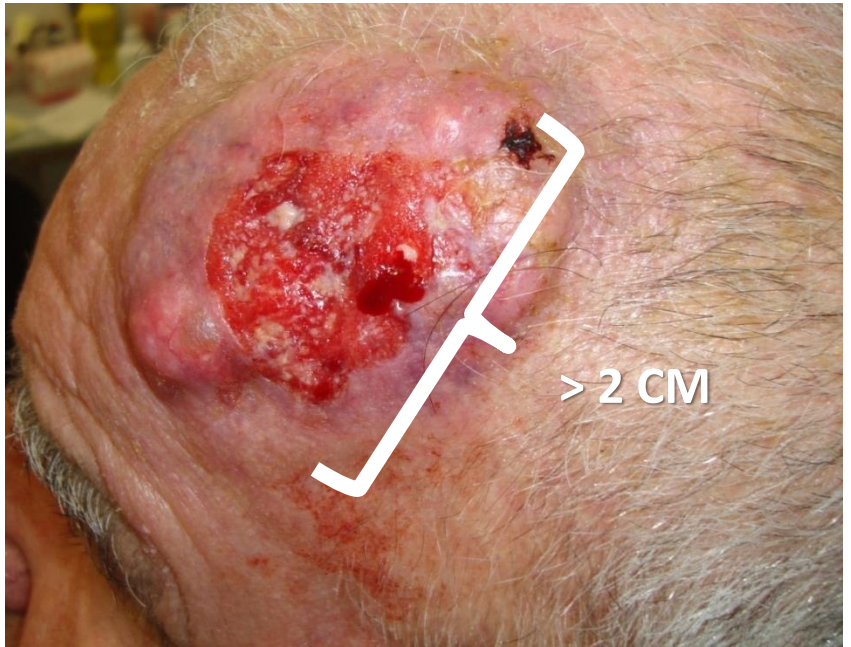
Tamaño tumoral

Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study

Kay D Brantsch, Christoph Meisner, Birgitt Schönfisch, Birgit Trilling, Jörg Wehner-Caroli, Martin Röcken, Helmut Breuninger

Lancet Oncol 2008; 9:713–20

TUMOR SIZE		
SIZE	**NODE +**	**PROGNOSIS**
≤ 2 CM	***<0.01%***	Good
2-5 CM	***7%***	Intermediate
≥5 CM	***20%***	Poor prognosis

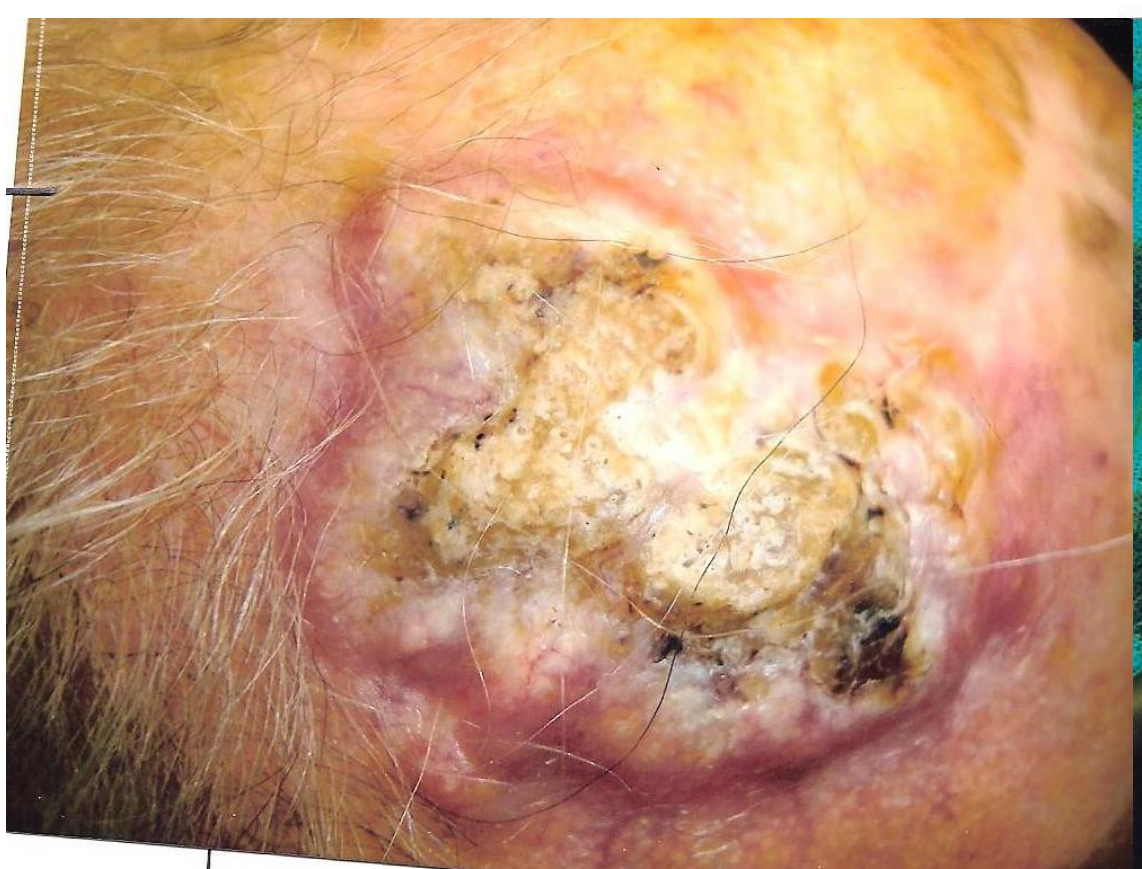


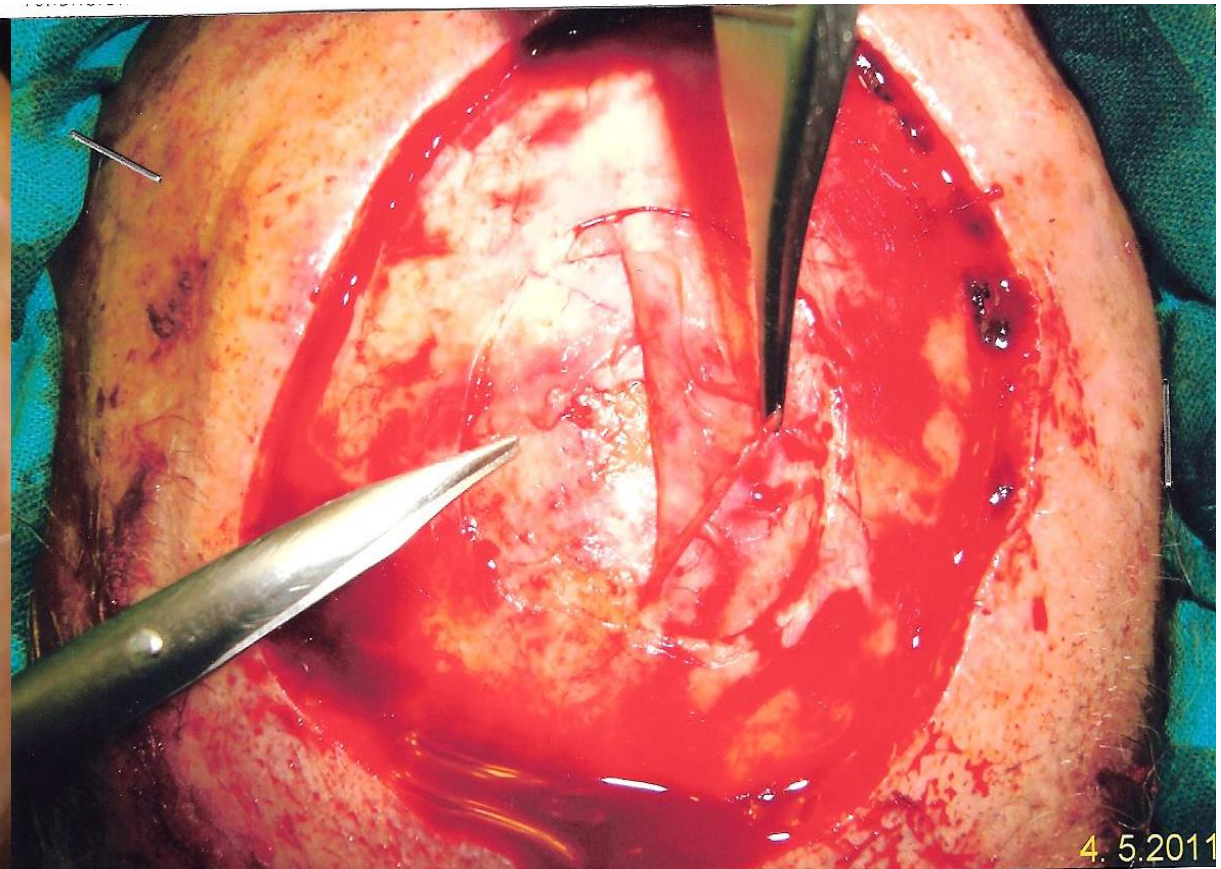
Nueva AJCC→ > 4cm → T3

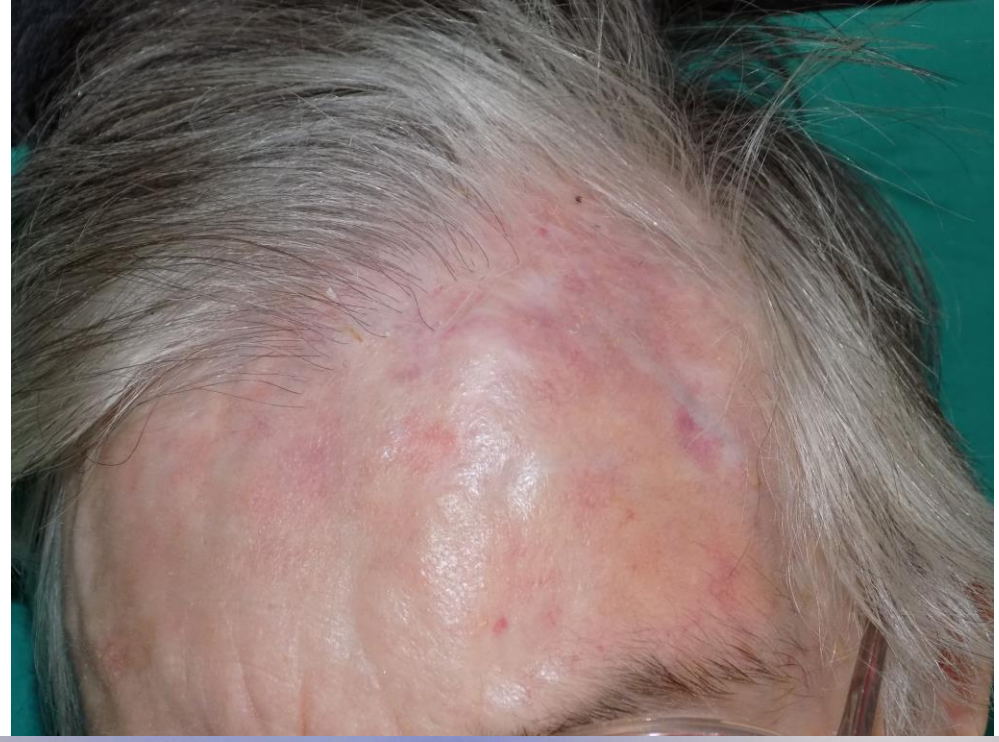
Afectación ósea

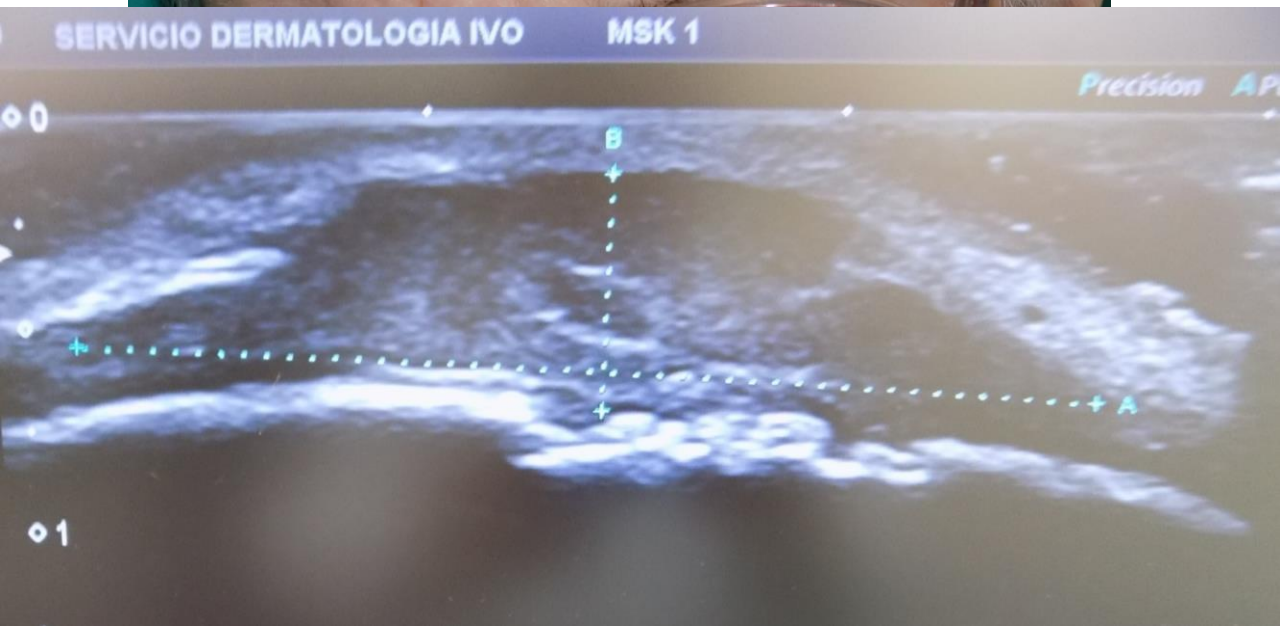
Alto riesgo de recurrencia local
Alto riesgo de extensión a ganglios
Dificultades en el tratamiento

Nueva AJCC→ EROSIÓN ÓSEA→ T3





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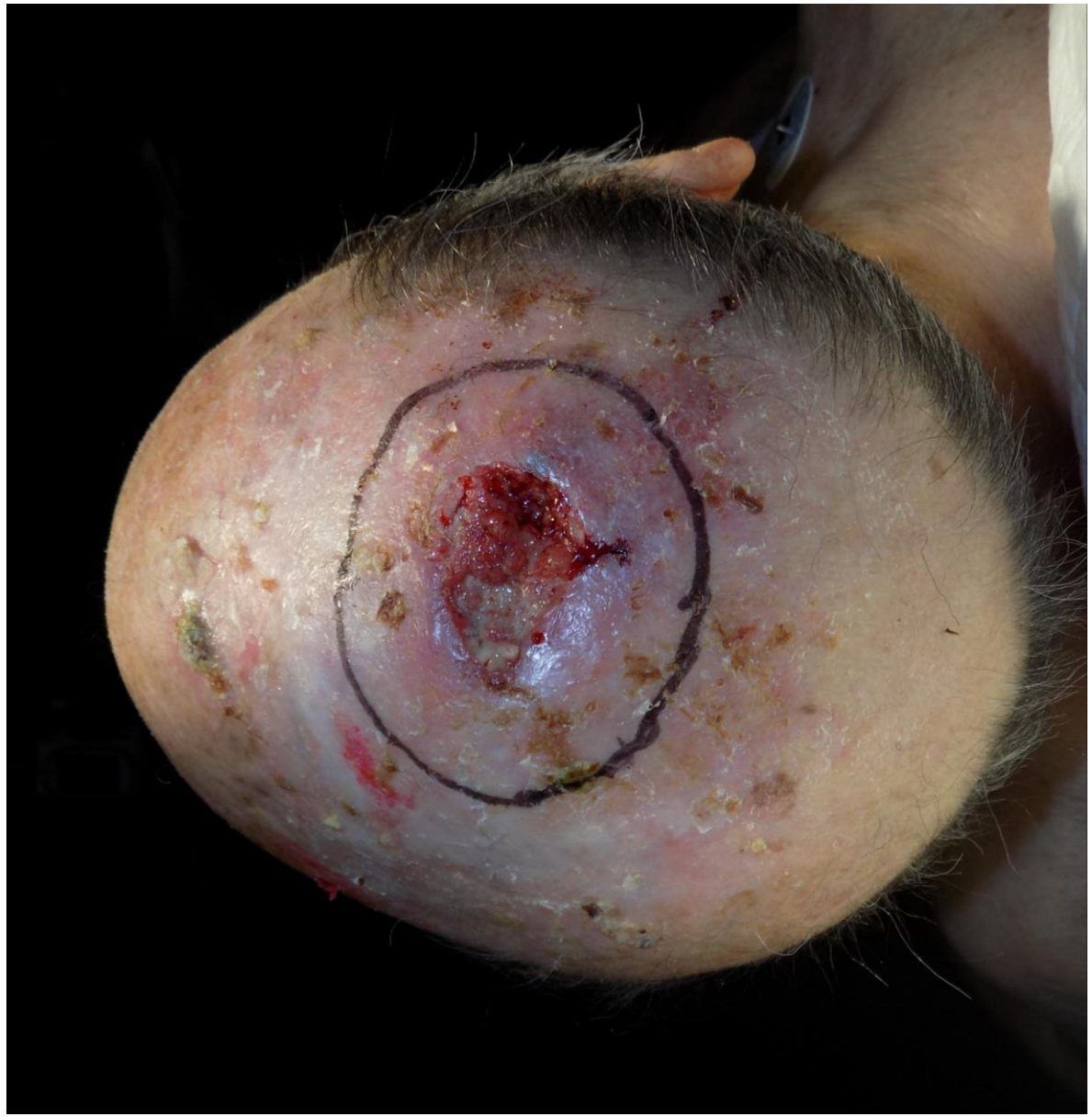

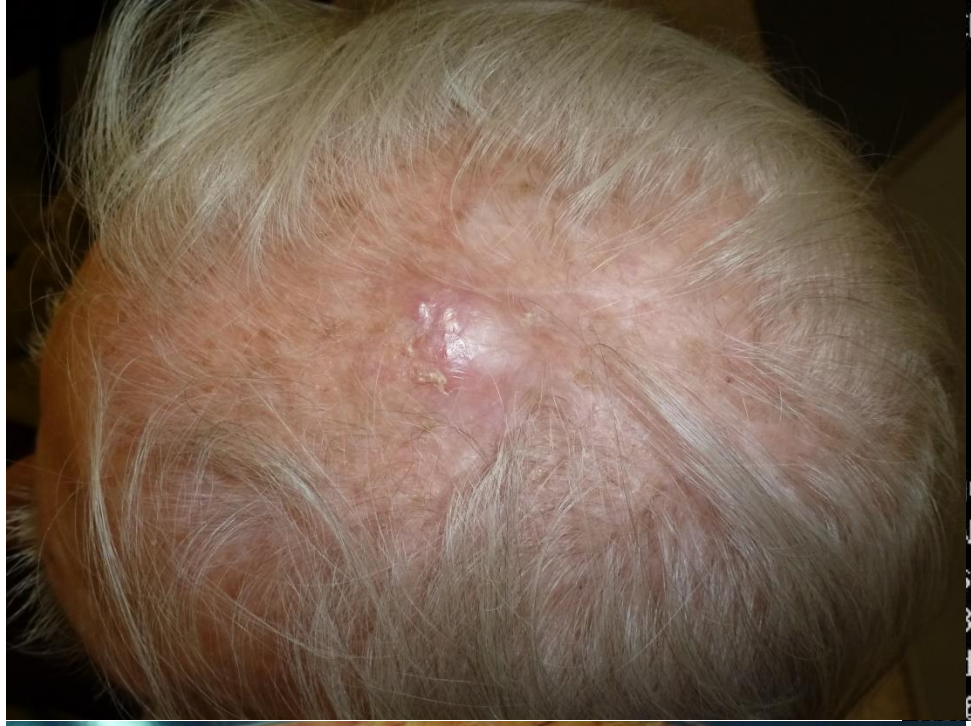

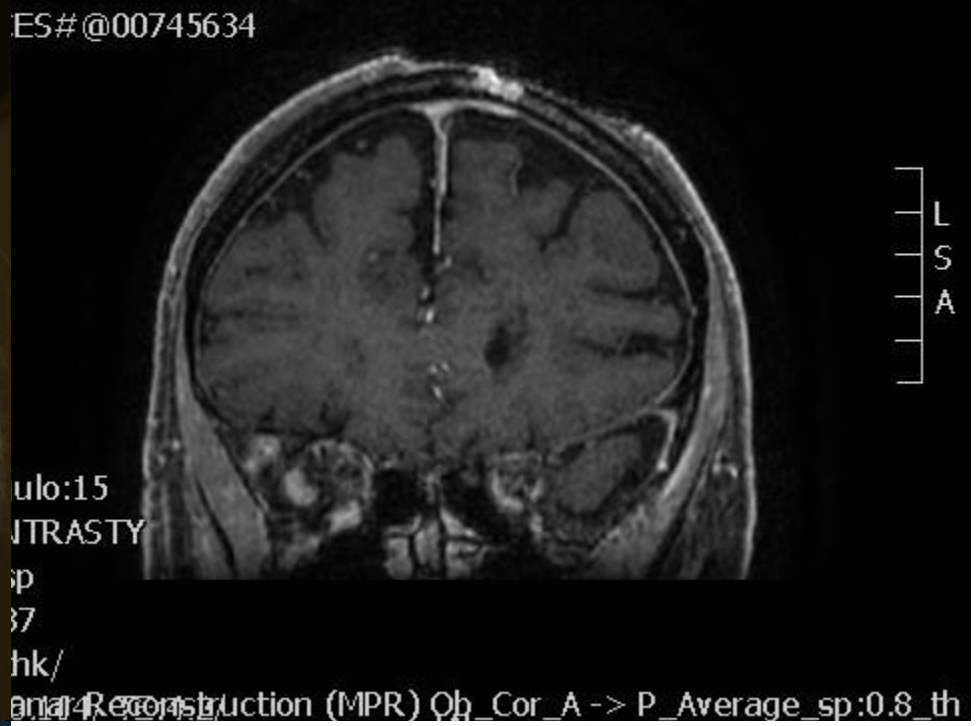
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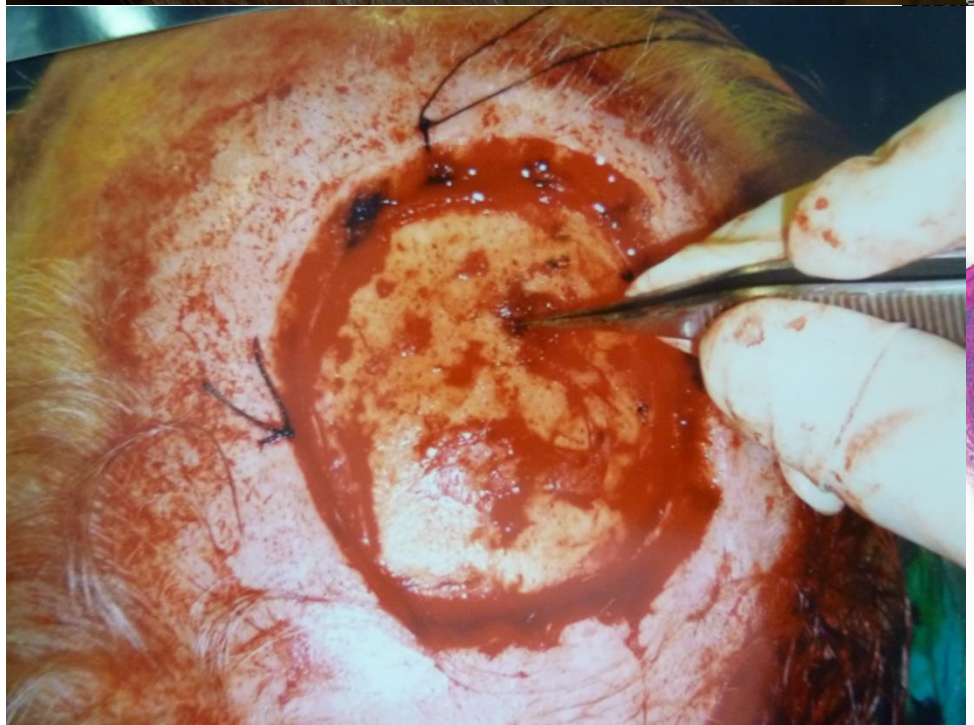
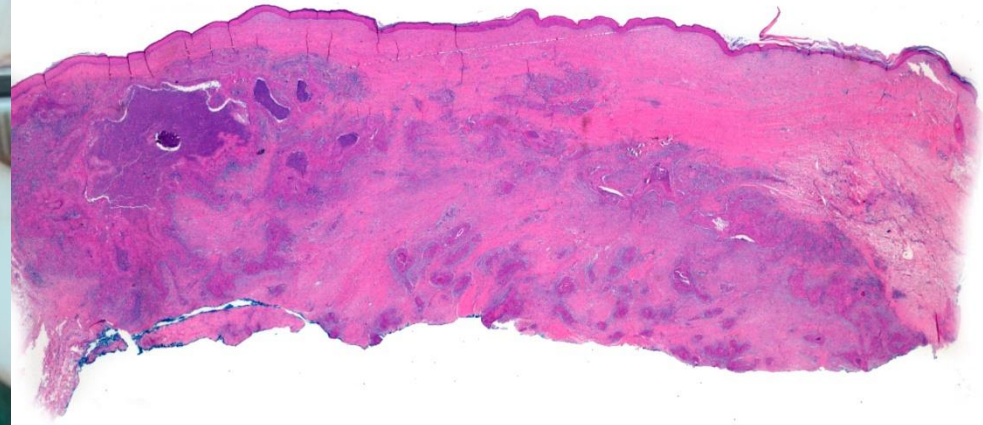




Received: 15 November 2016 | Accepted: 2 May 2017
DOI: 10.1002/jso.24693

RESEARCH ARTICLE

WILEY Journal of SURGICAL ONCOLOGY

Bone resection for facial cutaneous malignancies

Markus Brunner MD[1,2] | Sydney Ch´ng PhD[1] | Kerwin Shannon MBBS[1] | Anthony Clifford MBBS[1] | Bruce Ashford MBBS[1] | Michael Elliott MBBS[1,3] | Jonathan R. Clark MBBS[1,3]

J Surg Oncol. 2017 Sep;116(4):545-549

Research letter

Outcomes of radiation therapy for advanced T3/T4 nonmelanoma cutaneous squamous cell and basal cell carcinoma

DOI: 10.1111/bjd.15728

Dear Editor, Nonmelanoma cutaneous squamous and basal cell carcinoma (NMSC) is common, and most patients present with early stage (T1/T2) NMSC, which has an excellent prog-

86% (95% CI 73–99) for adjuvant RT. The 3-year DSS rate for cSCC patients was 64% (95% CI 53–75); and 38% (95% CI 22–54) and 93% (95% CI 78–96) for patients treated with definitive and adjuvant RT, respectively (Fig. 1b–d). Eight of 13 (62%) patients treated with palliative-intent RT experienced symptom relief (there was incomplete data for the fourteenth patient). On univariate analyses, nonhead and neck primary tumours ($P = 0{\cdot}016$) and nodal metastases ($P = 0{\cdot}049$) were associated with worse DSS for cSCC. No significant association

Br J Dermatol. 2018 Jan;178(1):e30-e32

Afectación ósea

- Poco frecuente
- Generalmente en extremidades y en calota
- Requiere RM y TAC con ventana ósea
- Supervivencia relacionada con afectación dural, margen quirúrgico e IPN

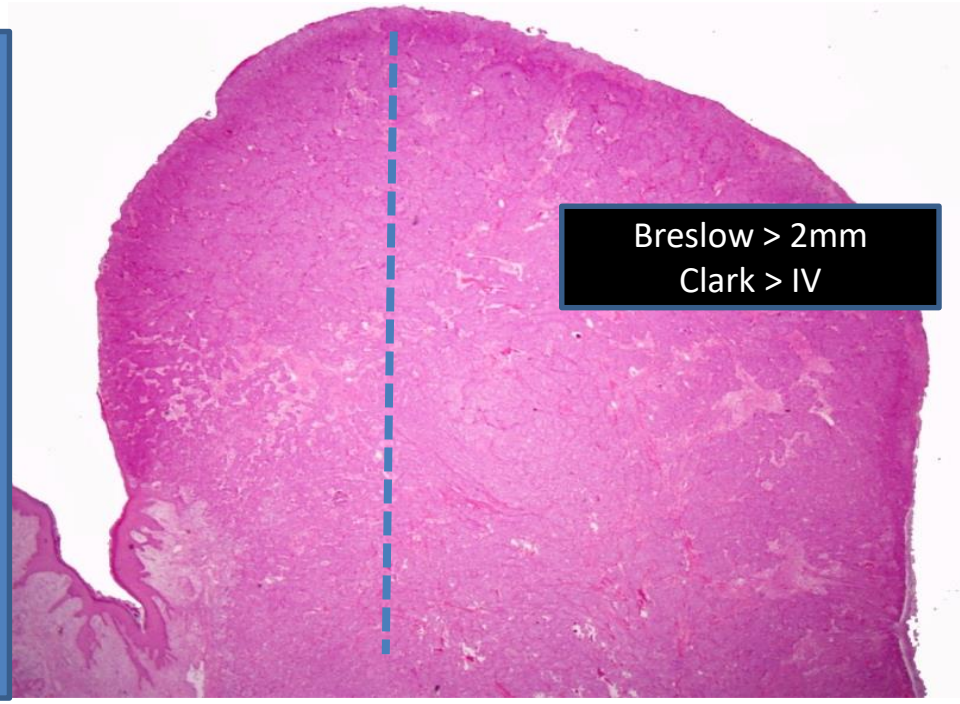
Profundidad tumoral

•Brantsch*, 3 risk groups

•≤2mm, no risk of metastasis

•2-4 mm, intermediate risk(4% M+)

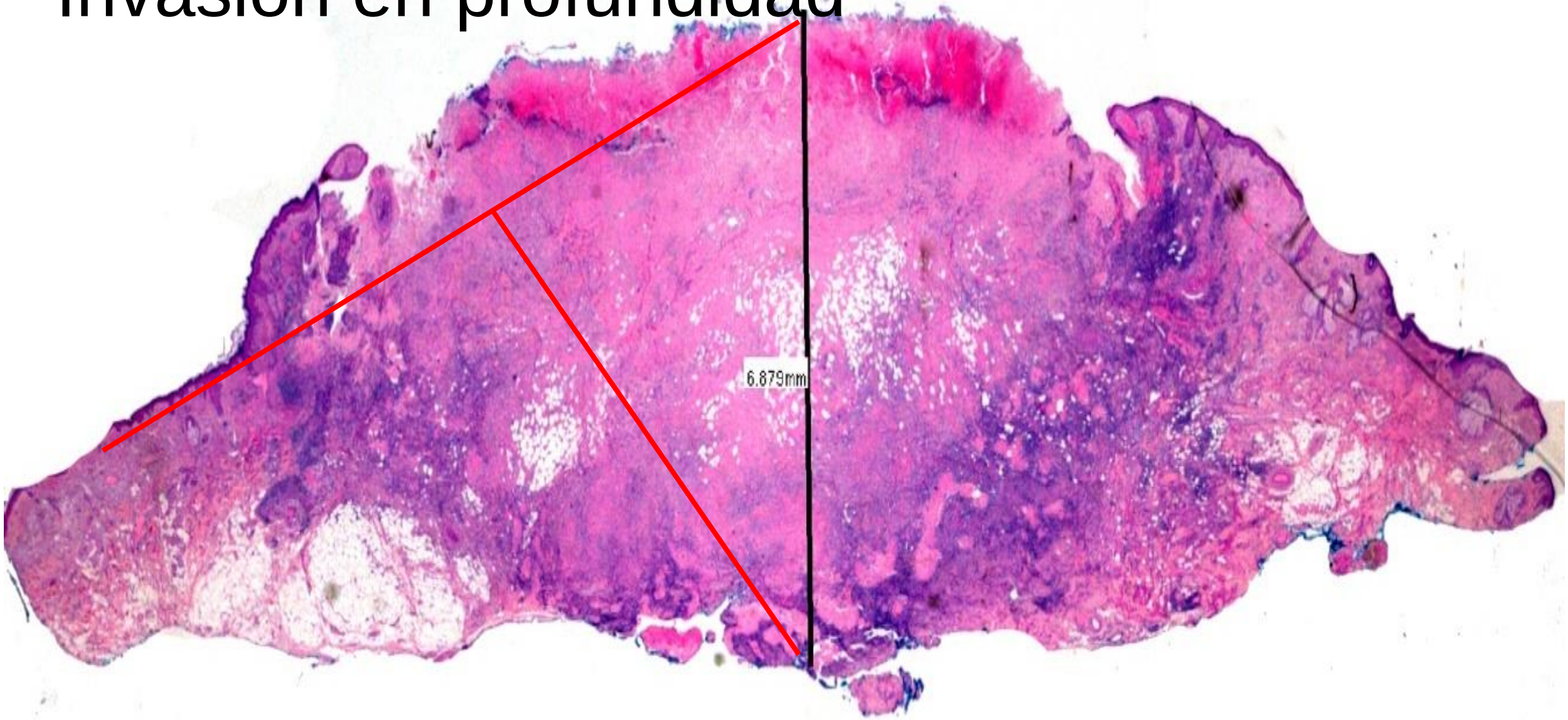
•≥ 6 mm, high risk (16% M+)



Nueva AJCC→ > 6mm o TCS → T3

**Brantsch KD, et al.Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008 ;9: 713-20*

Invasión en profundidad

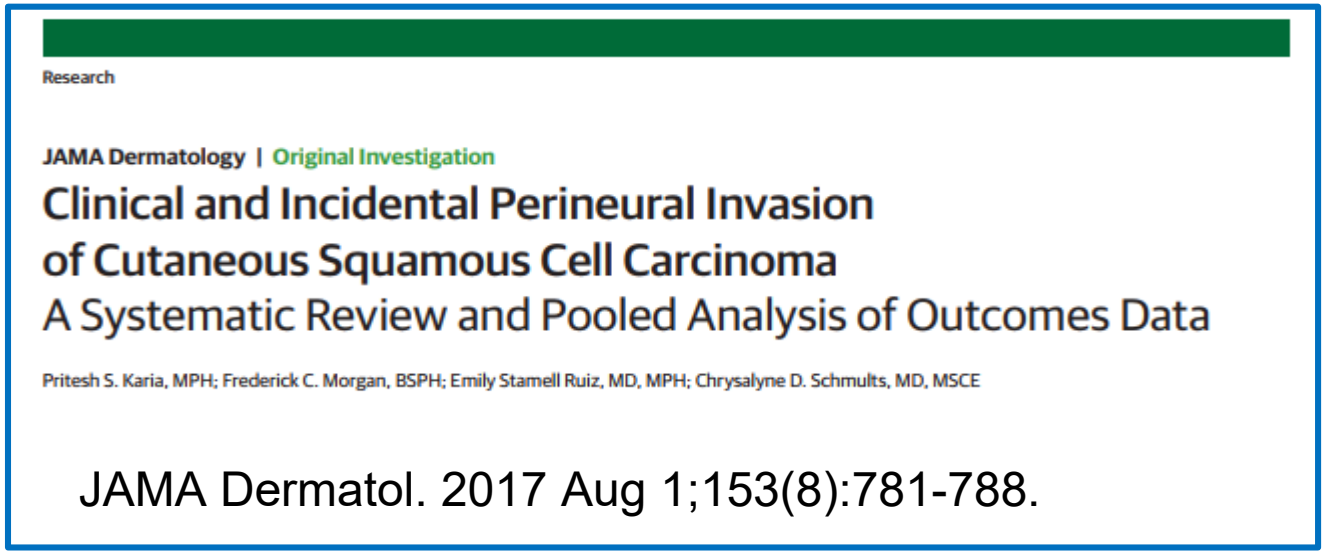


Espesor tumoral

Invasión tumoral

T3 > 6 mm o hasta la grasa

Relevancia de la IPN


Research

JAMA Dermatology | Original Investigation

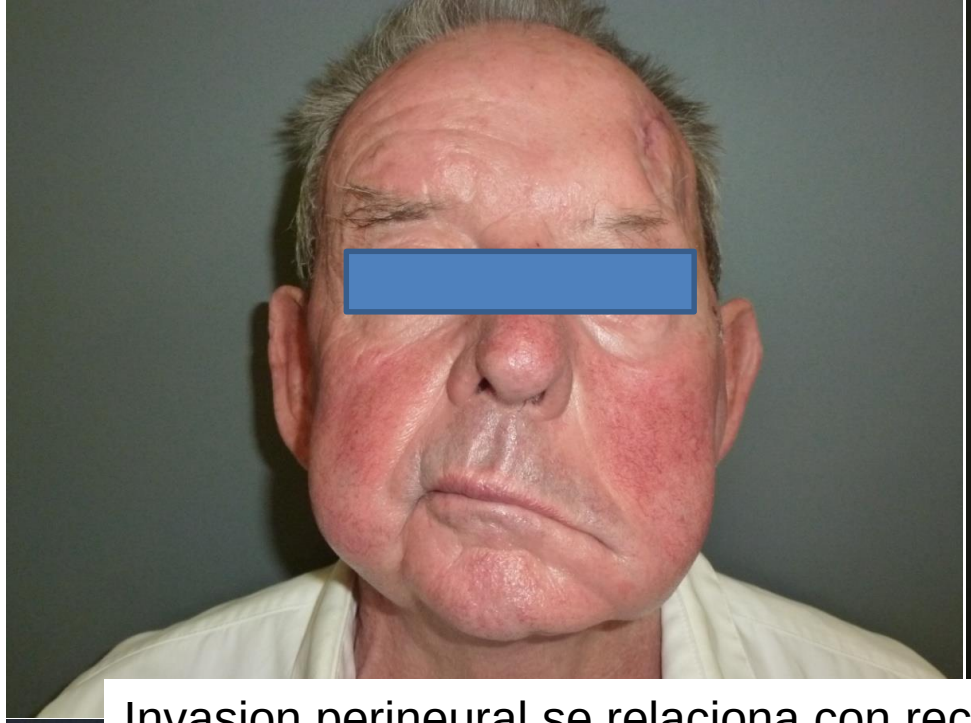
Clinical and Incidental Perineural Invasion of Cutaneous Squamous Cell Carcinoma

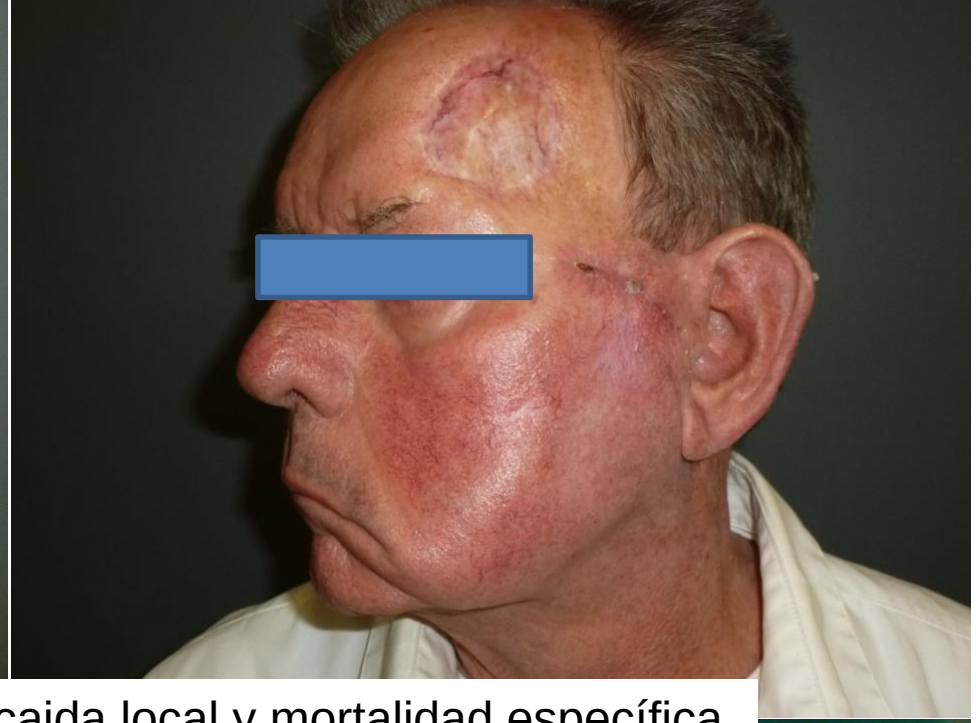
A Systematic Review and Pooled Analysis of Outcomes Data

Pritesh S. Karia, MPH; Frederick C. Morgan, BSPH; Emily Stamell Ruiz, MD, MPH; Chrysalyne D. Schmults, MD, MSCE

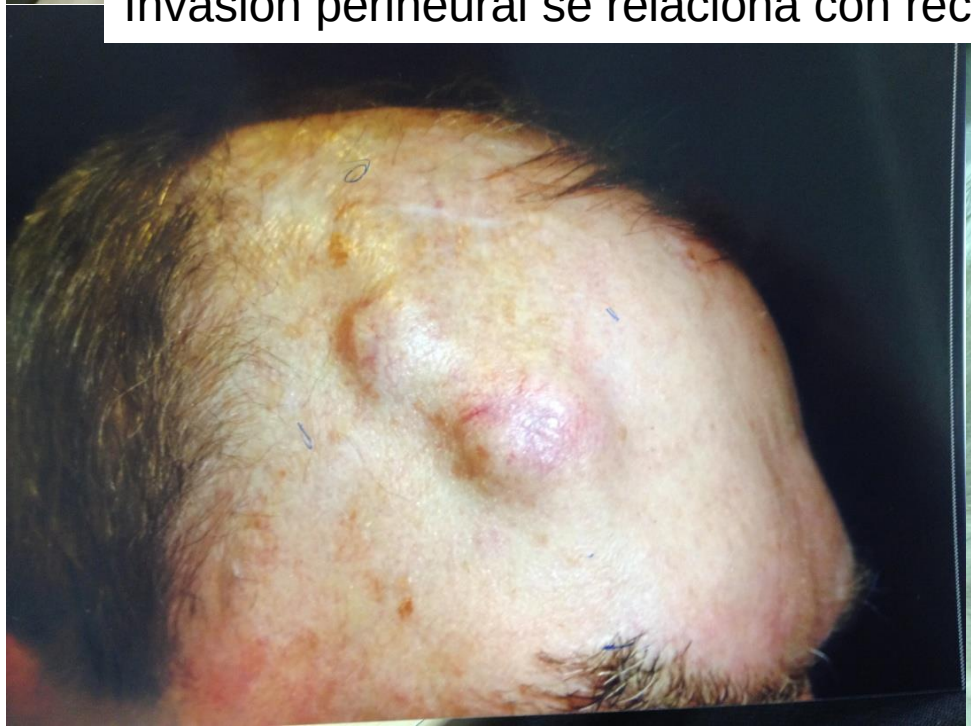
JAMA Dermatol. 2017 Aug 1;153(8):781-788.

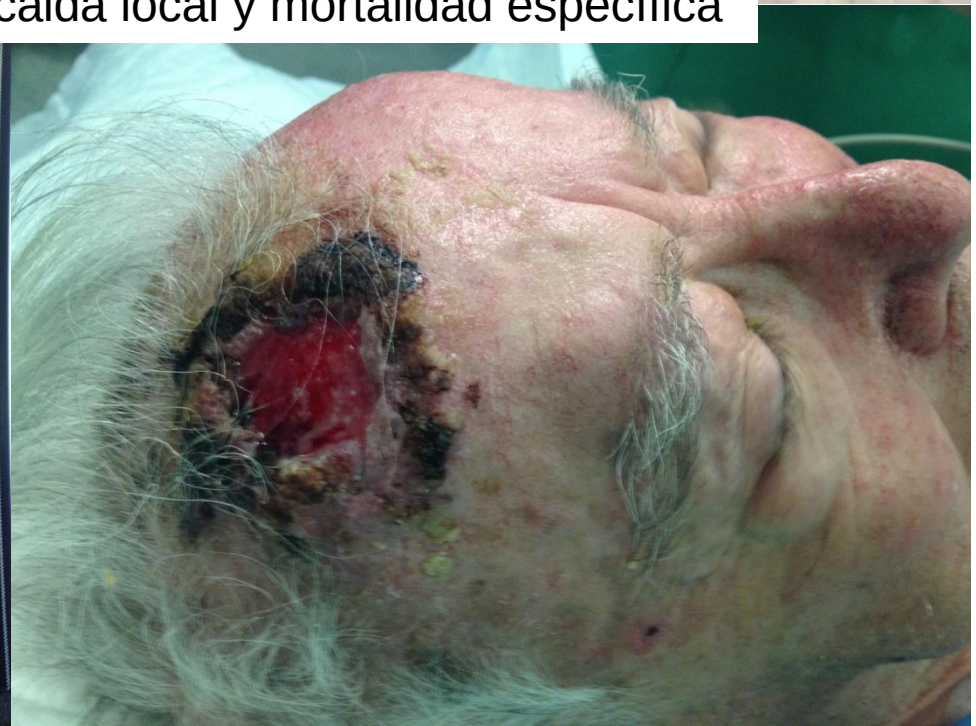
- **IPN clínica**: síntomas clínicos o detección radiológica
- **IPN incidental**: hallazgo casual en la histologia sin clínica asociada
- Revisión sistemática MEDLINE and EMBASE
- 12 estudios con 241 pacientes con IPN clínica y 381 pacientes con IPN incidental
- NO DIFERENCIAS EN AFECTACION NODAL O METASTASIS A DISTANCIA
- DIFERENCIAS SIGNIFICATIVAS EN LA **RECIDIVA** (37% VS 17%) Y LA **MUERTE ENFERMEDAD ESPECÍFICA** (27% VS 6%)
- La **invasion perineural clínica se asocial a riesgo de mortalidad de 30%**

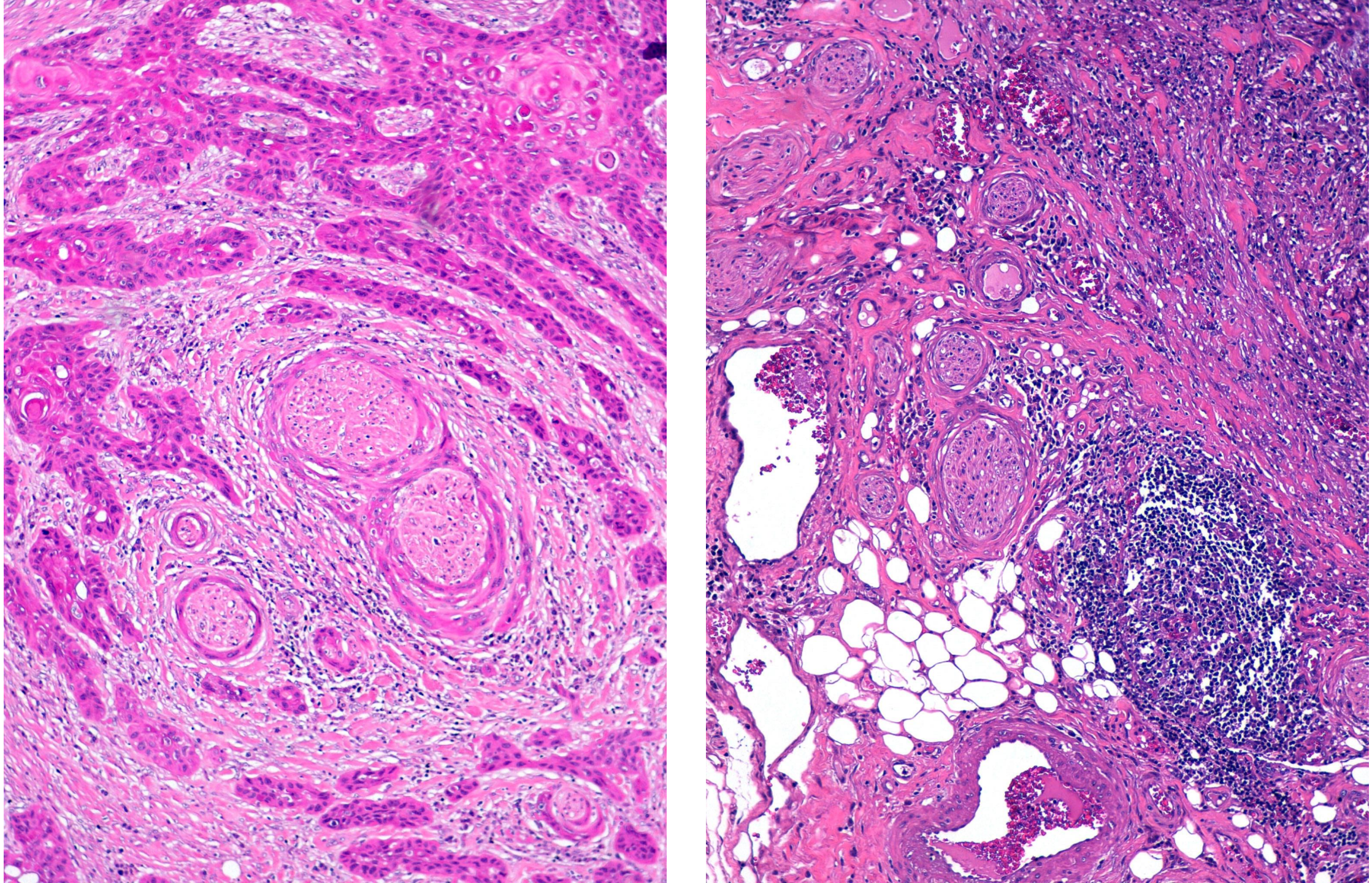


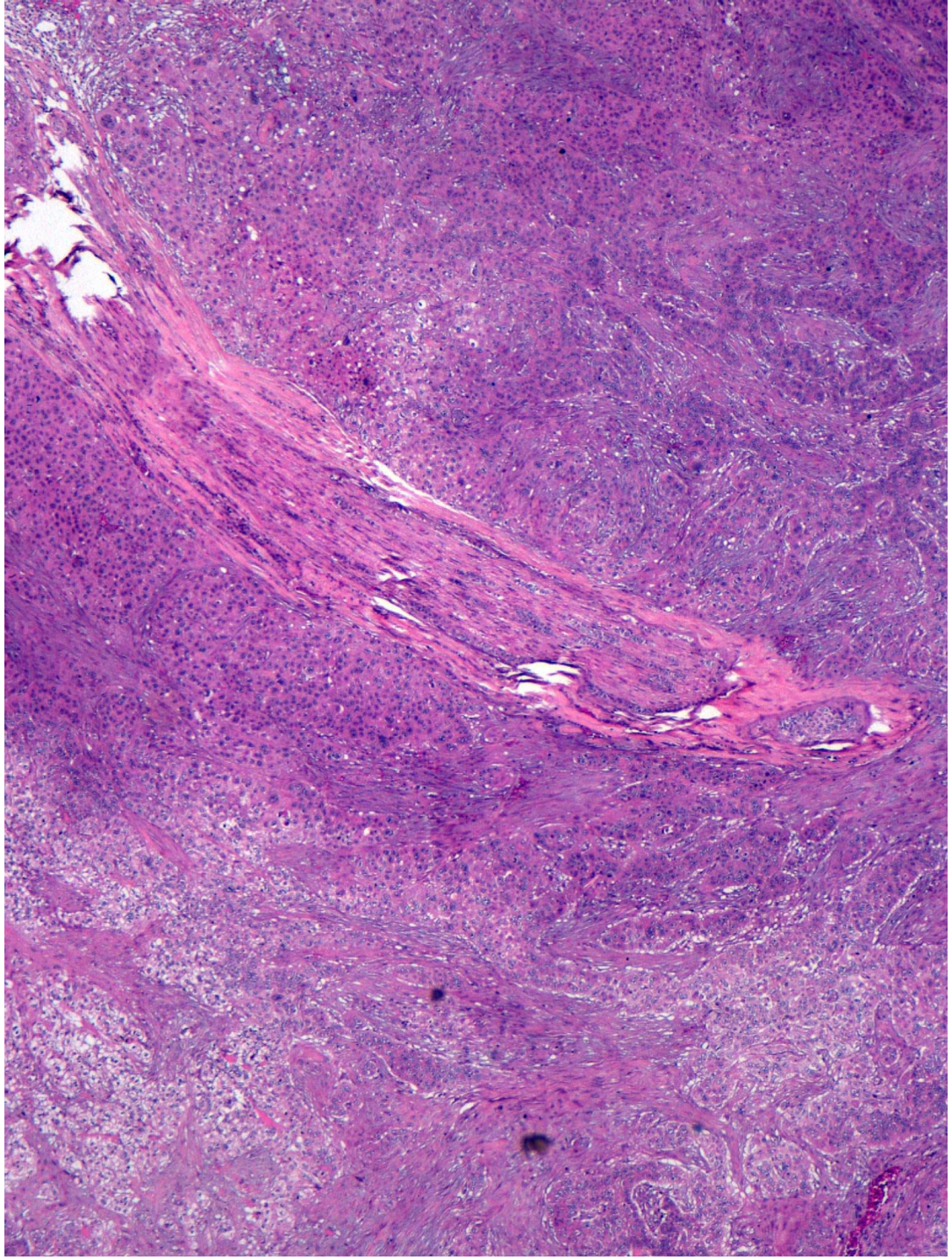


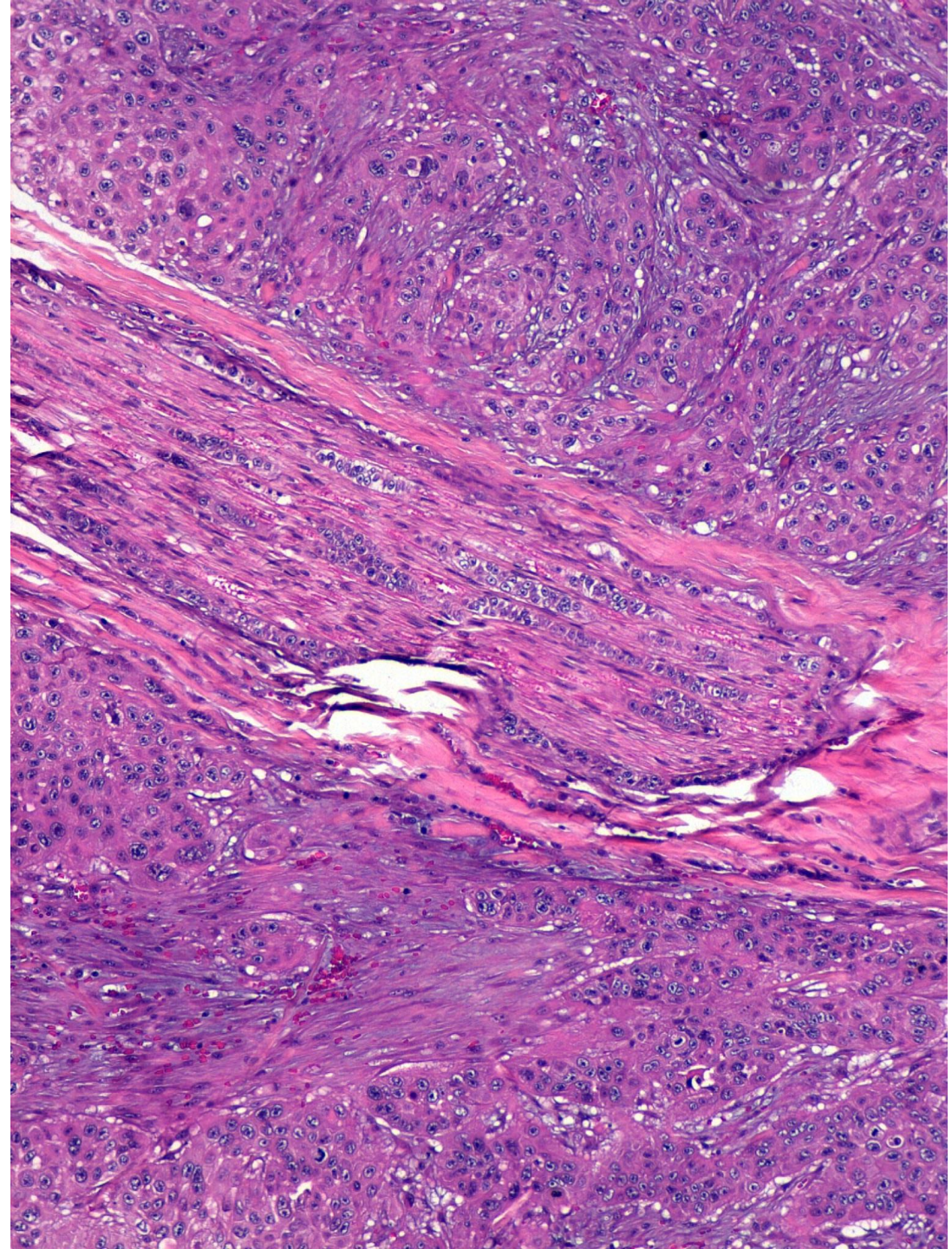
Invasion perineural se relaciona con recaida local y mortalidad específica



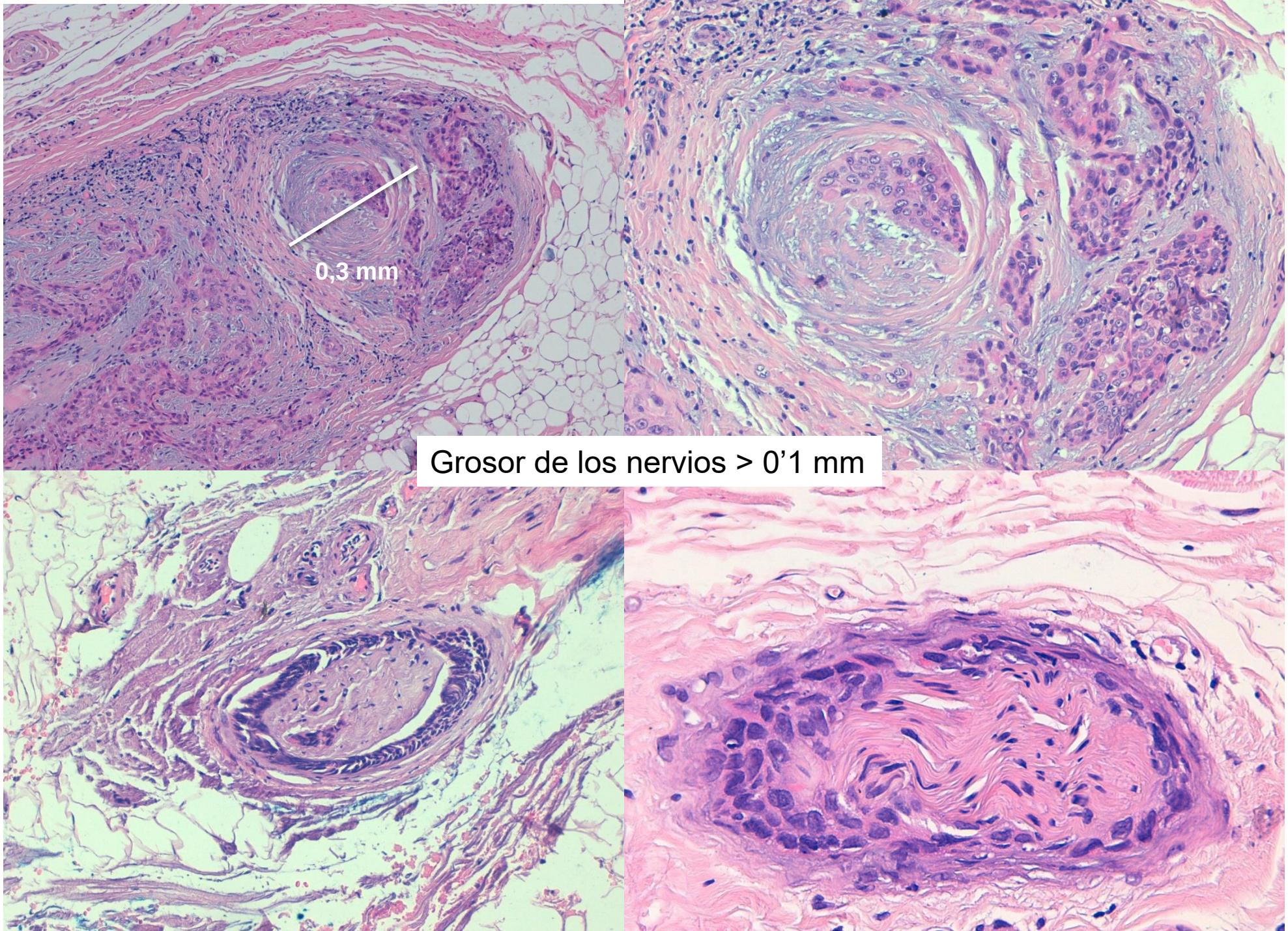




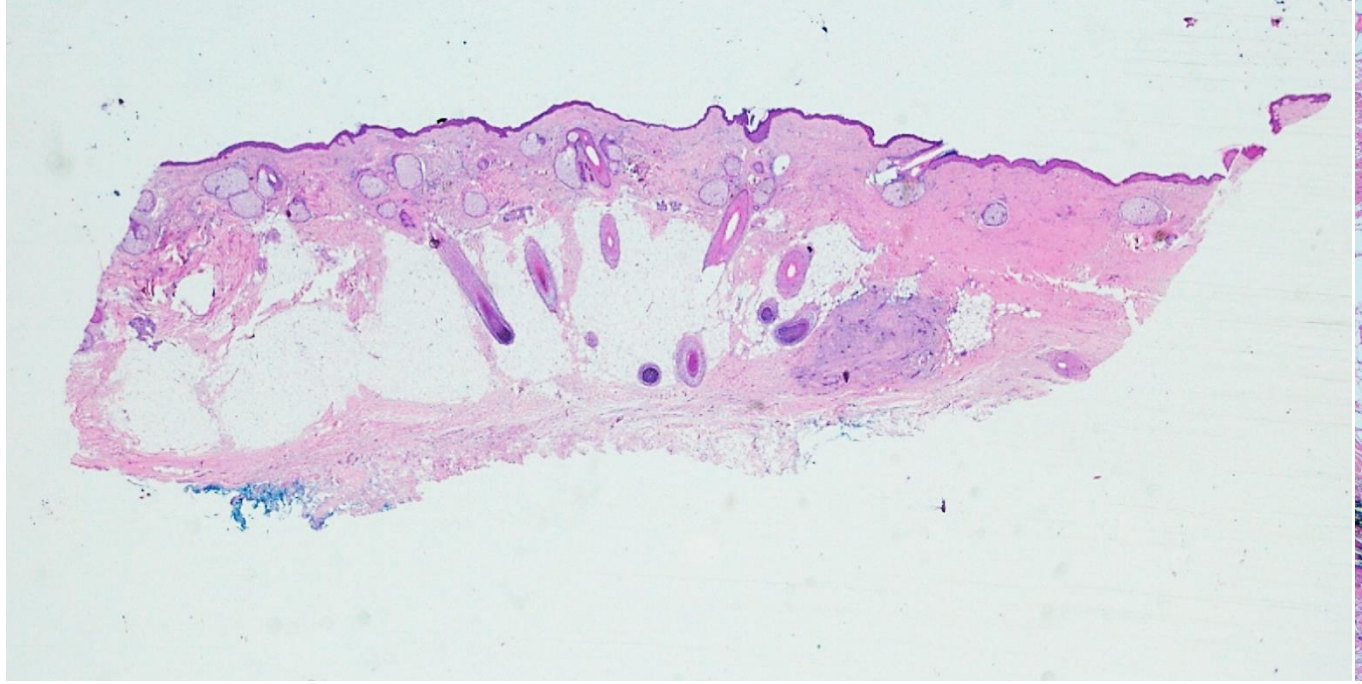


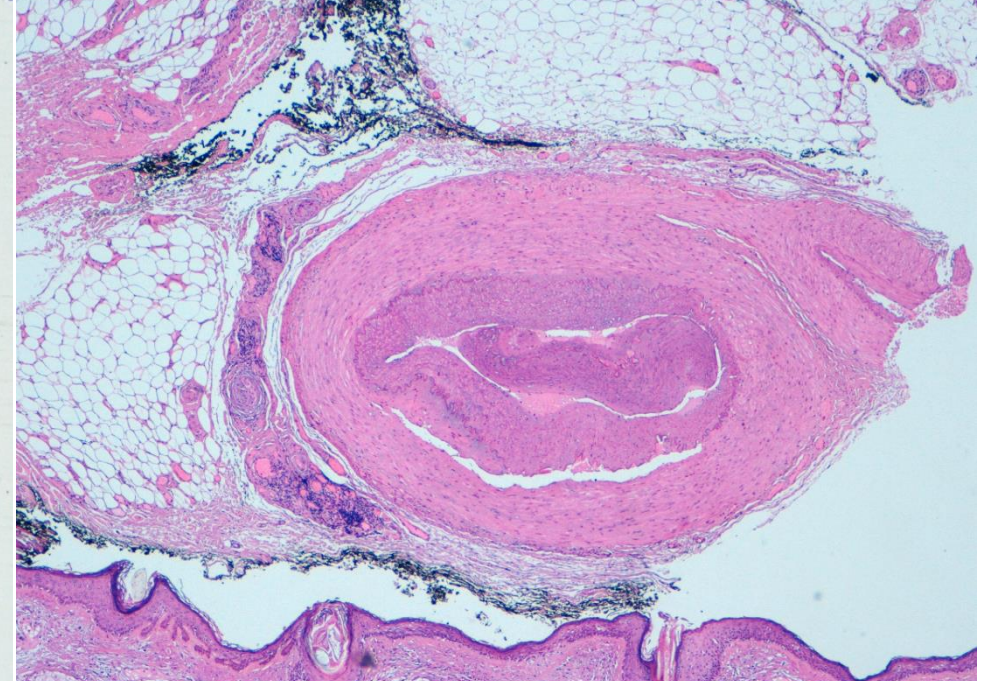


T3

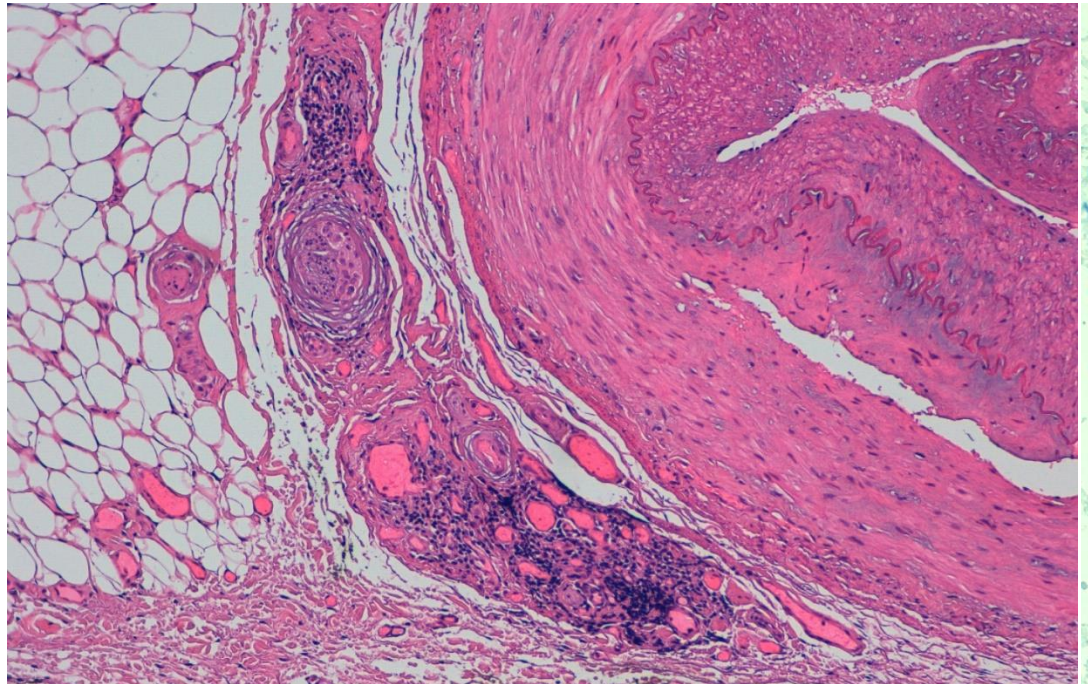


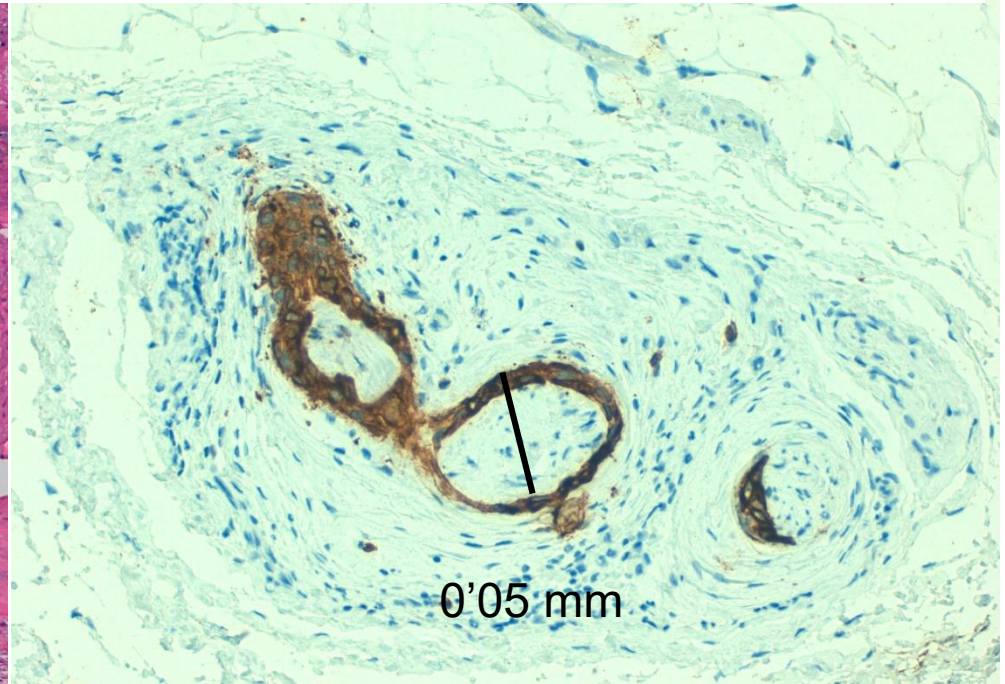
Grosor de los nervios > 0’1 mm

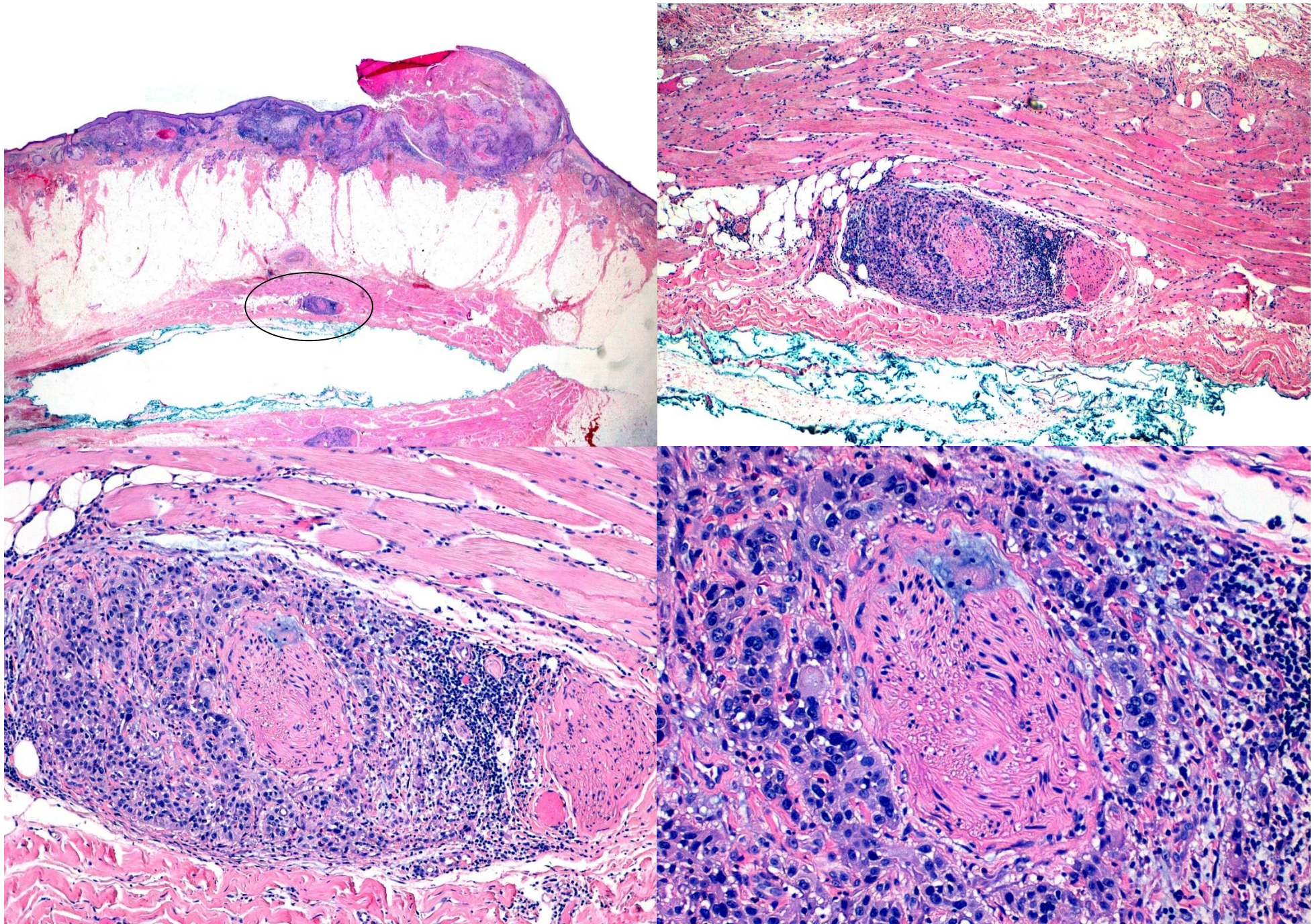




Grosor de los nervios de < 0’05 mm, pero mal pronóstico por estar a distancia del foco del tumor y en TCS



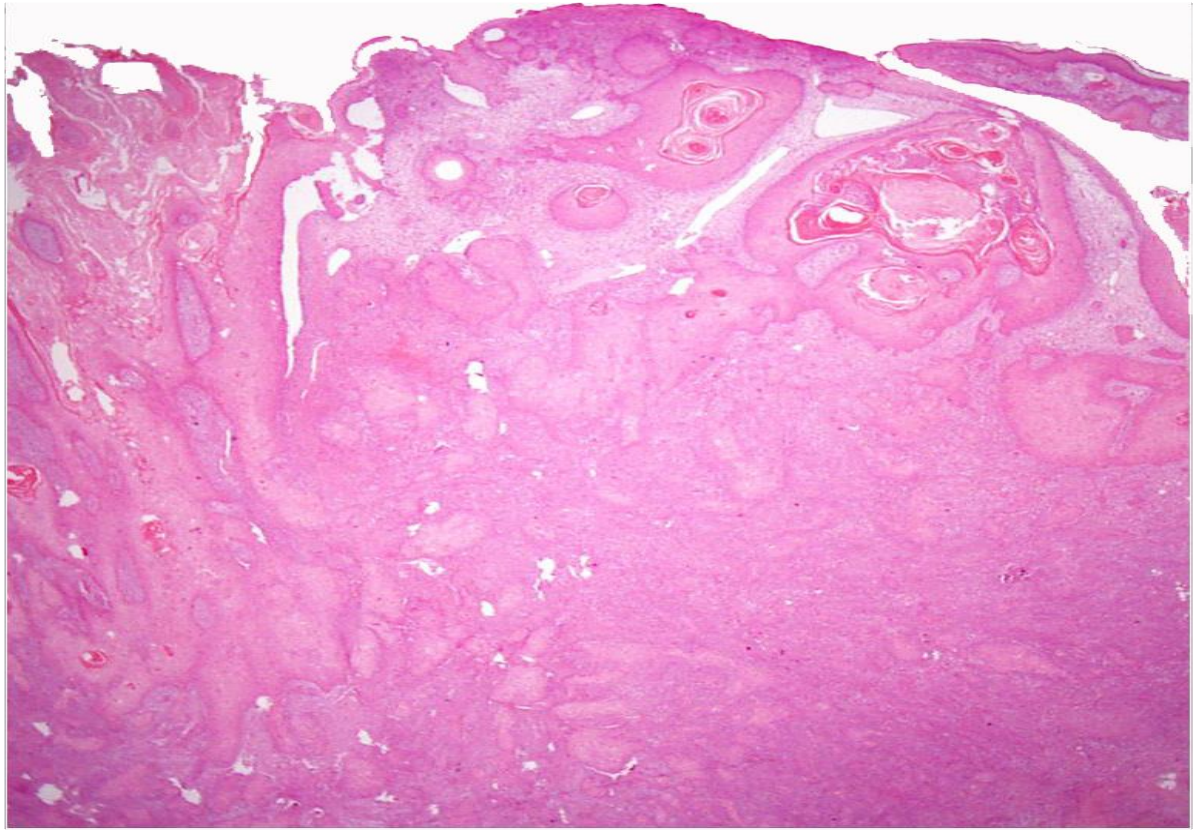


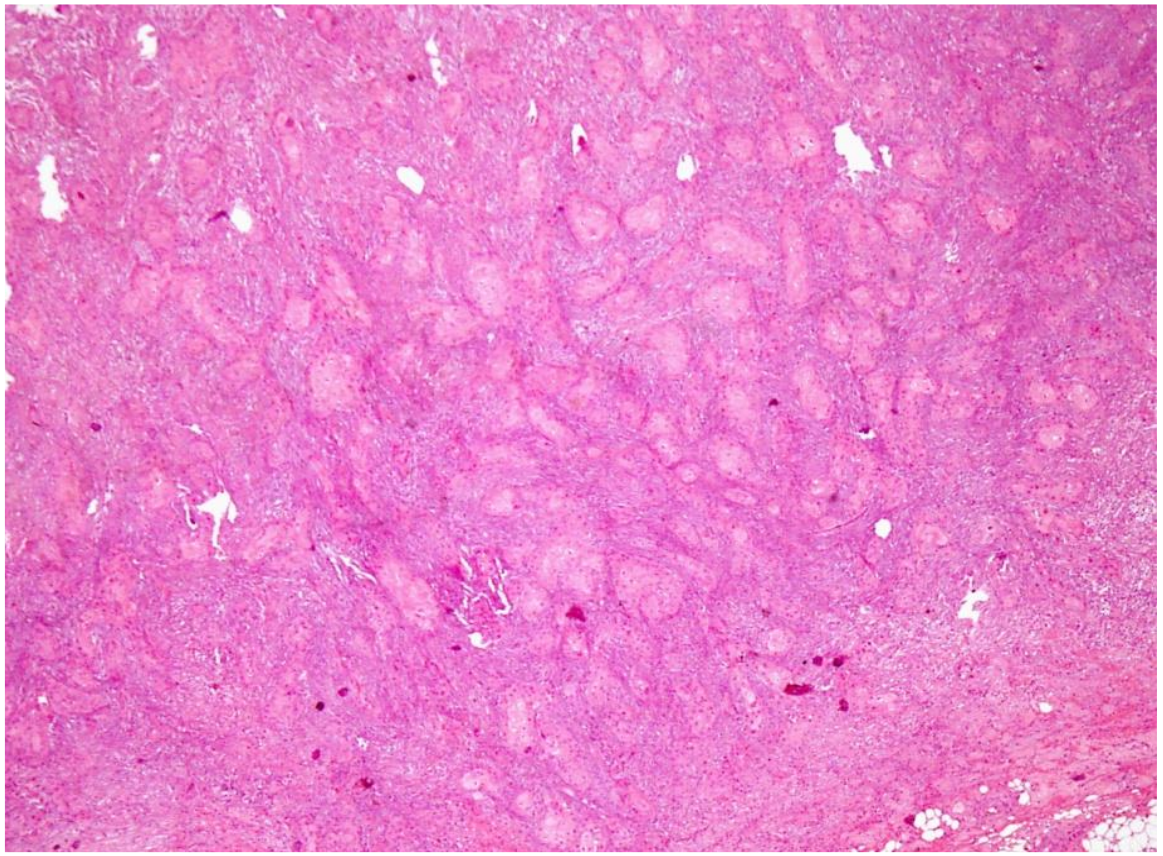


Diferenciación tumoral

- **156 N+ SCC.**
  - **12%, bien y moderadamente diferenciado**
  - **44%, pobremente diferenciados**

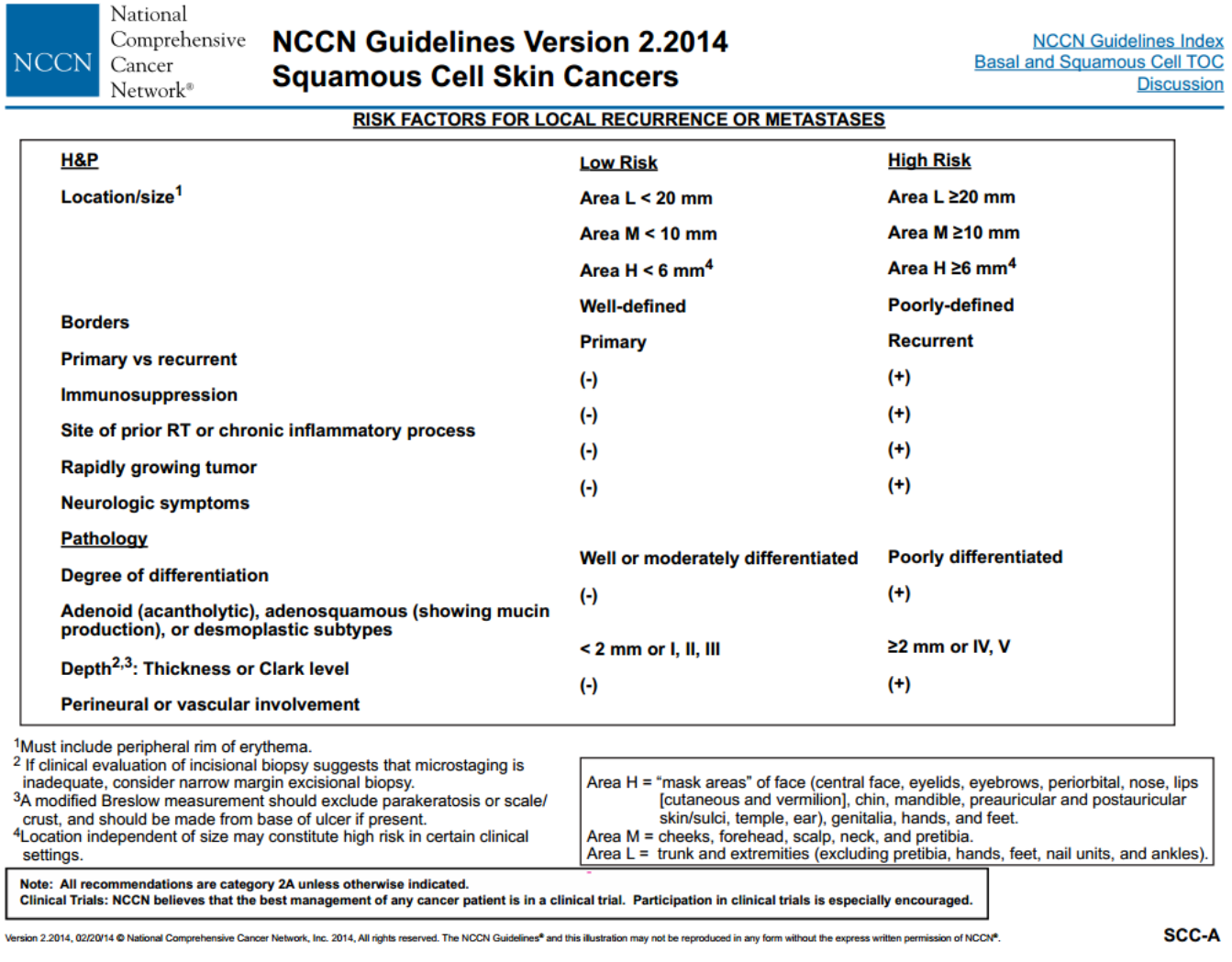
Veness MJ et al. High-RIsk cutaneous squamous cell carcinoma of the head and neck. Results from 266 treated patients with metastatic lymph node disease. Cancer 2006;106:2389-96.





Otros hallazgos de alto riesgo

5. Immunosupresion
6. Rápido crecimiento
7. Variantes histológicas (desmoplasico)
8. Invasion linfovascular



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Squamous Cell Skin Cancers

NCCN Guidelines Index
Basal and Squamous Cell TOC
Discussion

RISK FACTORS FOR LOCAL RECURRENCE OR METASTASES

H&P	Low Risk	High Risk
Location/size[1]	Area L < 20 mm	Area L ≥20 mm
	Area M < 10 mm	Area M ≥10 mm
	Area H < 6 mm[4]	Area H ≥6 mm[4]
Borders	Well-defined	Poorly-defined
Primary vs recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT or chronic inflammatory process	(-)	(+)
Rapidly growing tumor	(-)	(+)
Neurologic symptoms	(-)	(+)
Pathology		
Degree of differentiation	Well or moderately differentiated	Poorly differentiated
Adenoid (acantholytic), adenosquamous (showing mucin production), or desmoplastic subtypes	(-)	(+)
Depth[2,3]: Thickness or Clark level	< 2 mm or I, II, III	≥2 mm or IV, V
Perineural or vascular involvement	(-)	(+)

[1]Must include peripheral rim of erythema.
[2] If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
[3]A modified Breslow measurement should exclude parakeratosis or scale/crust, and should be made from base of ulcer if present.
[4]Location independent of size may constitute high risk in certain clinical settings.

Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SCC-A

Otros hallazgos de alto riesgo

- Variedades histológicas:
  - VARIEDAD DESMOPLASICA
  - TUMORES CON PATRON INFILTRATIVO DE CÉLULAS AISLADAS
- Presencia de invasión linfovascular

ORIGINAL ARTICLE

Survival of Patients with Cutaneous Squamous Cell Carcinoma: Results of a Prospective Cohort Study

Thomas K. Eigentler[1], Ulrike Leiter[1], Hans-Martin Häfner[1], Claus Garbe[1], Martin Röcken[1] and Helmut Breuninger[1]

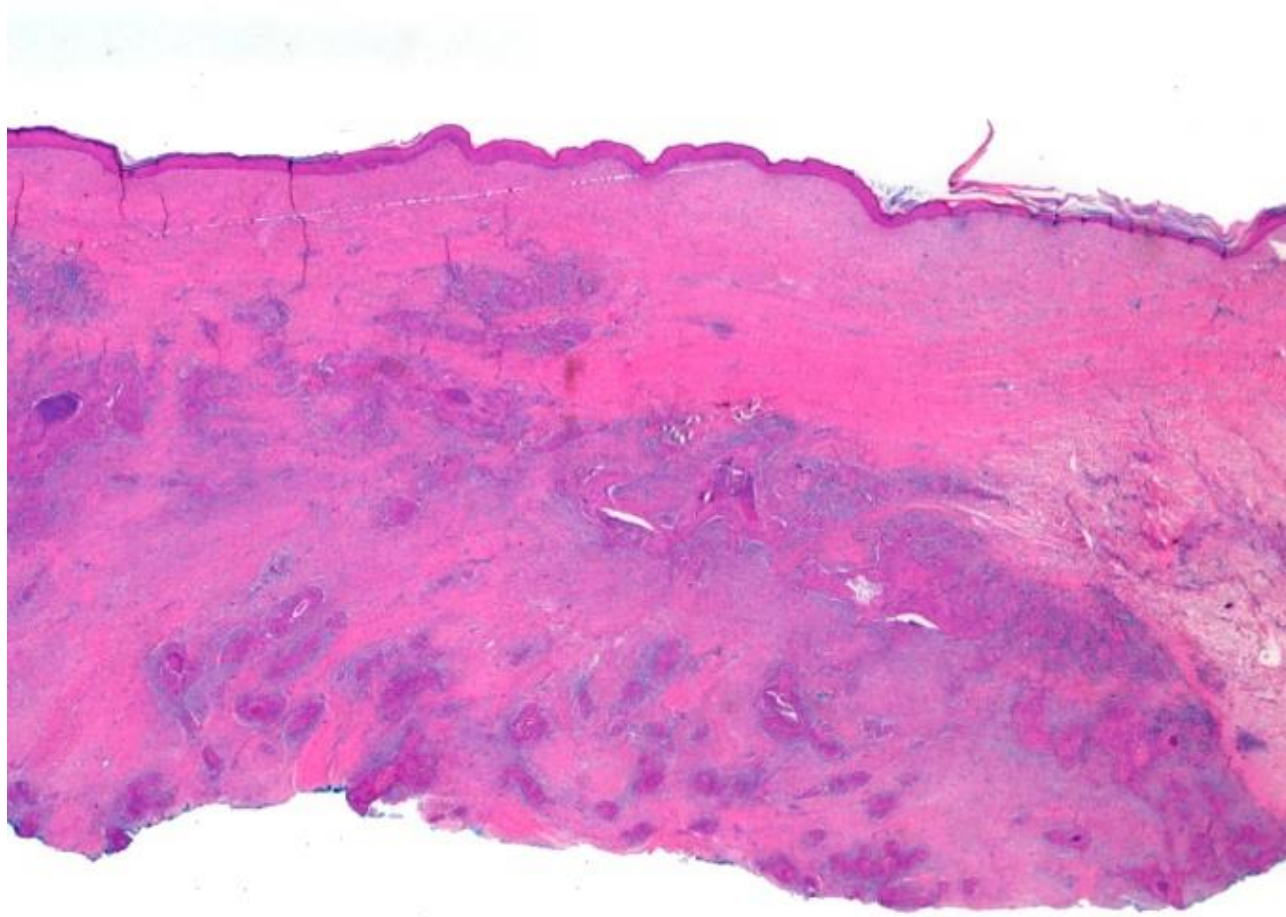
J Invest Dermatol. 2017 Nov;137(11):2309-2315

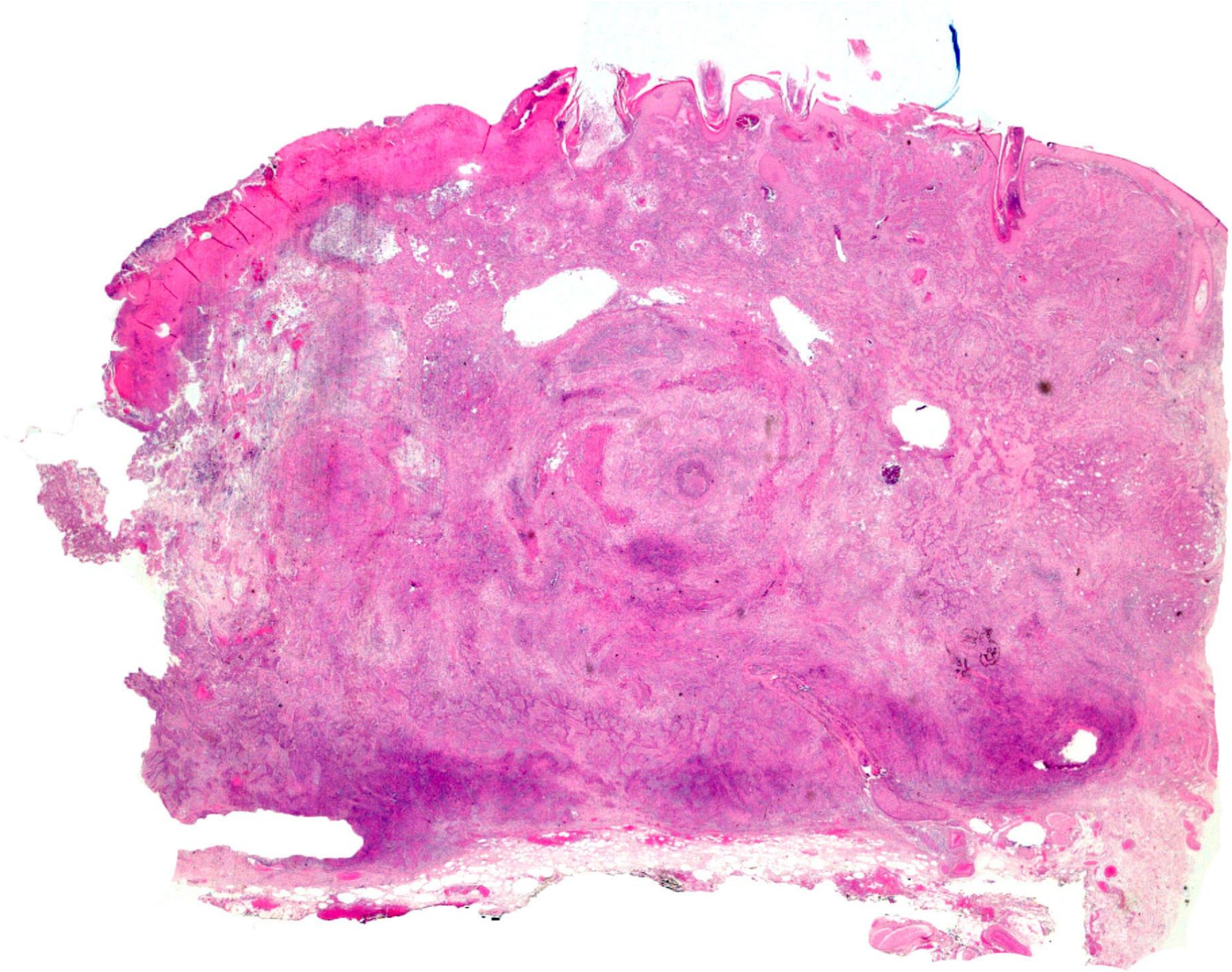
Table 2. Univariate and multivariate Cox regression models for cSCC-specific survival

		Univariate Model		Multivariate Models					
				Full model[1]		Best model[2]		Limited TNM model[3]	
Variable	Patients with Events/Number of Patients	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor thickness									
Small or intermediate	14/1,116	1	—	—	—	—	—	—	—
vs. Thick	26/318	8.64 (4.51–16.57)	<0.001	7.29 (3.52–15.10)	<0.001	6.73 (3.47–13.08)	<0.001	—	—
Tumor horizontal size									
Small or intermediate	23/1,322	1	—	—	—	—	—	—	—
vs. Large	13/83	9.54 (4.83–18.85)	<0.001	1.23 (0.62–2.43)	0.553	—	—	2.16 (1.16–4.02)	0.015
Tumor differentiation									
Good or moderate	25/1,234	1	—	—	—	—	—	—	—
vs. Poor	14/181	4.15 (2.16–7.99)	<0.001	1.08 (0.44–2.65)	0.868	—	—	1.0 (0.44–2.25)	0.992
Desmoplastic growth									
Absent	22/1,292	1	—	—	—	—	—	—	—
vs. Present	17/138	7.77 (4.12–14.68)	<0.001	5.14 (2.67–10.15)	<0.001	5.14 (2.68–9.83)	<0.001	—	—
Tumor site									
Other	32/1,136	1	—	—	—	—	—	—	—
vs. Ear	6/206	1.01 (0.42–2.40)	0.991	1.01 (0.20–5.08)	0.988	—	—	—	—
vs. Lip	2/92	0.59 (0.14–2.48)	0.473	0.99 (0.23–4.19)	0.984	—	—	—	—
>1 cSCC									
No	28/1,156	—	—	—	—	—	—	—	—
vs. Yes	2/92	1.55 (0.79–3.05)	0.205	1.07 (0.53–2.14)	0.858	—	—	—	—
Immunosuppression									
No	28/1,263	1	—	—	—	—	—	—	—
vs. Yes	12/171	3.32 (1.69–6.53)	<0.001	2.04 (1.01–4.13)	0.047	2.07 (1.04–4.12)	0.039	—	—
C-Index	—	—	—	0.828	—	0.835	—	0.573	—

Abbreviations: CI, confidence interval; HR, hazard ratio; TNM, tumor node metastases.

- Variedad desmoplásica se relaciona con baja supervivencia





J Cutan Pathol 2008: 35: 353–357
doi: 10.1111/j.1600-0560.2007.00808.x
Blackwell Munksgaard. Printed in Singapore

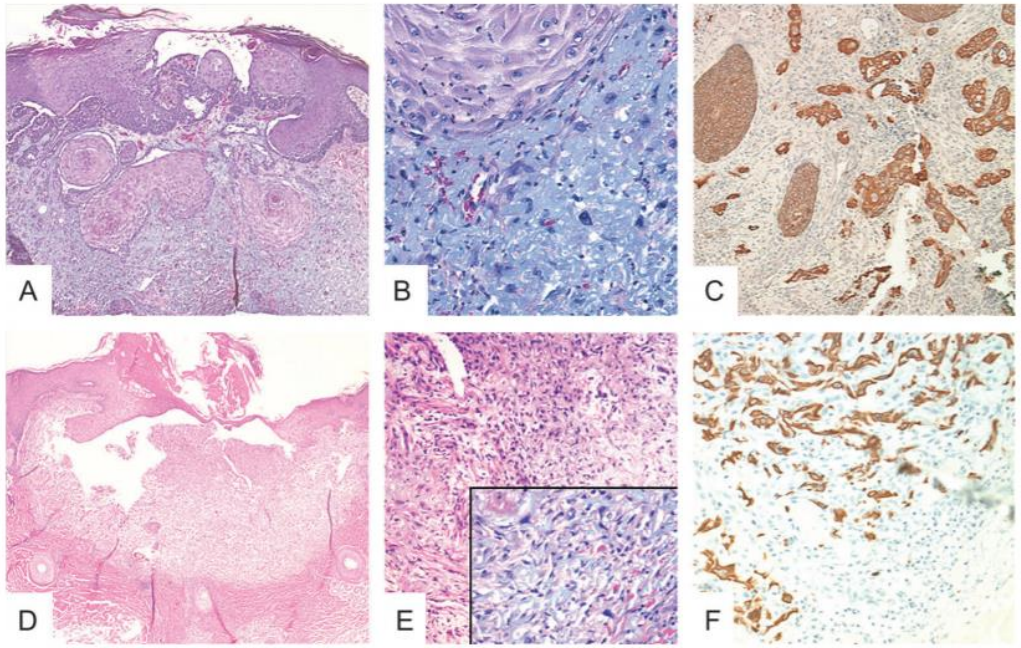
Journal of
Cutaneous Pathology

Squamous cell carcinomas with single cell infiltration: a potential diagnostic pitfall and the utility of MNF116 and p63

Numerous variants of squamous cell carcinoma (SCC) have been described. We recently encountered four examples of SCC composed

Christine J. Ko[1,2], Jennifer M. McNiff[1,2] and Earl J. Glusac[1,2]

Frente de infiltración formado por células aisladas
Generalmente localizado en la cara y el cuello
Más agresivo
Peor delimitación lateral



ases 6 (A–C) and 8 (D–F) showing well-differentiated and spindle cell squamous cell carcinoma, respectively, with peripheral s
tration highlighted by MNF116.

J Cutan Pathol 2016
doi: 10.1111/cup.12740
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

Tumor budding is an independent risk factor for lymph node metastasis in cutaneous squamous cell carcinoma: a single center retrospective study

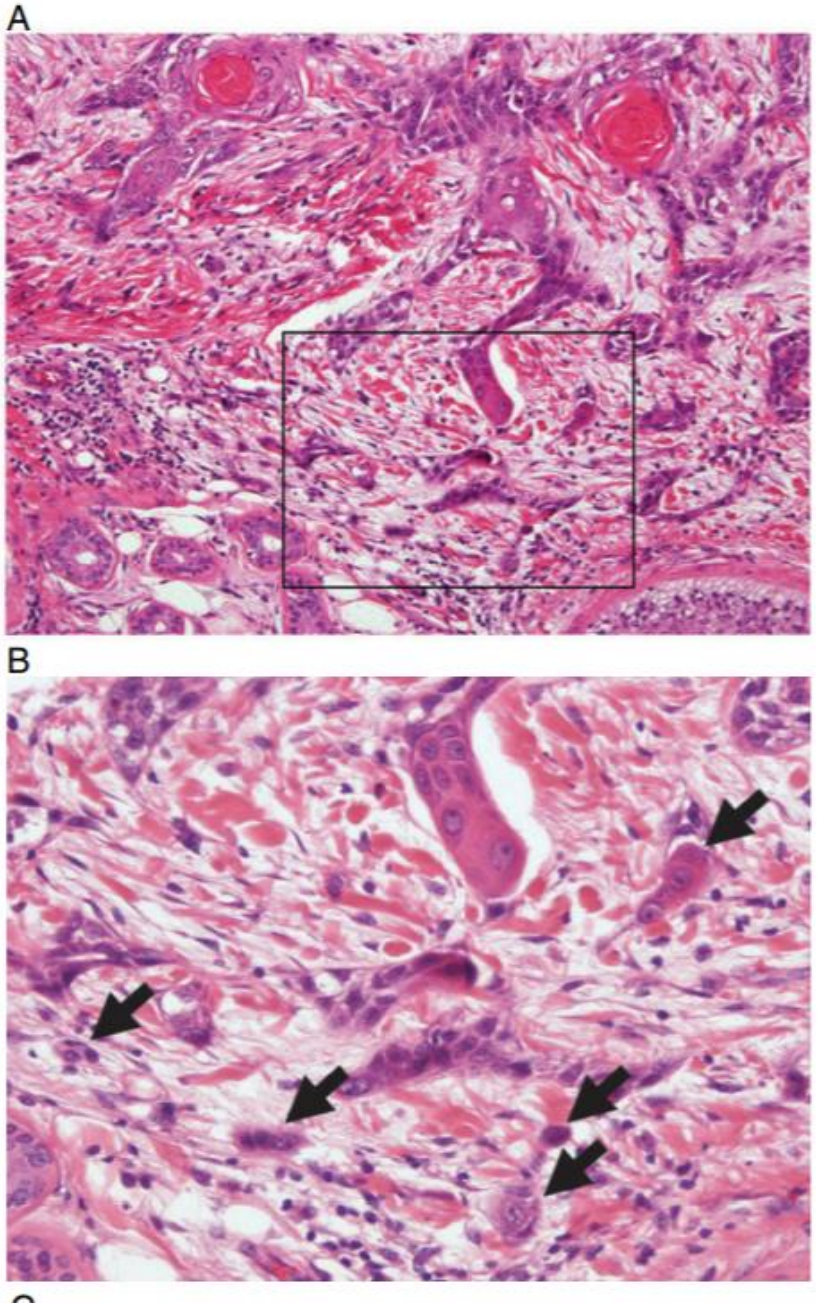
Background Although tumor budding is acknowledged as a risk factor for lymph node metastasis in certain types of carcinoma, it

Masakazu Fujimoto[1], Yuki Yamamoto[2], Ibu Matsuzaki[1]

Tumor budding in skin squamous cell carcinoma

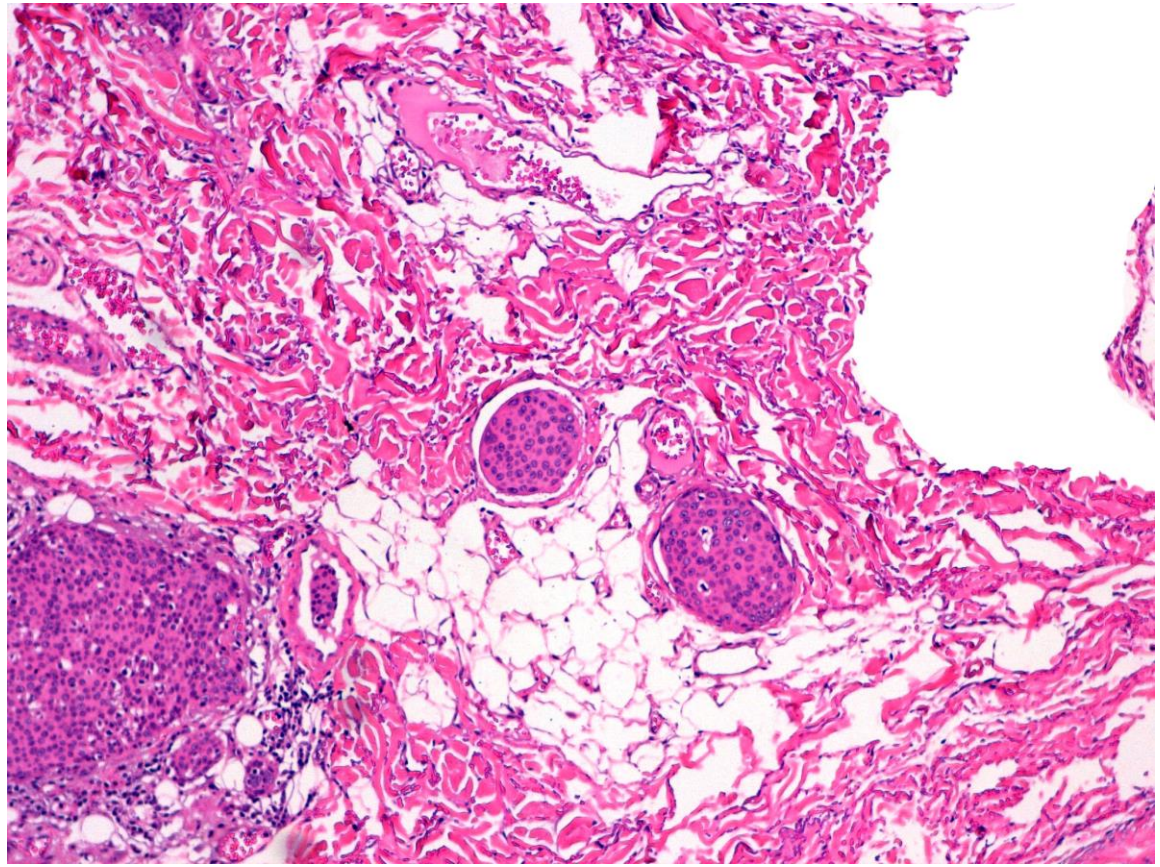
Table 1. Characteristics and statistical comparison of the primary cutaneous SCC with and without lymph node metastasis.

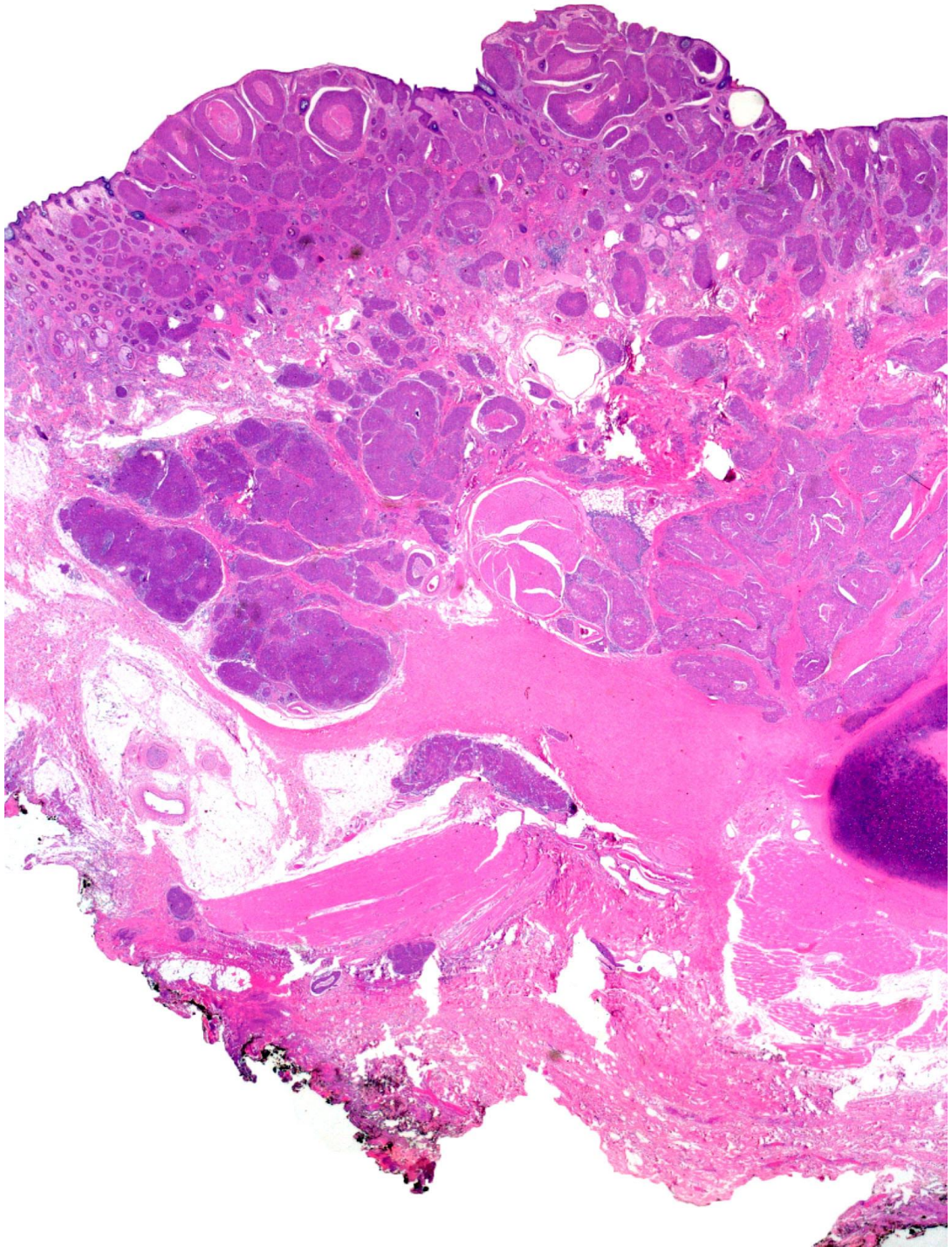
				Fisher's exact test			Multivariate logistic regression analysis		
Variable		N	%	MSCC (n = 15)	NMSCC (n = 144)	p	OR	95% CI	p
Age	>80	87	54.7	6	81	0.28			
	≤80	72	45.3	9	63				
Gender	Male	87	54.7	7	80	0.59			
	Female	72	45.3	8	64				
Primary site	Ear or hair-bearing lip	14	8.8	0	14	0.06			
	The other head and neck	78	49.1	5	73				
	Extremities	53	33.3	6	47				
	Trunk	14	8.8	4	10				
Tumor size	>2 cm	57	35.8	12	45	0.0003*	3.97	0.86–25.03	0.08
	<2 cm	102	64.2	3	99				
Tumor budding	Positive	51	32.1	14	37	< 0.0001*	16.93	2.53–340.43	0.0021*
	Negative	108	68.8	1	107				
Tumor thickness	>2 mm	126	79.2	15	111	0.042*			
	>3 mm	89	56	15	74	0.0001*			
	>4 mm	68	42.8	14	54	< 0.0001*	2.82	0.22–72.10	0.43
	>5 mm	52	32.7	11	41	0.0009*			
Clark level	≥IV	123	77.4	15	108	0.0237*			
	V	49	30.8	12	37	< 0.0001*	1.72	0.32–10.67	0.53
Invasion beyond the subcutaneous fat	Present	12	7.5	2	10	0.32			
	Absent	147	92.5	13	134				
Histology	Conventional SCC	154	96.7	15	139	1.00			
	Non-conventional SCC	5	3.1	0	5				
Tumor differentiation	Poor	17	10.7	6	11	0.0017*	1.99	0.46–8.69	0.35
	Well to moderate	142	89.3	9	133				
Perineural invasion	Present	8	5	1	7	0.56			
	Absent	151	95	14	137				
Tumor stage (AJCC-7)	pT1	38	23.9	0	38	0.0227*			
	pT2	121	76.1	15	106				

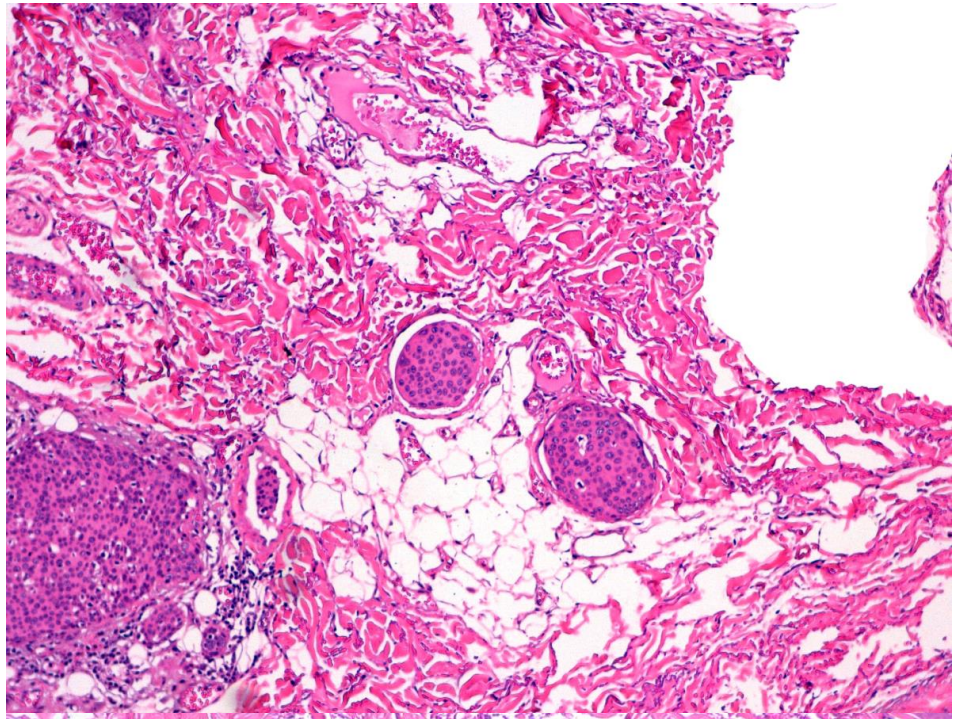


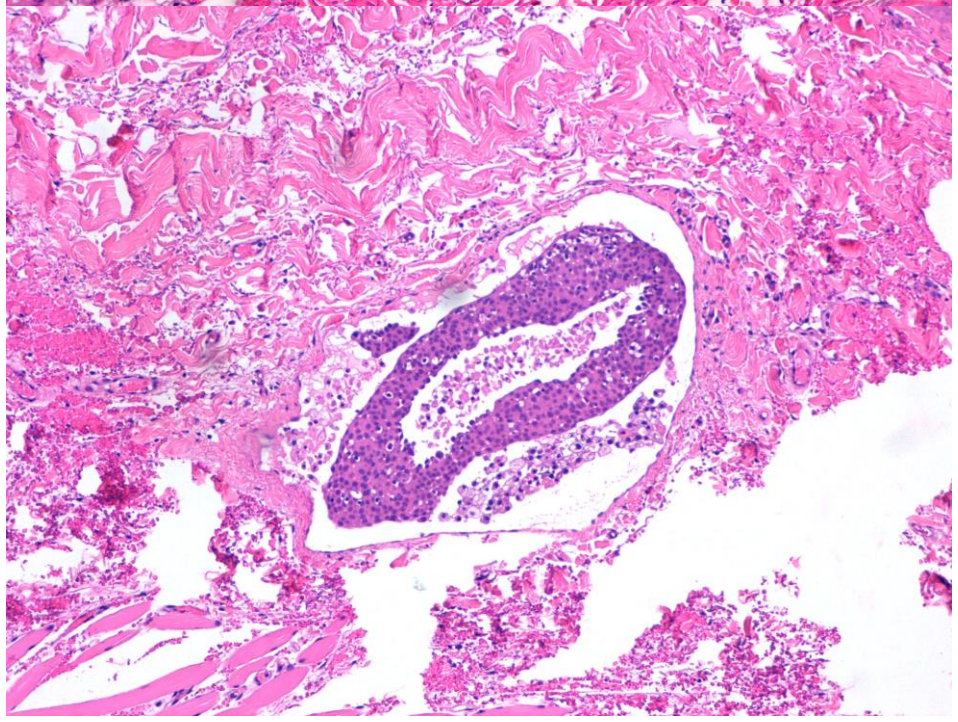
Invasión intravascular

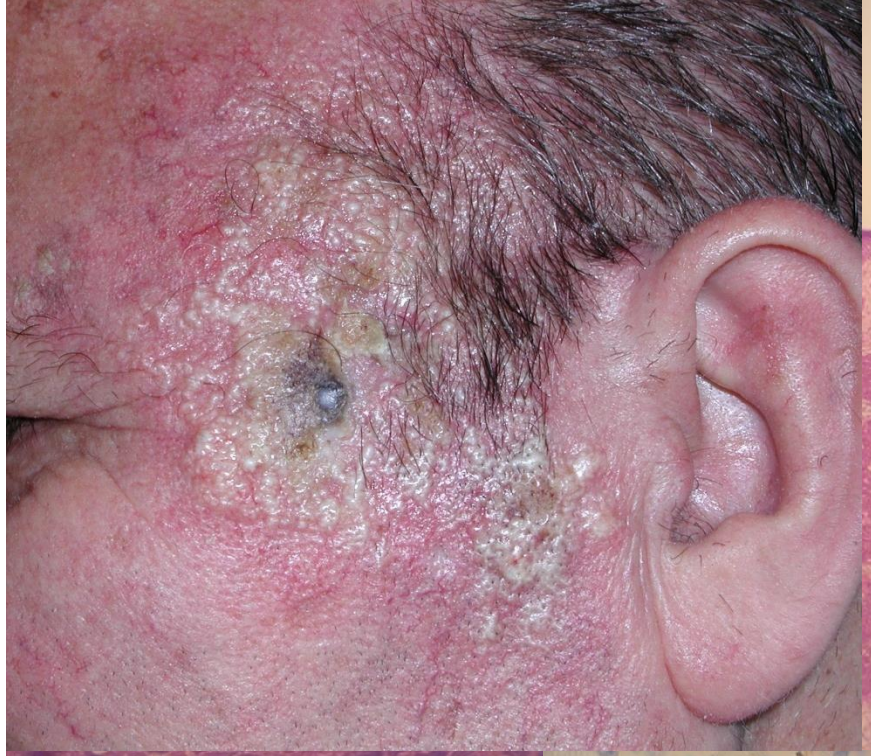
-naturaleza tumoral más agresiva
-mayor incidencia de metástasis, recurrencia local -Generalmente linfáticos cervicales
-solo un 34,4% de tasa de curación

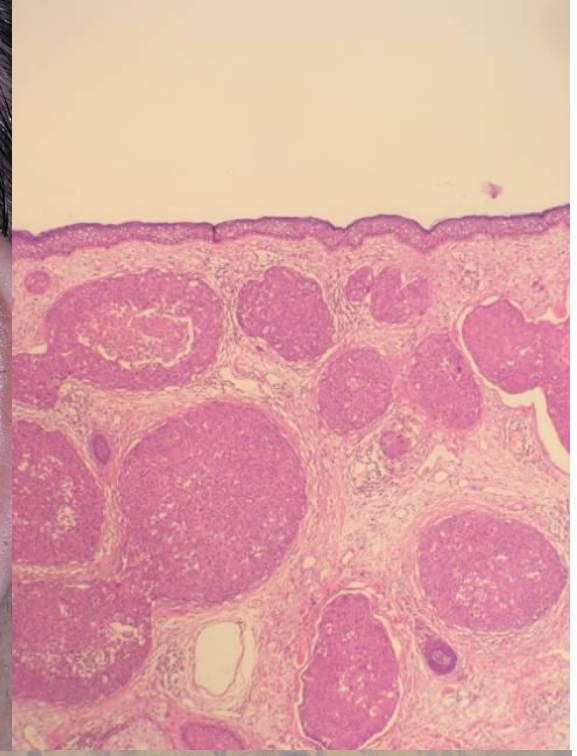


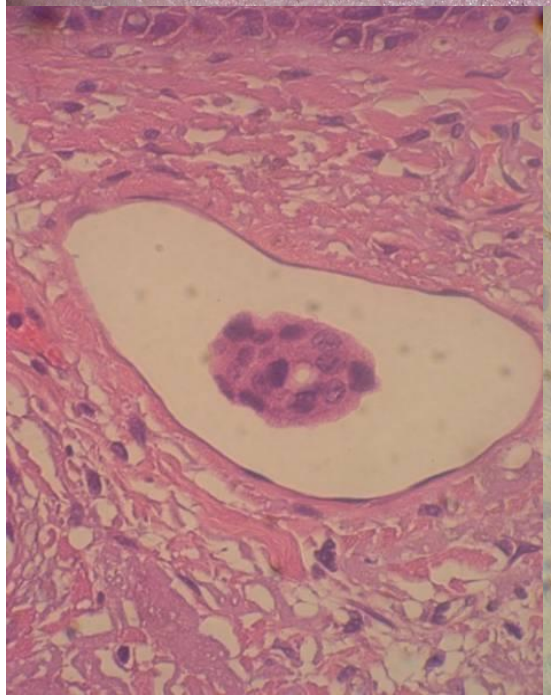


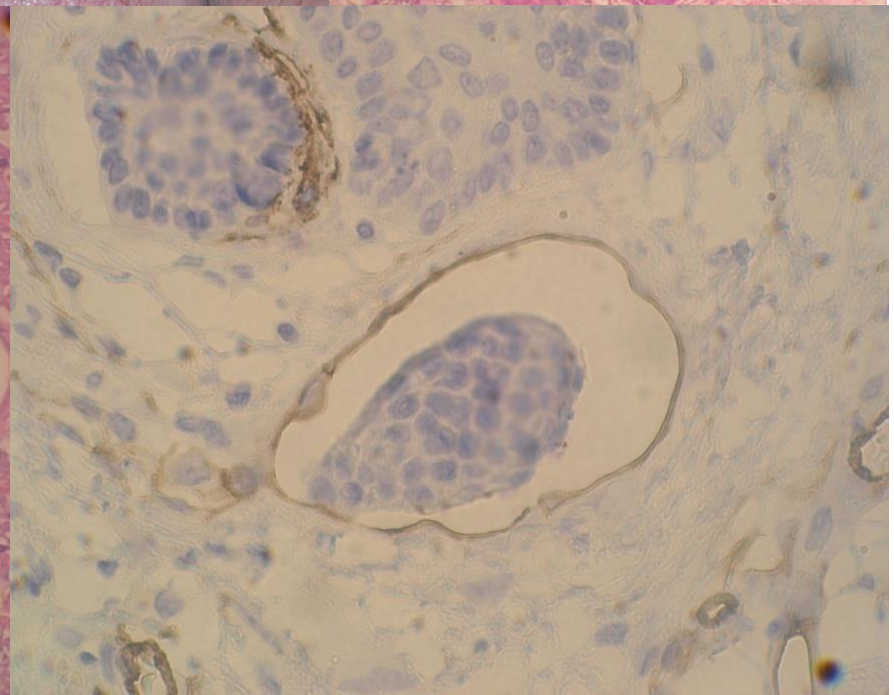












Invasión linfovascular se relaciona con riesgo de extensión nodal

(JAMA Otolaryngol Head Neck Surg. 2016; 1171-1176).

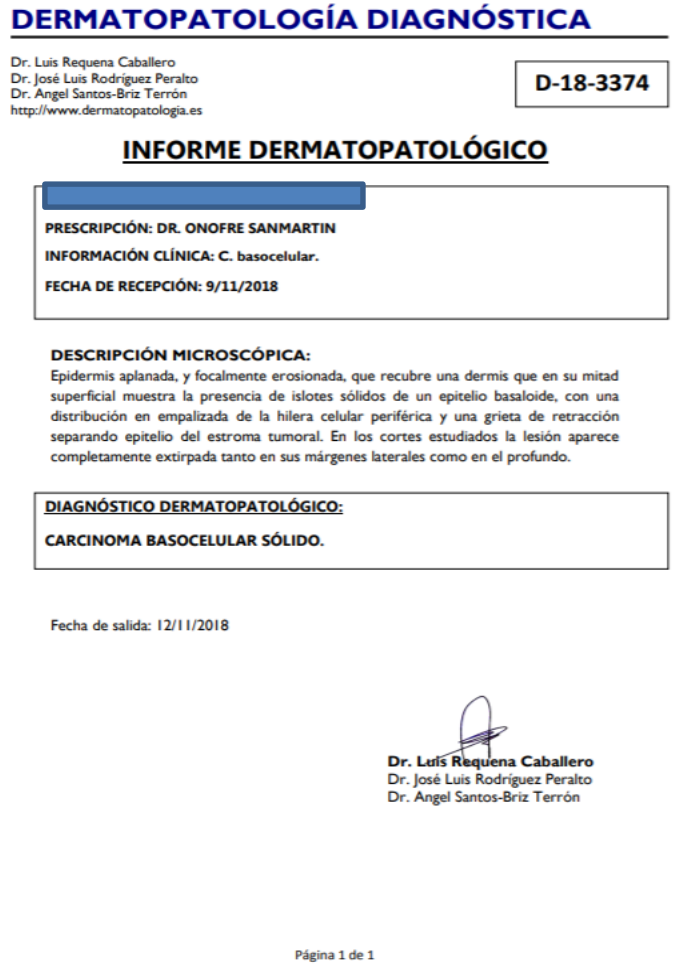
Hallazgos histológicos de riesgo en carcinoma epidermoide

- BAJO RIESGO
- Bien o moderadamente diferenciado (puentes intercelulares y perlas de queratina)
- Patrón sólido o en sábana
- QA asociada
- Tamaño menor de 4 cm
- Espesor tumoral mayor de 4 mm

- ALTO RIESGO
- Pobremente diferenciado
- Variedad desmoplásica
- Presencia de budding
- Lesión de novo (no QA asociada)
- Invasión perineural
- Invasión perivascular
- Tamaño mayor de 4 cm
- Espesor tumoral mayor de 4 mm

Requisitos en un informe histológico de carcinoma epidermoide

- Descripción de la pieza
- Tamaño tumoral
- Tipo histológico
- Grado de diferenciación
- Nivel de invasión tumoral
  - Afectación ósea
- Espesor tumoral / Invasion tumoral
- Invasion perineural
  - Diámetro del nervio afecto
- Invasión linfovascular
- Márgenes quirúrgicos



DERMATOPATOLOGÍA DIAGNÓSTICA

Dr. Luis Requena Caballero
Dr. José Luis Rodríguez Peralto
Dr. Angel Santos-Briz Terrón
http://www.dermatopatologia.es

D-18-3374

INFORME DERMATOPATOLÓGICO

[redacted]

PRESCRIPCIÓN: DR. ONOFRE SANMARTIN

INFORMACIÓN CLÍNICA: C. basocelular.

FECHA DE RECEPCIÓN: 9/11/2018

DESCRIPCIÓN MICROSCÓPICA:

Epidermis aplanada, y focalmente erosionada, que recubre una dermis que en su mitad superficial muestra la presencia de islotes sólidos de un epitelio basaloide, con una distribución en empalizada de la hilera celular periférica y una grieta de retracción separando epitelio del estroma tumoral. En los cortes estudiados la lesión aparece completamente extirpada tanto en sus márgenes laterales como en el profundo.

DIAGNÓSTICO DERMATOPATOLÓGICO:

CARCINOMA BASOCELULAR SÓLIDO.

Fecha de salida: 12/11/2018

Dr. Luis Requena Caballero
Dr. José Luis Rodríguez Peralto
Dr. Angel Santos-Briz Terrón

Página 1 de 1

STUDY

Evaluation of AJCC Tumor Staging for Cutaneous Squamous Cell Carcinoma and a Proposed Alternative Tumor Staging System

Anokhi Jambusaria-Pahlajani, MD, MSCE; Peter A. Kanetsky, PhD, MPH; Pritesh S. Karia, MPH; Wei-Ting Hwang, PhD; Joel M. Gelfand, MD, MSCE; Faith M. Whalen, MD; Rosalie Elenitsas, MD; Xiaowei Xu, MD, PhD; Chrysalyne D. Schmults, MD, MSCE

Importance: This study proposes an alternative tumor staging system for cutaneous squamous cell carcinoma (CSCC) that more precisely defines the small subset of tumors with a high risk of metastasis and death.

Objective: To identify risk factors for poor outcomes in CSCC and evaluate the 2010 American Joint Committee on Cancer (AJCC) tumor (T) staging system's ability to stratify occurrence of these outcomes.

Design: Retrospective cohort study.

Setting: A single academic hospital.

Participants: Study participants were identified via a pathology and dermatopathology database search for patients diagnosed as having high-risk CSCC.

Results: Two hundred fifty-six primary high-risk CSCCs were included. Outcomes for AJCC tumor stages T2 to T4 were statistically indistinguishable because only 4 cases (<2% of the cohort) were AJCC stages T3 or T4, which require bone invasion. Subsequently, the bulk of poor outcomes (83% of nodal metastases, 92% of deaths from CSCC) occurred in AJCC stage T2 cases. An alternative tumor staging system was developed with the aim of better stratifying this stage T2 group. Four risk factors were found to be statistically independent prognostic factors for at least 2 outcomes of interest in multivariate modeling. These factors (poor differentiation, perineural invasion, tumor diameter ≥2 cm, invasion beyond subcutaneous fat) were incorporated in the alternative staging with 0 factors indicating T1, 1 factor indicating T2a; 2 to 3 factors, T2b; and 4 factors or bone invasion, T3. Stages T2a and T2b significantly differed in incidences of all 4 end points. Stage T2b tumors comprised only 19% of the cohort but accounted for 72% of nodal metastases and 83% of deaths from CSCC.

Conclusions and Relevance: The proposed alternative tumor staging system offers improved prognostic discrimination via stratification of stage T2 tumors. Validation in other cohorts is needed. Meanwhile, stage T2b tumors are responsible for most poor outcomes and may be a focus of high-risk CSCC study.

JAMA Dermatol. 2013;149(4):402-410.
Published online January 16, 2013.
doi:10.1001/jamadermatol.2013.2456

Jambusaria- Pahlajani A et al.

Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system.

Department of Dermatology, Mayo Clinic Florida, Jacksonville, USA.

JAMA Dermatol. 2013 Apr;149(4):402-10.

- To identify risk factors for poor outcomes in CSCC and evaluate the AJCC staging system's ability to stratify occurrence of these outcomes.
- 2056 primay high-risk scc included. Retrospective cohort study
- Outcomes for AJCC tumor stages T2 to T4 were statistically indistinguishable because only 4 cases (<2% of the cohort) were AJCC stages T3 or T4, which require bone invasion.
- **The bulk of poor outcomes (83% of nodal metastases, 92% of deaths from CSCC) occurred in AJCC stage T2 cases.**
- Alternative tumor staging system was developed with the aim of better stratifying this stage T2 group.
- Four risk factors were found to be statistically independent prognostic factors in multivariate modeling.

Table 2. Fully Adjusted Multivariate Models for Each Outcome of Interest

Tumor Characteristic	SHR (95% CI)			All-Cause Death, HR (95% CI)
	Local Recurrence	Nodal Metastasis	Disease-Specific Death	
Poorly differentiated	2.5 (0.8-7.5)[a]	3.3 (1.4-7.8)	4.1 (1.1-14.9)	1.9 (1.1-3.3)
Diameter ≥2 cm	4.2 (1.4-13.3)	NS	3.7 (0.9-15.1)[a]	2.6 (1.5-4.3)
PNI	NS	2.2 (0.9-5.1)[a]	3.4 (0.9-13.3)[a]	NS
Depth beyond subcutaneous fat	NS	7.2 (3.1-17.1)	4.1 (1.3-13.4)	NS
Immunosuppression	3.5 (1.2-10.7)	NS	NS	NS

Abbreviations: HR, hazard ratio; NS, not significant; PNI, perineural invasion; SHR, subhazard ratio.
[a]The variable was included in final multivariate model (although 95% confidence interval included 1) because addition of the variable changed the SHR by at least10%, and the variable is considered clinically relevant in cutaneous squamous cell carcinoma outcomes (see "Methods" section).

Table 3. Alternative T Staging System

Alternative T Staging System	Definition	Patients in Study Cohort, No. (%)
T0	In situ SCC	Not included
T1	0 Risk factors[a]	134 (52)
T2a	1 Risk factor[a]	67 (26)
T2b	2-3 Risk factors[a]	49 (19)
T3	4 Risk factors[a] or bone invasion	6 (2)

[a]Risk factors include tumor diameter 2 cm or greater, poorly differentiated histologic characteristics, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone invasion, which automatically upgrades tumor to alternative stage T3).

Jambusaria- Pahlajani A et al.

Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system.

Department of Dermatology, Mayo Clinic Florida, Jacksonville, USA.

JAMA Dermatol. 2013 Apr;149(4):402-10.

- Risk factors: 1) poor differentiation, 2) perineural invasion, 3) tumor diameter ≥2 cm, and 4) invasion beyond subcutaneous fat
- 0 factors indicating T1,
- 1 factor indicating T2a;
- 2 to 3 factors, T2b;
- and 4 factors or bone invasion, T3.
- **Stage T2b tumors comprised only 19% of the cohort but accounted for 72% of nodal metastases and 83% of deaths from CSCC.**
- The proposed alternative tumor staging system offers improved prognostic discrimination via stratification of stage T2 tumors..

Accepted Manuscript

"Comparing the eighth and the seventh editions of the ajcc staging system and the brigham and women's hospital alternative staging system for cutaneous squamous cell carcinoma: implications for clinical practice"

J. Cañueto, MD PhD, J. Burguillo, PhD, D. Moyano-Bueno, MD, A. Viñolas-Cuadros, MD, A. Conde-Ferreirós, MD, Luis Antonio Corchete-Sánchez, J. Pérez-Losada, MD PhD, C. Román-Curto, MD PhD

- AJCC-8 es más distintivo, que el AJCC-7, y predice mejor pronóstico en CEC
- Sólo específico de cabeza y cuello
- No incluye grado de diferenciación que permite distinguir subgrupos de pacientes con mayor riesgo
- BWH mejora la precisión del AJCC-8 en la predicción de eventos negativos en el carcinoma epidermoide cutáneo

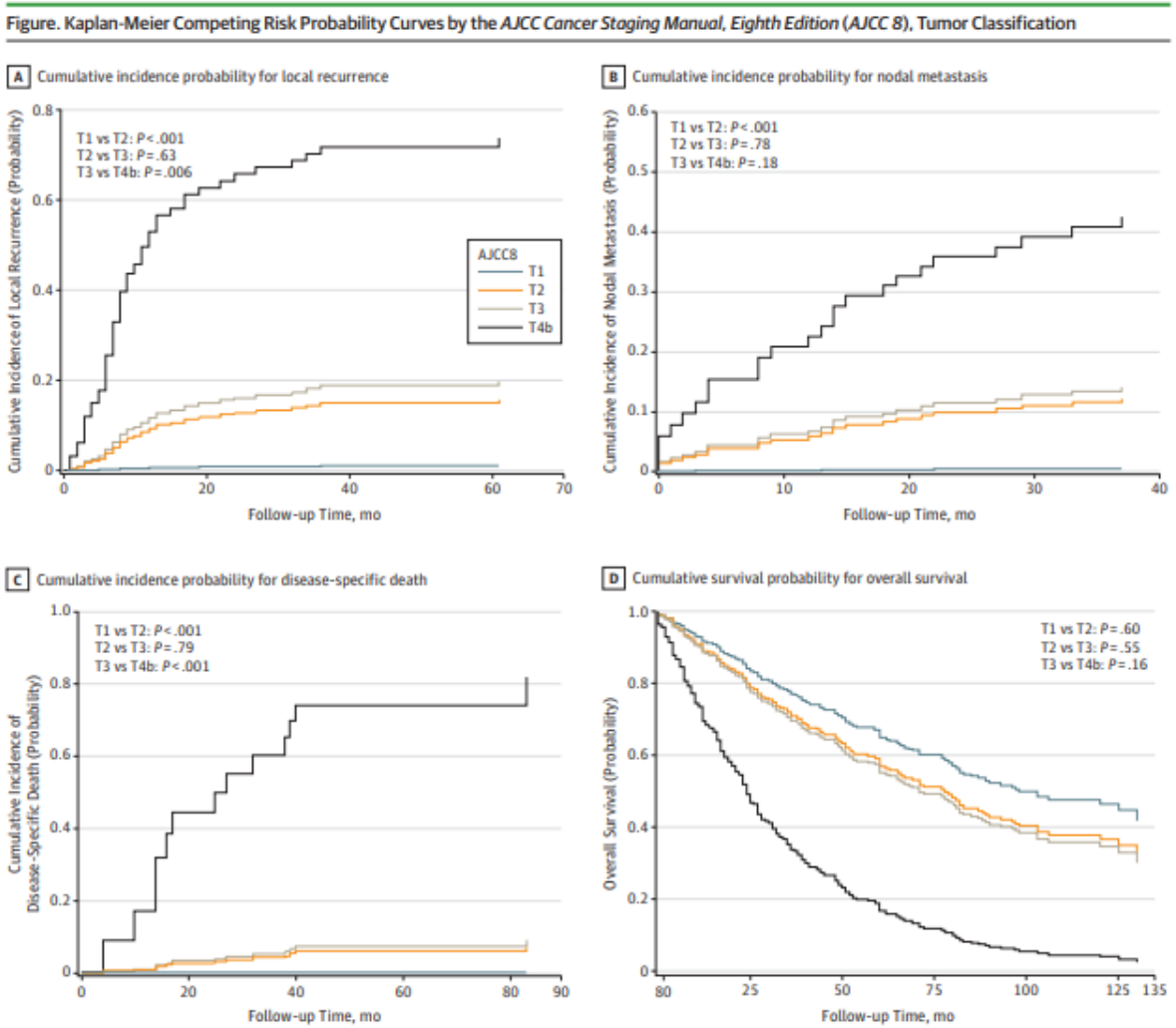
DISTINCTIVENESS AMONG STAGING SYSTEMS						
	Disease-specific poor outcome			Major events		
		Yes	No		Yes	No
AJCC-7	T1 (n=73)	11 / 73 (15.06%)	62 / 73	T1 (n=73)	3 / 73 (4.11%)	70 / 73
	T2 (n=110)	40 / 110 (36.36%)	70 / 110	T2 (n=110)	20 / 110 (18.18%)	90 / 110
	T3 (n=3)	1 / 3 (33.33%)	2 / 3	T3 (n=3)	0 / 3 (0%)	3 / 3
AJCC-8	T1 (n=78)	6 / 78 (7.69%)	72 / 78	T1 (n=78)	2 / 78 (2.56%)	76 / 78
	T2 (n=11)	2 / 11 (18.18%)	9 / 11	T2 (n=11)	1 / 11 (9.09%)	10 / 11
	T3 (n=97)	44 / 97 (45.36%)	53 / 97	T3 (n=97)	20 / 97 (20.62%)	77 / 97
BWH's	T1(n=75)	8 / 75 (10.66%)	67 / 75	T1(n=75)	3 / 75 (4 %)	72 / 75
	T2a (n=59)	17 / 59 (28.81%)	42 / 59	T2a (n=59)	6 / 59 (10.17%)	53 / 59
	T2b (n=47)	22 / 47 (46.8%)	25 / 47	T2b (n=47)	9 / 47 (19.14%)	38 / 47
	T3 (n=5)	5 / 5 (100%)	0 / 5	T3 (n=5)	5 / 5 (100 %)	0 / 5
HOMOGENEITY AMONG STAGING SYSTEMS						
	Disease-specific poor outcome (n=52)			Major events (n=23)		
AJCC-7	T1 and T2	51 of 52 (98.07%)		T1 and T2	23 of 23 (100%)	
AJCC-8	T1 and T2	8 of 52 (15.38%)		T1 and T2	3 of 23 (13.04%)	
BWH's	T1 and T2a	25 of 52 (48.07%)		T1 and T2a	9 of 23 (39.13%)	
MONOTONICITY AMONG STAGING SYSTEMS						
	Disease-specific poor outcome (n=52)			Major events (n=23)		
AJCC-7	T3	1 of 52 (1.93%)		T3	0 of 23 (0 %)	
AJCC-8	T3	44 of 52 (84.61%)		T3	20 of 23 (86.96 %)	
BWH's	T2b and T3	27 of 52 (51.93%)		T2b and T3	14 of 23 (60.86 %)	

Karia PS (Brigham and Women's Hospital, Harvard Medical School)

Comparison of Tumor Classifications for Cutaneous Squamous Cell Carcinoma of the Head and Neck in the 7th vs 8th Edition of the AJCC Cancer Staging Manual.

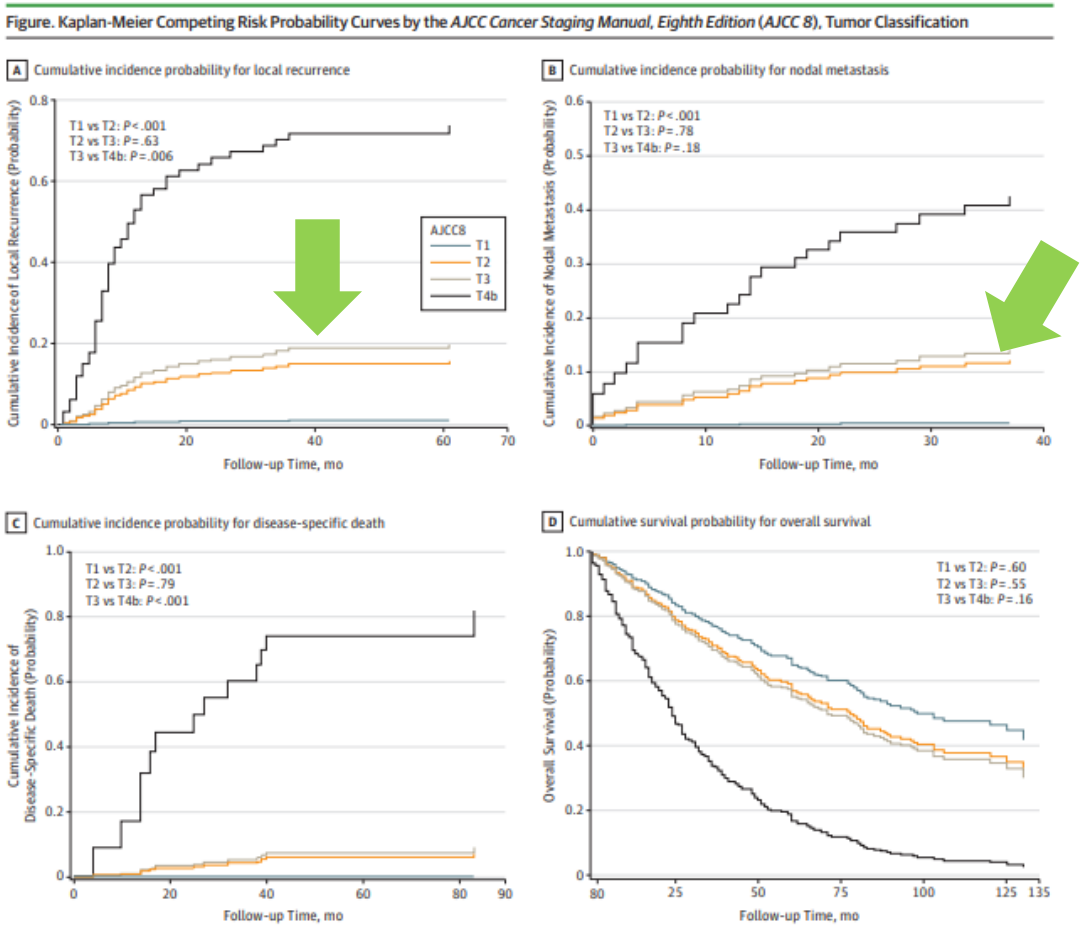
JAMA Dermatol. 2018 Feb 1;154(2):175-181

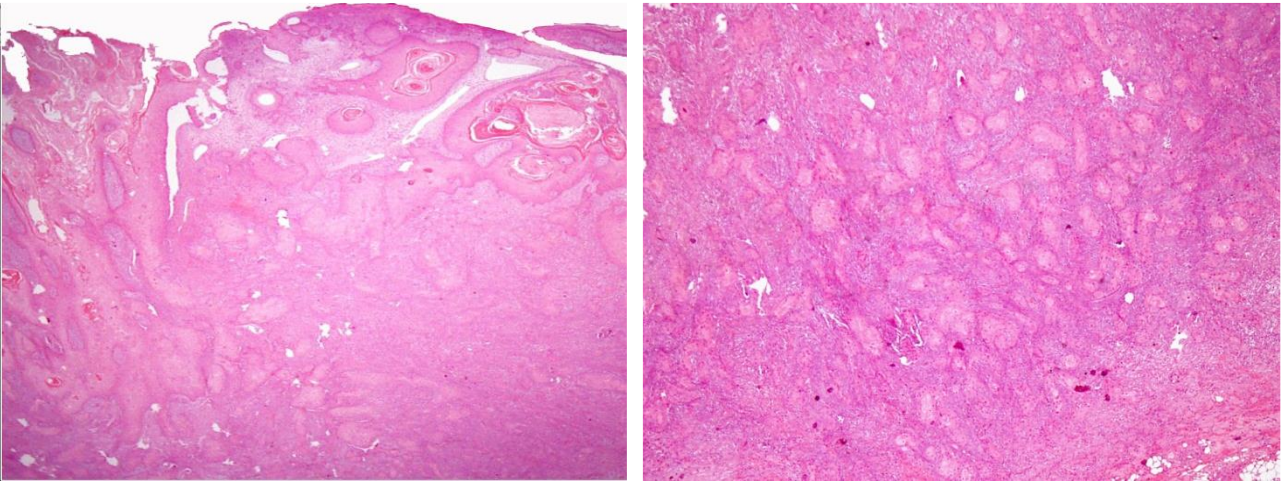
- **OBJETIVO**: comparar la clasificacion AJCC-7 y AJCC-8 en sus pacientes
- **METODOS**: Estudio retrospectivo de cohortes con 680 CEC
- **RESULTADOS**:
- La **AJCC 7 no estratifica** bien los pacientes (solo el 16% de los eventos negativos en el CEC ocurrieron en los T3 y T4.
- La **AJCC 8 estratifica mejor los casos**, el 70% de los eventos negativos ocurren en T3 y T4 y suponen solo el 17% de los casos.



Karia PS (Brigham and Women's Hospital, Harvard Medical School)
Comparison of Tumor Classifications for Cutaneous Squamous Cell Carcinoma of the Head and Neck in the 7th vs 8th Edition of the AJCC Cancer Staging Manual.
JAMA Dermatol. 2018 Feb 1;154(2):175-181

- **Sin embargo algo falla!!→no hay diferencias significativas entre T2 y T3**





No se recoge el grado de diferenciación histológico

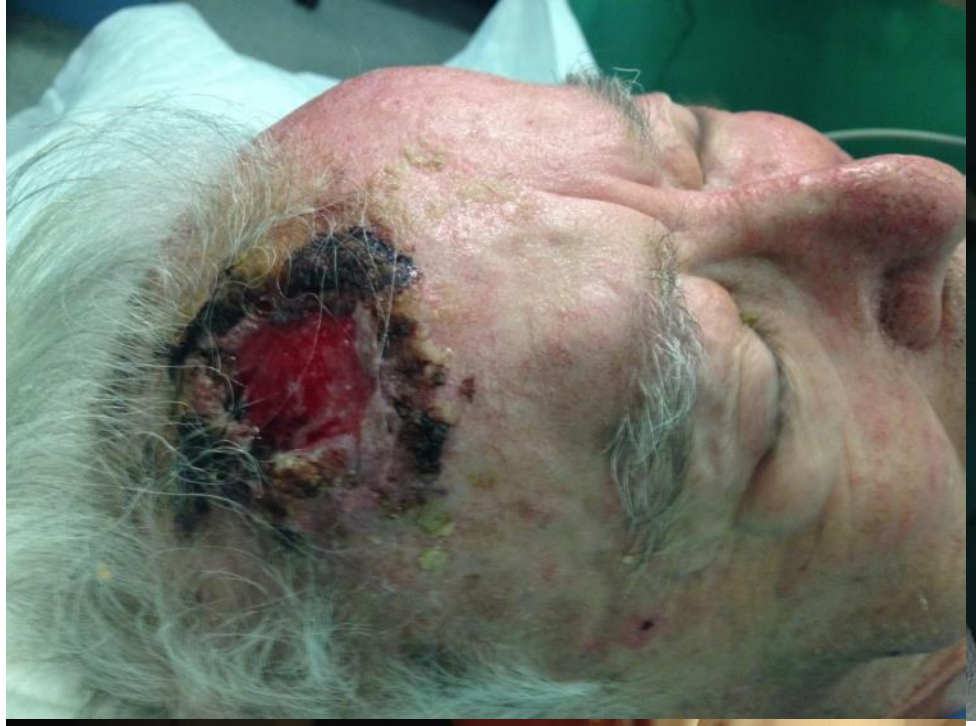
¿hacia dónde vamos en estos criterios de alto riesgo?

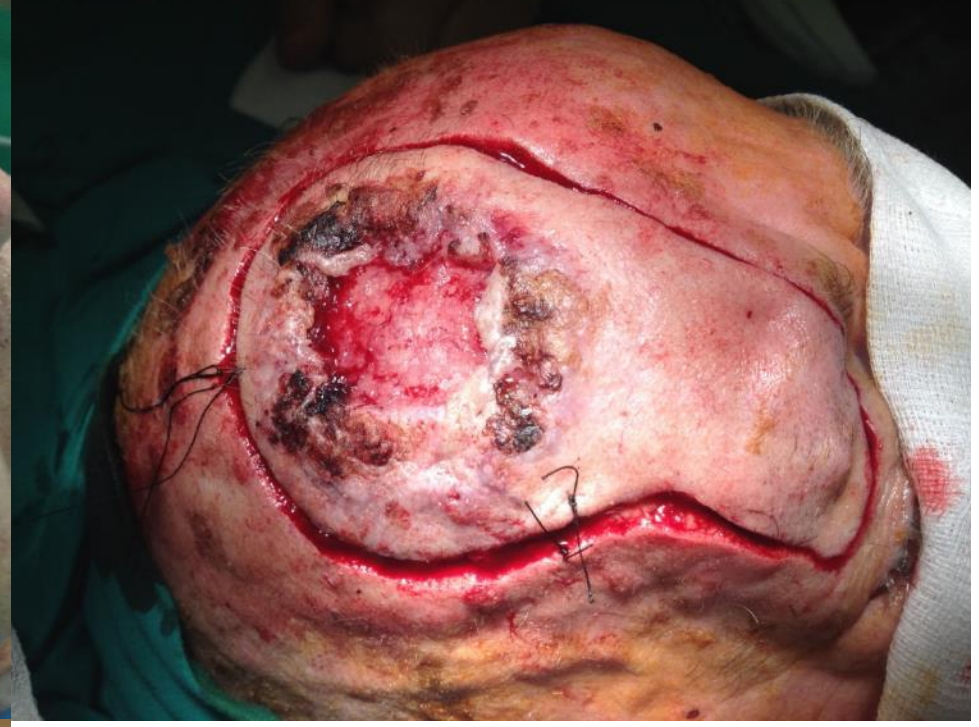
- **Schmults C. A multi-gene risk signature for improved identification of cutaneous squamous cell carcinoma (cSCC) patients with a high risk of recurrence. J Clin Oncol 36, 2018 (suppl; abstr 9577). ASCO 2018**
- **Identificacion mRNA de genes alterados previamente descritos en CEC**
- **18 genes se expresan de forma diferencia entre los tumores recurrentes y no recurrentes**
- **´Kit genético con 71% sensibilidad 90% especificidad 50% VPP y 96% VPN para recurrencia**

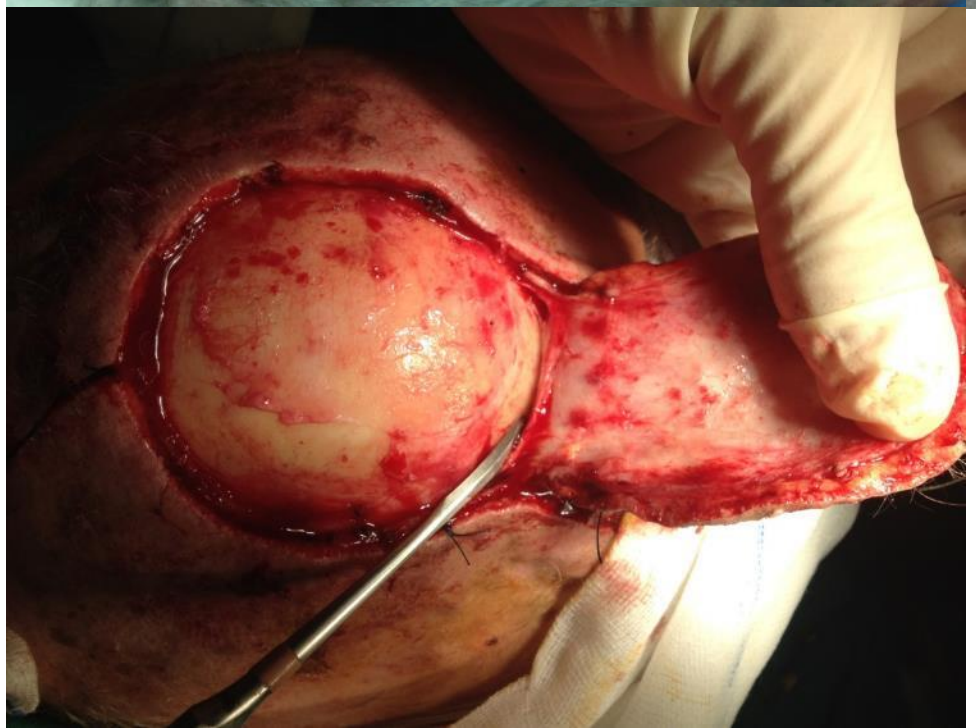
osanmartinj@gmail.com

Carcinoma escamoso cutáneo

TRATAMIENTO CECAR







- CEC de alto riesgo requiere extirpación con estudio completo de márgenes quirúrgicos **(MOHS o CIRUGIA 3D)**
- Frecuentemente PRECISA **RADIOTERAPIA ADYUVANTE**

Tratamiento mediante CMM del CECAR

- Estudio retrospectivo de 647 CECAR tratados con CMM , seguimiento medio de 37 meses
- Tasas de evolución negativa tras tratamiento con CMM en CECAR
- 19 recaidas locales (2,9%)
- 31 metastasis ganglionares (4,8%)
- 7 metastasis a distancia (1,1%)
- 7 fallecimientos por la enfermedad (1,1%)
- Dos factores se asociaron de forma significativa con la recurrencia en el estudio multivariado
  - Invasion hasta la grasa
  - Pobre diferenciacion histológica

Accepted Manuscript

Clinical outcomes in high-risk squamous cell carcinoma patients treated with Mohs micrographic surgery alone

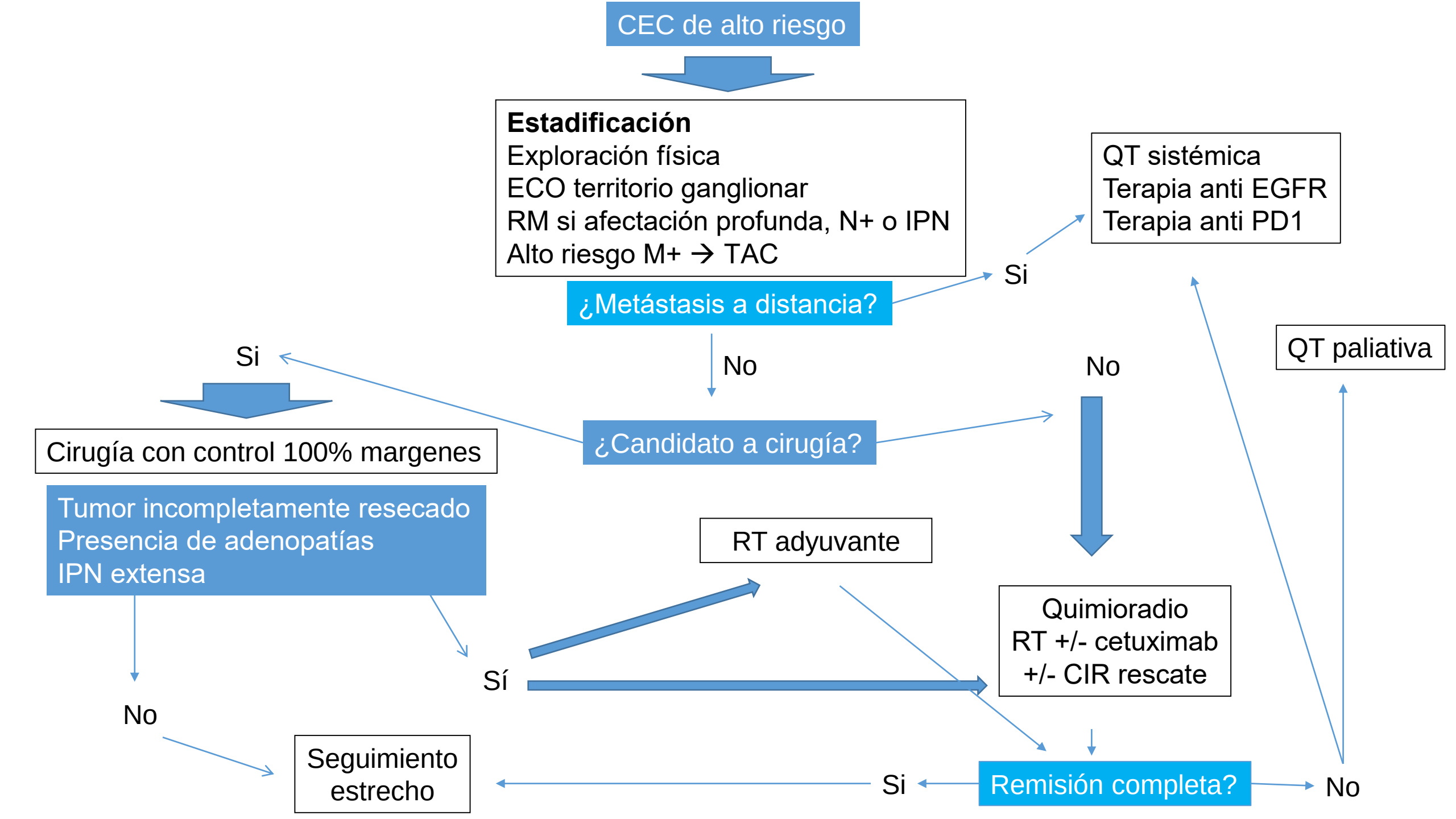
Gerardo Marrazzo, MD, John A. Zitelli, MD, David Brodland, MD

PII: S0190-9622(18)32592-1

DOI: 10.1016/j.jaad.2018.09.015

Table 4: Proportion of measured outcomes occurring within each stage (for both AJCC T stage and BWH stage)

	Number/Total Number (%)				
Stage	Number (%)	Local Recurrence	Nodal Metastasis	Distant Metastasis	Disease-Specific Death
AJCC					
T1	232 (35.9%)	1/19 (5.3%)	3/31 (9.6%)	0/7 (0%)	0/7 (0%)
T2	411 (63.5)	18/19 (94.7%)	27/31 (87.1%)	6/7 (85.7%)	7/7 (100%)
T3/T4	4 (0.6)	0/25 (0%)	1/31 (3.2%)	1/7 (14.3%)	0/7 (0%)
BWH					
T1	235 (36.3)	2/19 (10.5%)	3/31 (9.6%)	0/7 (0%)	0/7 (0%)
T2a	267 (41.3)	2/19 (10.5%)	4/31 (12.9%)	0/7 (0%)	0/7 (0%)
T2b	129 (19.9)	10/19 (52.6%)	19/31 (61.3%)	3/7 (42.9%)	4/7 (57.1%)
T3	16 (2.5)	5/19 (26.3%)	5/31 (16.1%)	4/7 (57.1%)	3/7 (42.9%)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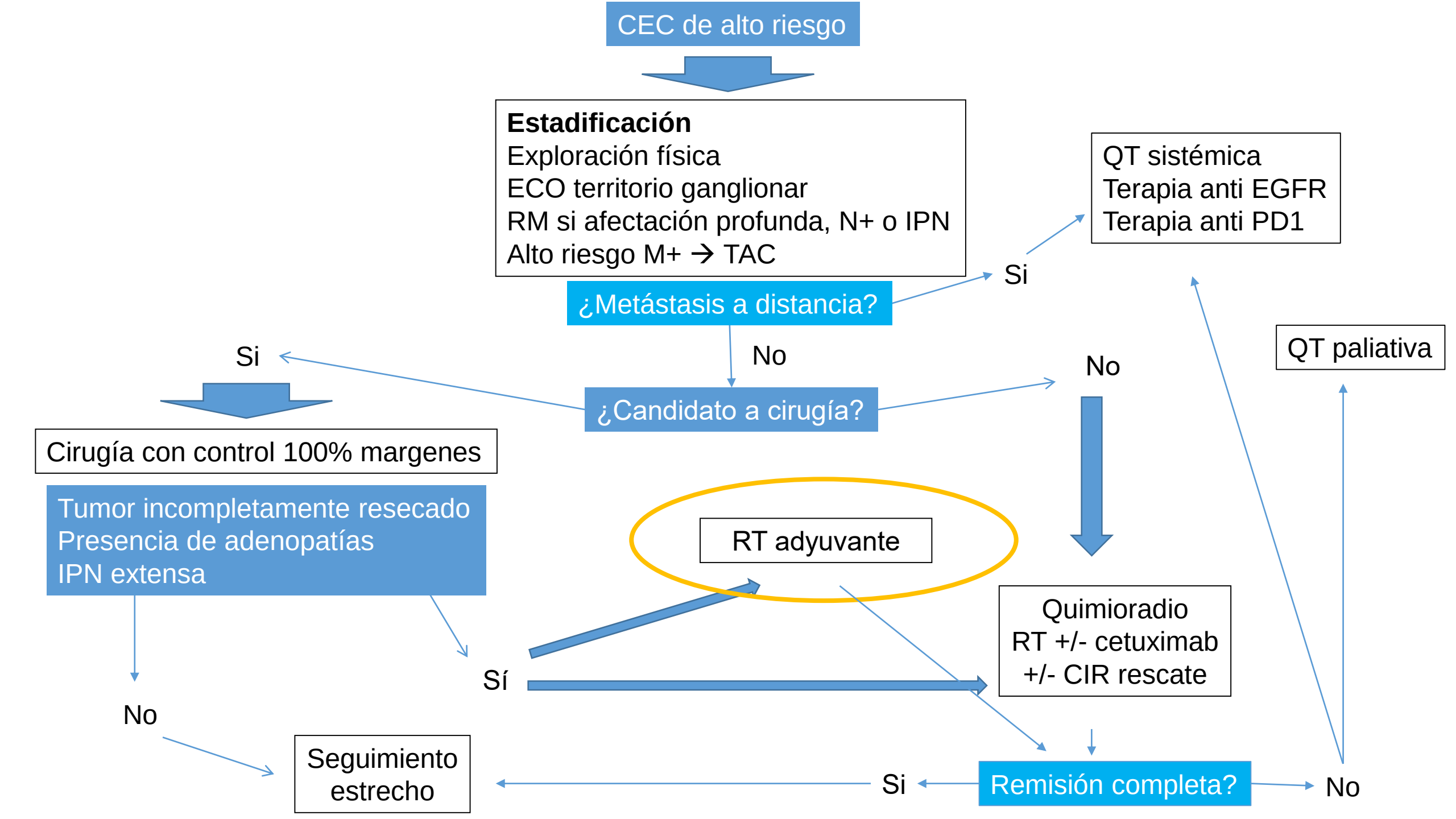
ECO territorio ganglionar
RM si afectación profunda, N+ o IPN
Alto riesgo M+ → TAC
¿Metástasis a distancia?
Si
QT sistémica
Terapia anti EGFR
Terapia anti PD1
No
Si
¿Candidato a cirugía?
No
QT paliativa
Cirugía con control 100% margenes
Tumor incompletamente resecado
Presencia de adenopatías
IPN extensa
RT adyuvante
Quimioradio
RT +/- cetuximab
+/- CIR rescate
Sí
No
Seguimiento estrecho
Si
Remisión completa?
No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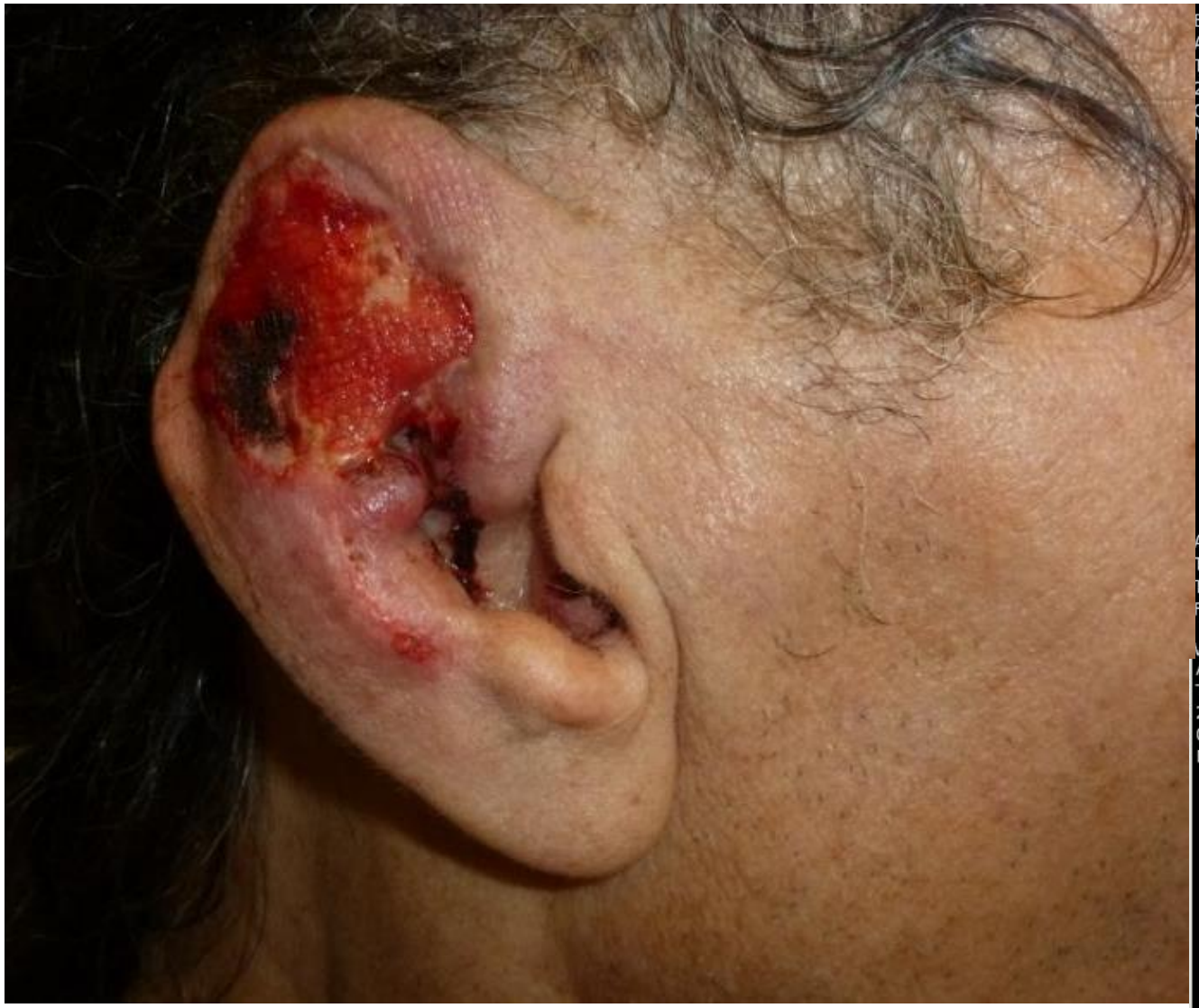
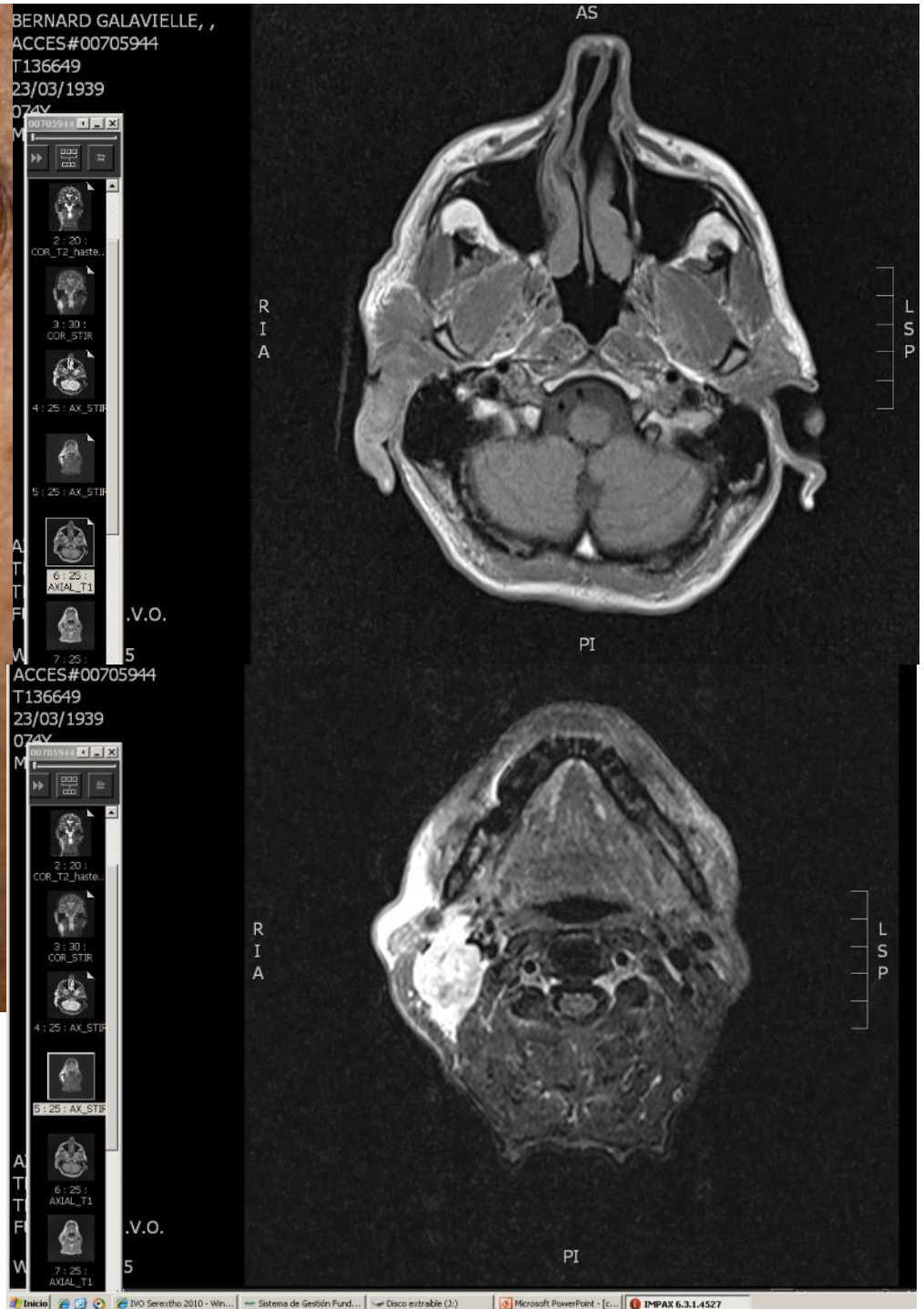


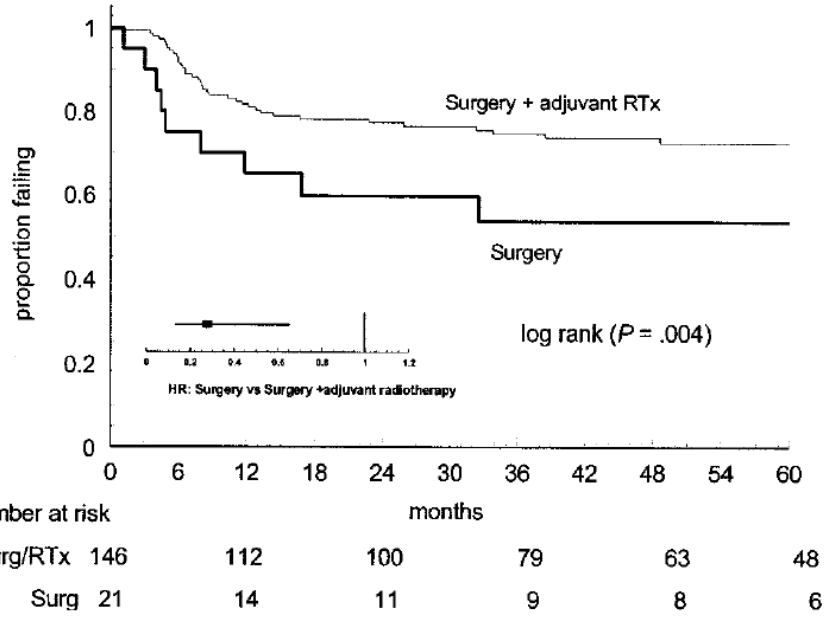


La afectación nodal requiere tratamiento quirúrgico frecuentemente completado con RT adyuvante

The Laryngoscope
Lippincott Williams & Wilkins, Inc.

Surgery and Adjuvant Radiotherapy in Patients with Cutaneous Head and Neck Squamous Cell Carcinoma Metastatic to Lymph Nodes: Combined Treatment Should be Considered Best Practice

Michael J. Veness, MMed, FRANZCR; Gary J. Morgan, FRACDS, FRACS; Carsten E. Palme, FRACS; Val Gebski, BA, MStat



- 167 pacientes con CEC y N+
- 27/167→ CIR
- 146/167 → CIR + RT adyuvante
- 28% de tasa global de recaída, generalmente locoregional (74% casos)
- 20% de recaídas en CIR + RT ---------- 43% de recaídas en CIR sola
- Significativa supervivencia libre de enfermedad superior en CIR + RT

Actitud frente a la IPN

Research

JAMA Dermatology | Original Investigation

Clinical and Incidental Perineural Invasion of Cutaneous Squamous Cell Carcinoma

A Systematic Review and Pooled Analysis of Outcomes Data

Pritesh S. Karia, MPH; Frederick C. Morgan, BSPH; Emily Stamell Ruiz, MD, MPH; Chrysalyne D. Schmults, MD, MSCE

JAMA Dermatol. 2017 Aug 1;153(8):781-788.

Table 3. Summary of Recommendations and Quality of Evidence for Included Studies

Source	Grade of Recommendation[a]	Quality of Evidence[b]	Summary of Recommendations
Clinical PNI			
Sapir et al,[33] 2016	2A	B	Adjuvant radiotherapy and posttreatment surveillance recommended after considering patient preference, age, and comorbidities
Balamucki et al,[21] 2012	2A	B	
Warren et al,[24] 2016	2A	B	
Panizza et al,[26] 2012	2A	B	
Gluck et al,[30] 2009	2A	B	
Solares et al,[27] 2012	2B	C	
Incidential PNI			
Kropp et al,[25] 2013	2A	B	Small-caliber PNI (<0.1 mm): adjuvant radiotherapy and posttreatment surveillance not recommended; large-caliber PNI (≥0.1 mm): adjuvant radiotherapy and posttreatment surveillance recommended after considering patient preference, age, and comorbidities
Carter et al,[10] 2013	2A	B	
Balamucki et al,[21] 2012	2A	B	
Lin et al,[28] 2012	2A	B	
DeAmbrosis et al,[29] 2010	2B	C	
Geist et al,[31] 2008	2B	C	
Ampil et al,[32] 1995	2B	C	

Abbreviation: PNI, perineural invasion.

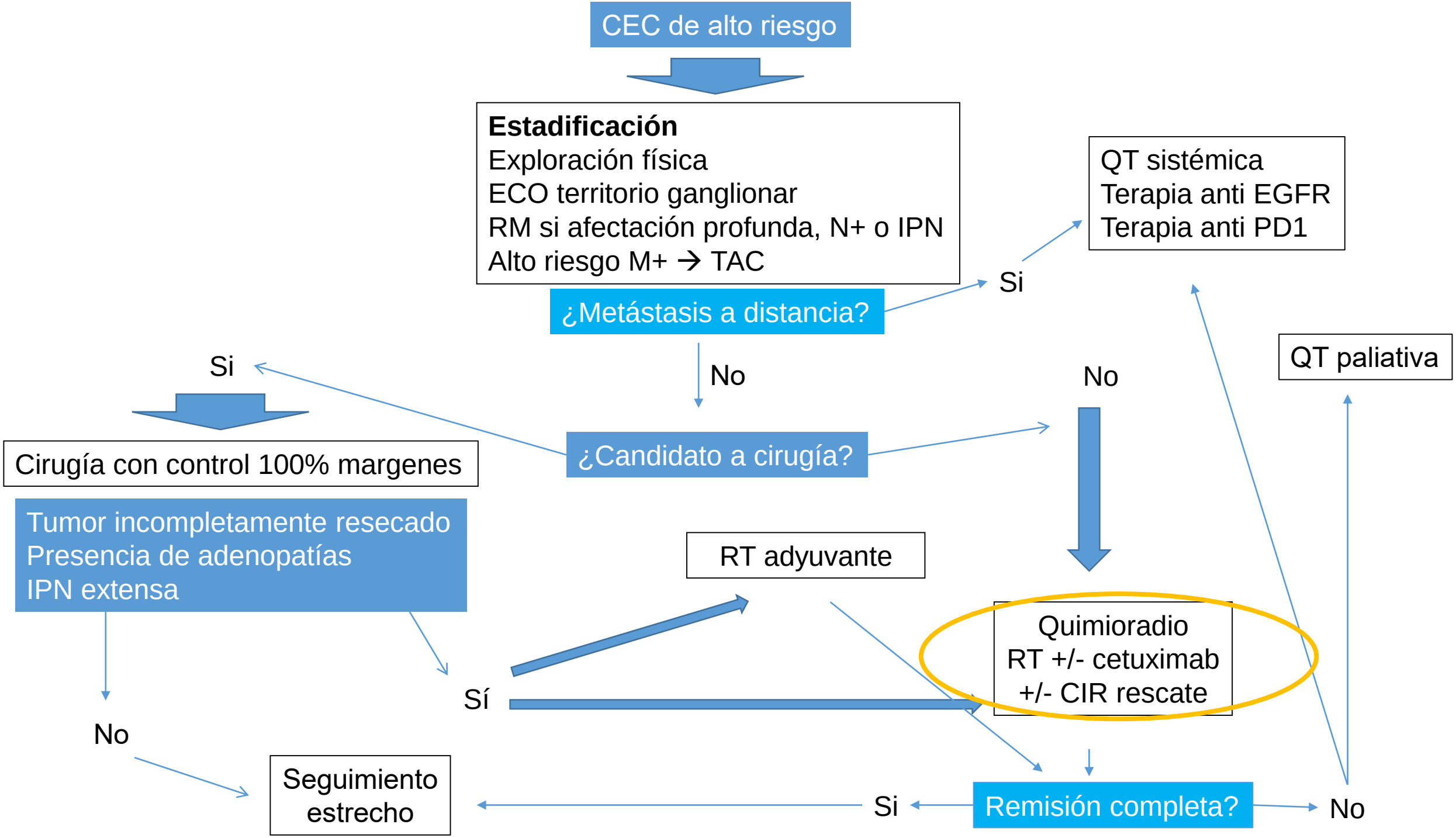
[a] Based on Robinson et al,[34] in which 1 indicates strong recommendation and high-quality, patient-oriented evidence; 2A, weak recommendation and limited-quality, patient-oriented evidence; and 2B, weak recommendation and low-quality evidence.

[b] A indicates systematic review or meta-analysis of good-quality cohort studies that can apply to most patients; B, systematic review or meta-analysis of lower-quality cohort studies with inconsistent results that may vary depending on circumstances, patients, or societal values; retrospective cohort studies; case-control studies; and C, consensus guidelines, usual practice, expert opinion, and case series.

Radioterapia adyuvante en CEC avanzado

- Parece útil en:
- Imposibilidad de obtención de márgenes negativos
- Presencia de invasión perineural significativa
- Afectación parotídea extensa
- Afectación nodal
- Dosis recomendada 45–55 Gy en fracciones de 2.0–2.5 Gy.
- **Cuando exista resto tumoral importante**→ Quimio-radio

Stratigos et al. / European Journal of Cancer 51 (2015) 1989–2007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Alto riesgo M+ → TAC
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Terapia anti EGFR
Terapia anti PD1
No
Si
¿Candidato a cirugía?
Cirugía con control 100% margenes
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QT paliativa
Tumor incompletamente resecado
Presencia de adenopatías
IPN extensa
RT adyuvante
Sí
Quimioradio
RT +/- cetuximab
+/- CIR rescate
No
Seguimiento estrecho
Si
Remisión completa?
No

Quimio-RT en CEC avanzado

- Regímenes basados en platinos
- Regímenes basados en cetuximab

Quimio-radioterapia en CEC localmente avanzado

- Estudio prospectivo
- 19 pacientes evaluables con enfermedad local o locoregional avanzada
- Radioterapia + Cisplatino / Carboplatino
- 70 Gy en 35 fracciones
- Cisplatino semanal a dosis de 40mg/m2
- 10 respuestas completas
- 2 respuestas parciales con rescate quirúrgico
- ORR del 63%
- Todos los pacientes con enfermedad residual fallecieron por la enfermedad
- Tras seguimiento medio de 40 meses, 2 recaídas

ORIGINAL ARTICLE

Prospective study of definitive chemoradiation in locally or regionally advanced squamous cell carcinoma of the skin

Michelle K. Nottage, MBChB,[1]* Charles Lin, MBBS,[1] Brett G. M. Hughes, MBBS (Hons),[1,2] Lizbeth Kenny, MBBS,[1,2] David D. Smith, PhD,[3] Kathleen Houston, MBChB,[1,2] Alessandra Francesconi, MBBS[1,2]

[1]Cancer Care Services, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia, [2]The School of Medicine, University of Queensland, Herston, Australia, [3]Queensland Institute of Medical Research, Herston, Queensland, Australia.

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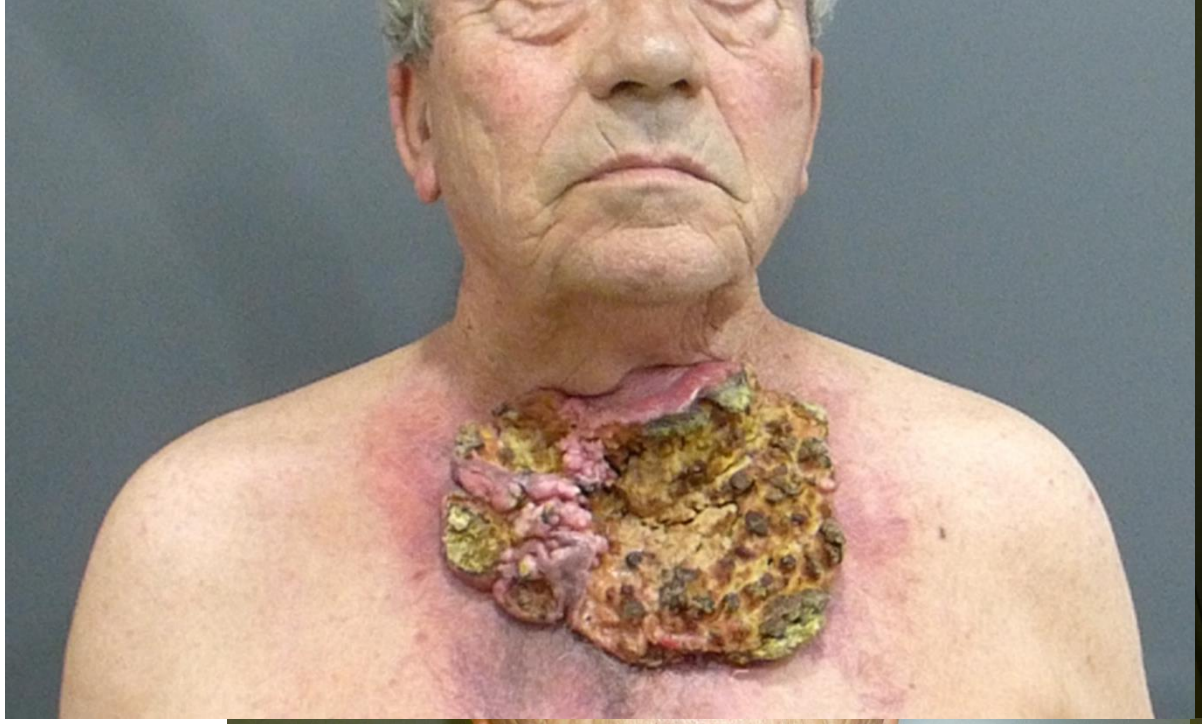
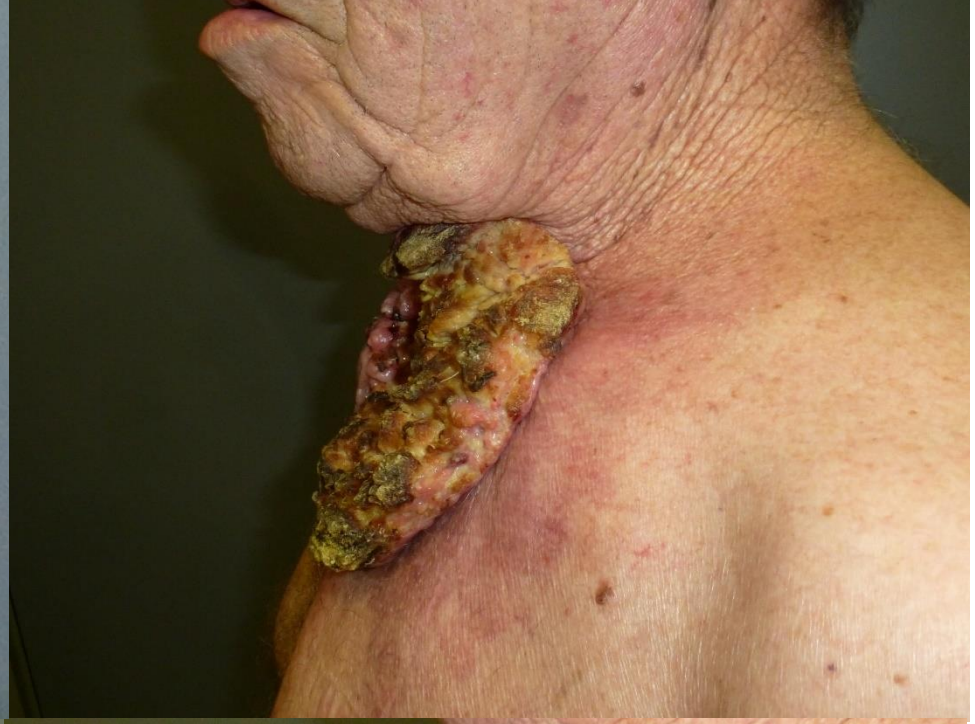
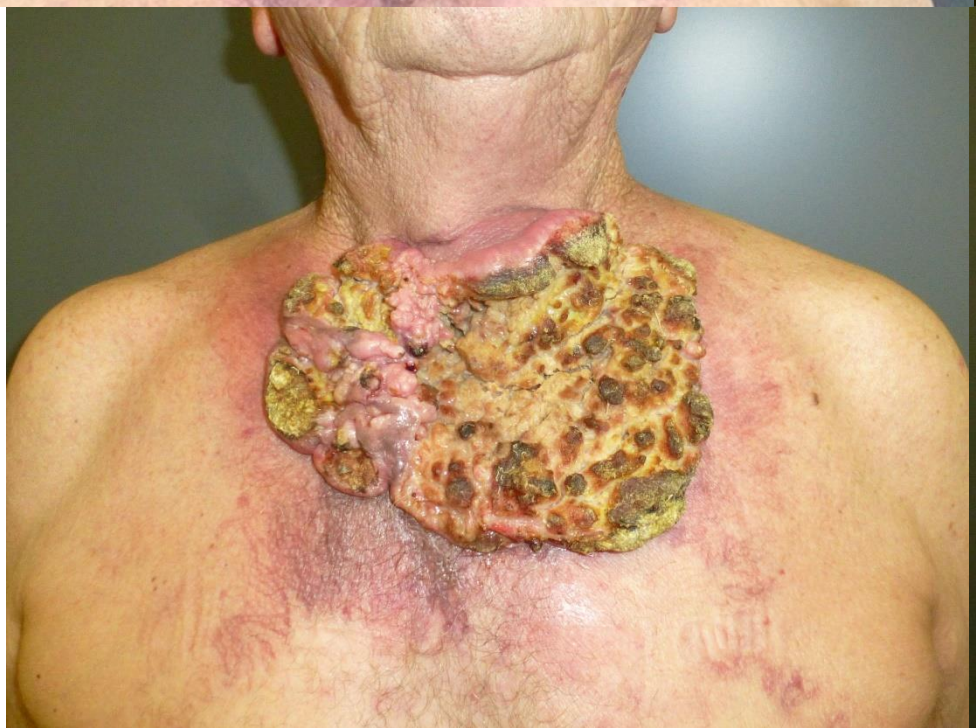
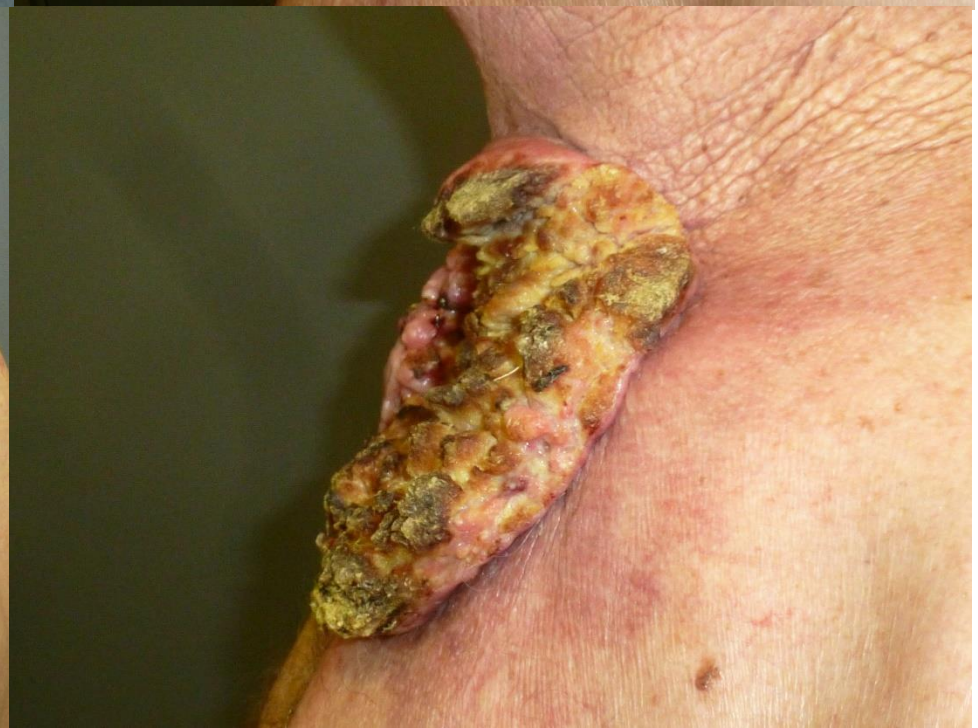
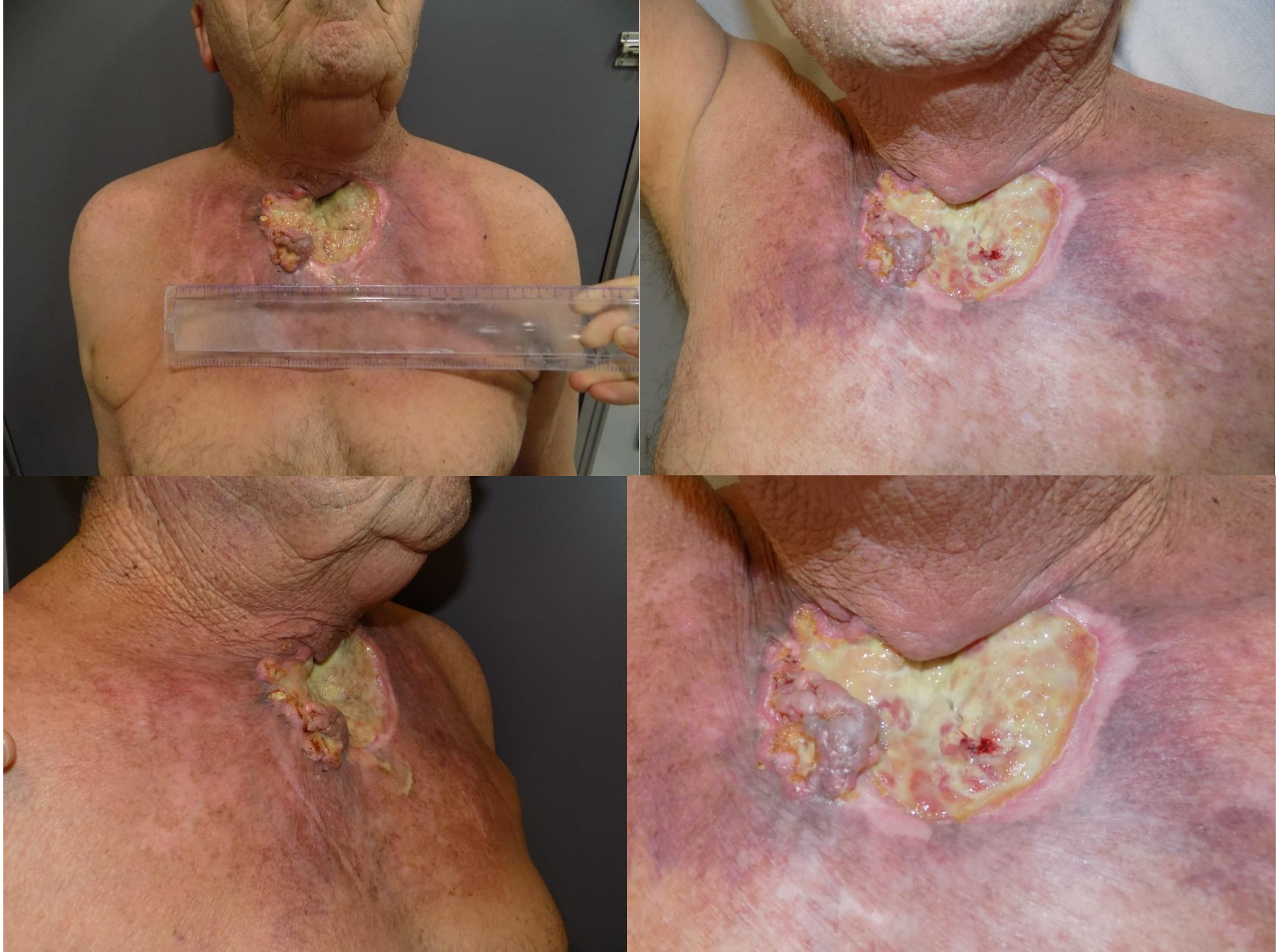
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.24662

Nottage MK
Prospective study of definitive chemoradiation in locally or regionally advanced cutaneous squamous cell carcinoma of the skin
Head and Neck 2017; 39: 679-683

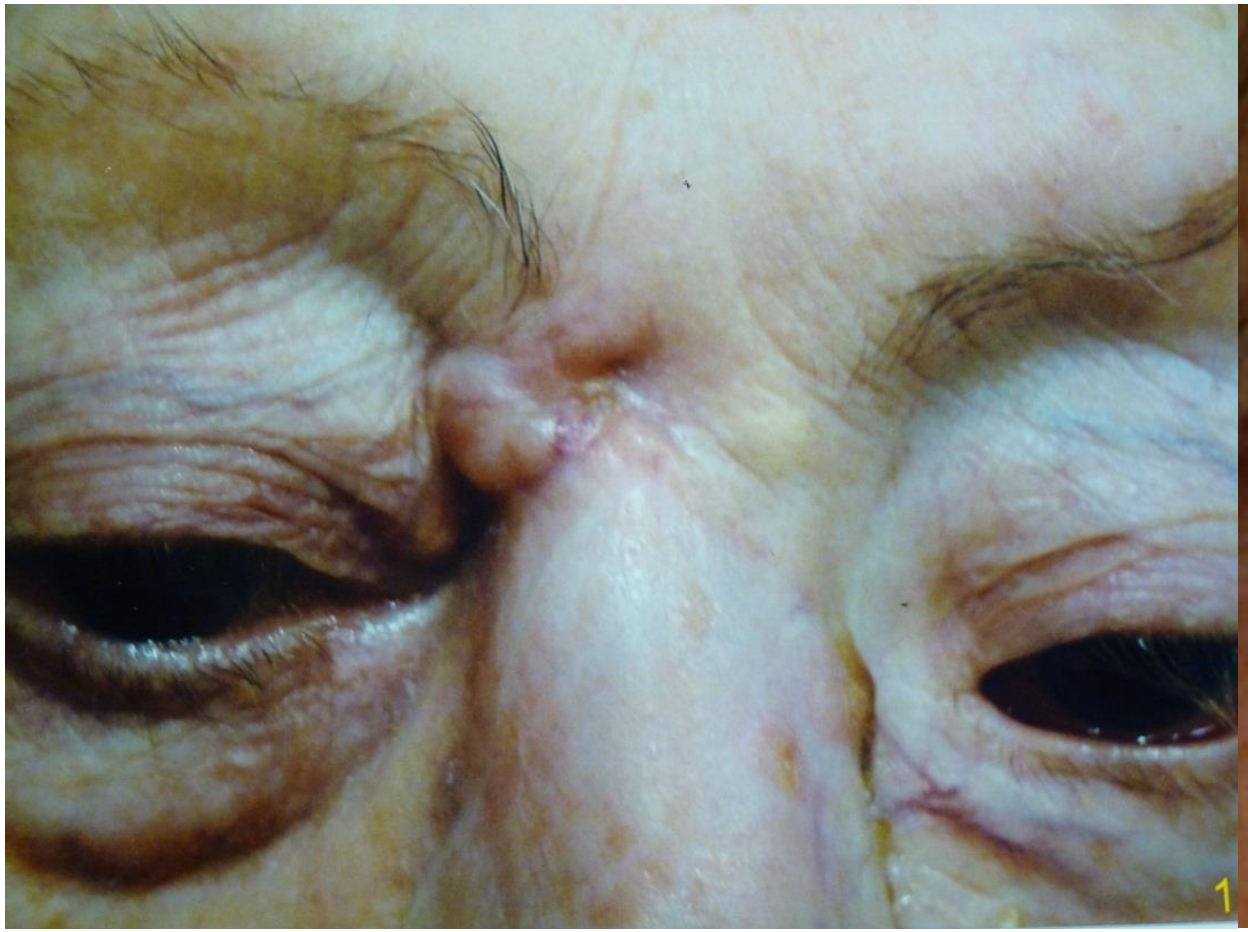


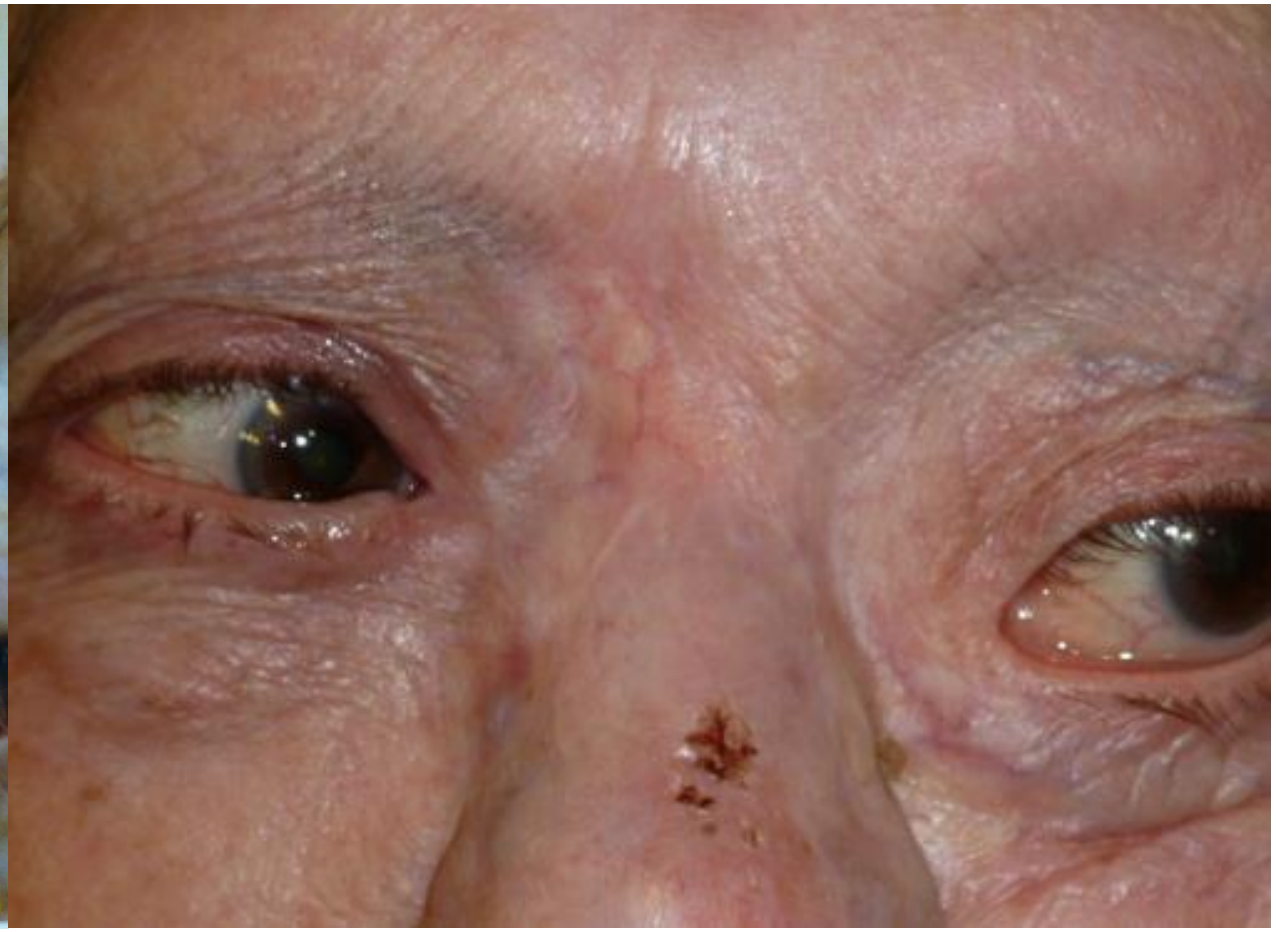
Cetuximab-RT en CEC localmente avanzado

Autor/año	Tipo estudo	Edad	Dosis RT (Gy)	Duración TTO cetuximab (semanas)	Respuesta	Intervalo libre de enfermedad (meses)
Kanakamedla 2010	Caso	78	n/r	8	RC	5
Goppner 2010	Caso	85	45	(<12)	RC	14
Wollina 2011	Caso	77	60	6	RC	3
Giacchero 2011	Serie 4 casos	67-78	50-70	7-18	RC 75% RP 25%	3-21
Alter 2013	Caso	61	24	5	RP	5
Preneau 2014	Fase II 5 pts	62-86	60-70	n/r	RP 80%	4-8
Samstein 2014	Serie 12 casos	47-90	12-80	4-32	RC 33% RP 25%	3-12

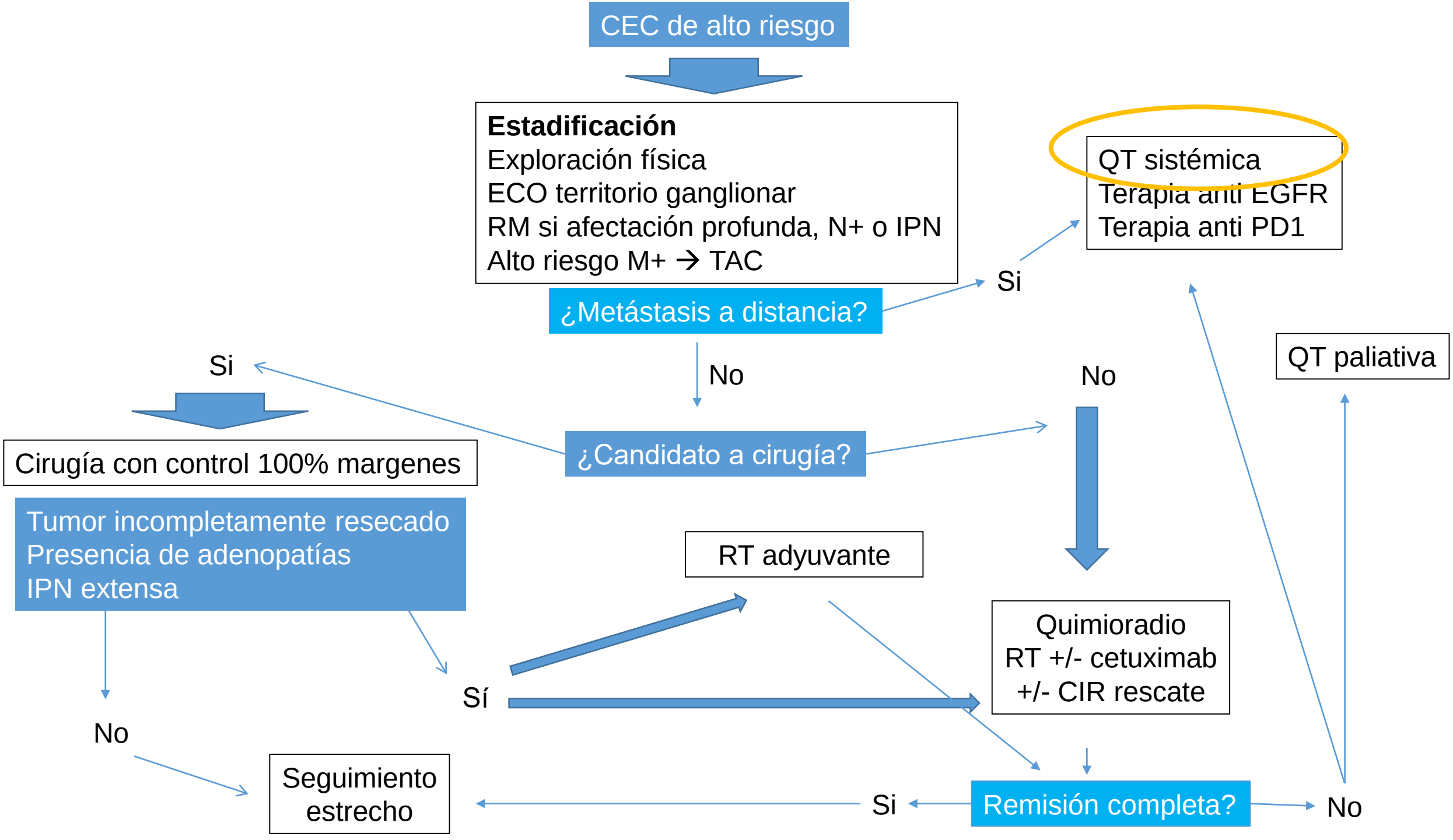
Cetuximab-RT en CEC localmente avanzado

- Ausencia de ensayos clínicos controlados
- Generalmente utilizada en **pacientes de edad avanzada** con poca tolerancia a la quimioterapia
- Respuestas completas en un 30-40% de los pacientes
- Duración de respuesta media de 8 meses
- Efectos adversos cutáneos graves frecuentes (80%) que deben ser tenidos en cuenta
- Cetuximab semanal a dosis medias de 250 mg/m2
- Dosis de RT de 60-70 Gy





CEC recurrente afectando hueso y órbita
RT + cetuximab x 3 meses
Respuesta completa– Seguimiento de 36 meses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Cirugía con control 100% margenes
¿Candidato a cirugía?
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Presencia de adenopatías
IPN extensa
RT adyuvante
Sí
Quimioradio
RT +/- cetuximab
+/- CIR rescate
No
Seguimiento estrecho
Si
Remisión completa?
No

CEC localmente avanzado, tratamiento sistémico

- La **radioterapia paliativa** y la **quimioterapia sistémica** clásica ofrecen beneficio clínico modesto
- Son necesarias alternativas terapéuticas con mayor eficacia
- Se han producido recientemente dos importantes avances en el tratamiento del CEC avanzado:
  - **Introducción de la terapia dirigida antiEGFR**
  - **Introducción del la inmunoterapia anti PD1**

Tratamiento sistémico del CEC avanzado

REVIEW ARTICLE

BJD
British Journal of Dermatology

Systemic treatment of locally advanced nonmetastatic cutaneous squamous cell carcinoma: a review of the literature

R. Behshad,*† J. Garcia-Zuazaga*† and J.S. Bordeaux*†

British Association of Dermatologists 2011 **165,** pp1169–1177

- 28 estudios observacionales con 119 pacientes
- Ningún estudio controlado
- 72% de respuestas globales
- Importante sesgo de publicación

- Terapias dirigidas antiEGFR → ORR 100%
- QT oral → ORR 20%
- QT endovenosa → ORR 68%
- QT intraarterial → ORR 100%

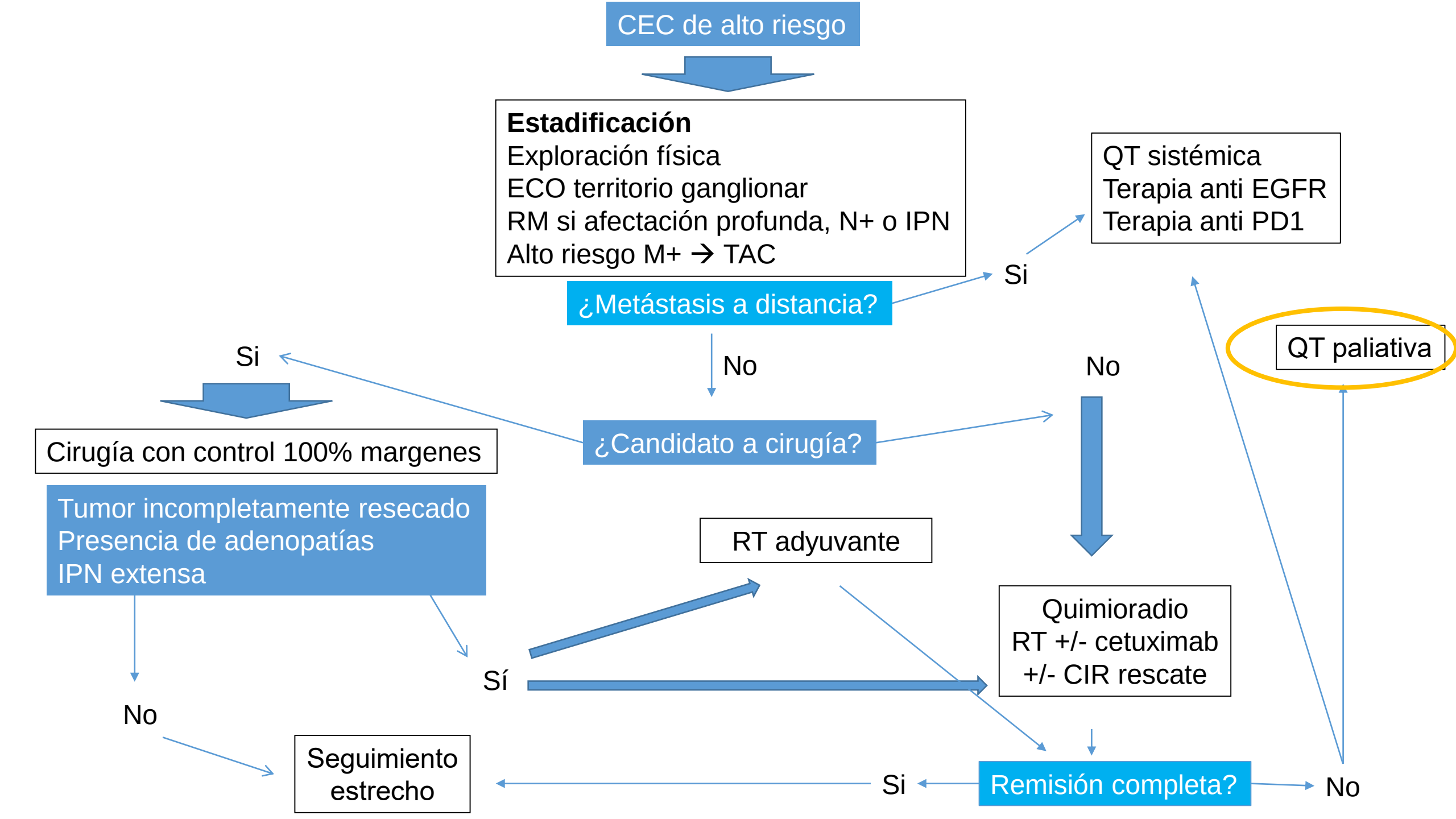
Quimioterapia convencional en CEC avanzado

- Platinos como fármacos más eficaces
- Tb. 5-fu, capecitabina, taxanos, bleomicina, mtx, adr, ifosfamida
- Tasa de respuesta del 80% , rápida recidiva posterior
- Mayor eficacia en regimenes de poliquimioterapia
- Posiblemente **Cisplatino + 5-fu +/- taxanos como primera linea**

Table 7
Synopsis of prospective studies of systemic therapies in advanced or metastatic cutaneous squamous cell carcinoma (cSCC) (adapted from Breuninger et al., 2012 [1]).

Reference	Trial design	Patients	Chemotherapy	RR	Comments
Chemotherapy					
Cartei et al. (2000) [80]	Prospective Observational	14	Oral 5-FU 175 mg/m^2 for 3 weeks every 5 weeks	2 PR (14.3%) 7 SD (50%)	Aggressive, multiple, recurrent SCCs in aged patients
Sadek et al. (1990) [79]	Prospective observational	14/13 evaluable	Cisplatin bolus injection 5-FU and Bleomycin continuous 5-day infusion	4 CR (30%) 7 PR (54%) 2 SD (16%)	Advanced SCC of the skin or lip
Guthrie et al. (1990) [81]	Prospective Observational	12	Cisplatin and doxorubicin ($n = 7$) Neoadjuvant to surgery or radiation ($n = 5$)	4 CR (33%) 3 PR (25%)	
Khansur et al. (1991) [82]	Prospective observational	7	Cisplatin and 5-FU every 21 days	3 CR (43%) 3 PR (43%) 1 SD (14%)	
No authors listed, 1976 [99]	Phase III randomised control trial	70 advanced SCC – 6 cutaneous SCCs	Bleomycin twice weekly versus other cytotoxic drugs	39% RR	Only three patients with cutaneous squamous cell carcinoma (cSCC) in the treatment arm
Targeted therapies/EGFR Inhibitors					
Maubec et al. (2011) [89]	Phase II uncontrolled trial	36	Cetuximab administered weekly	2 CR 8 PR 25 DCR (disease control rate)	Unresectable or metastatic cSCC. Chemotherapy-naive patients
Glisson et al. (2006) [100]	Phase II uncontrolled trial	18/17 evaluable	Gefitinib orally for 4 weeks	4 SD	
Lewis (2012) [91]	Prospective phase II clinical trial	23/22 evaluable	Gefitinib for two cycles prior to surgery and/or radiotherapy (plus maintenance gefitinib for 12 months)	4 CR 6 PR 5 SD 7 PD	Aggressive cSCC of the head and neck
Heath et al. (2013) [101]	Non-randomised single-arm phase I clinical trial	15	Erlotinib combined with postoperative adjuvant therapy	2 year OS 65% 2 year DFS 60%	
Kalapurakal et al. (2012) [102]	Retrospective study	4	Cetuximab administered weekly	3 CR 1 PR	Recurrent cSCC with a history of multiple recurrences in the past
Read (2007) [103]	Case report	3	Erlotinib for 1–3 months	1 CR 1 PR 1 PD	

Abbreviations: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.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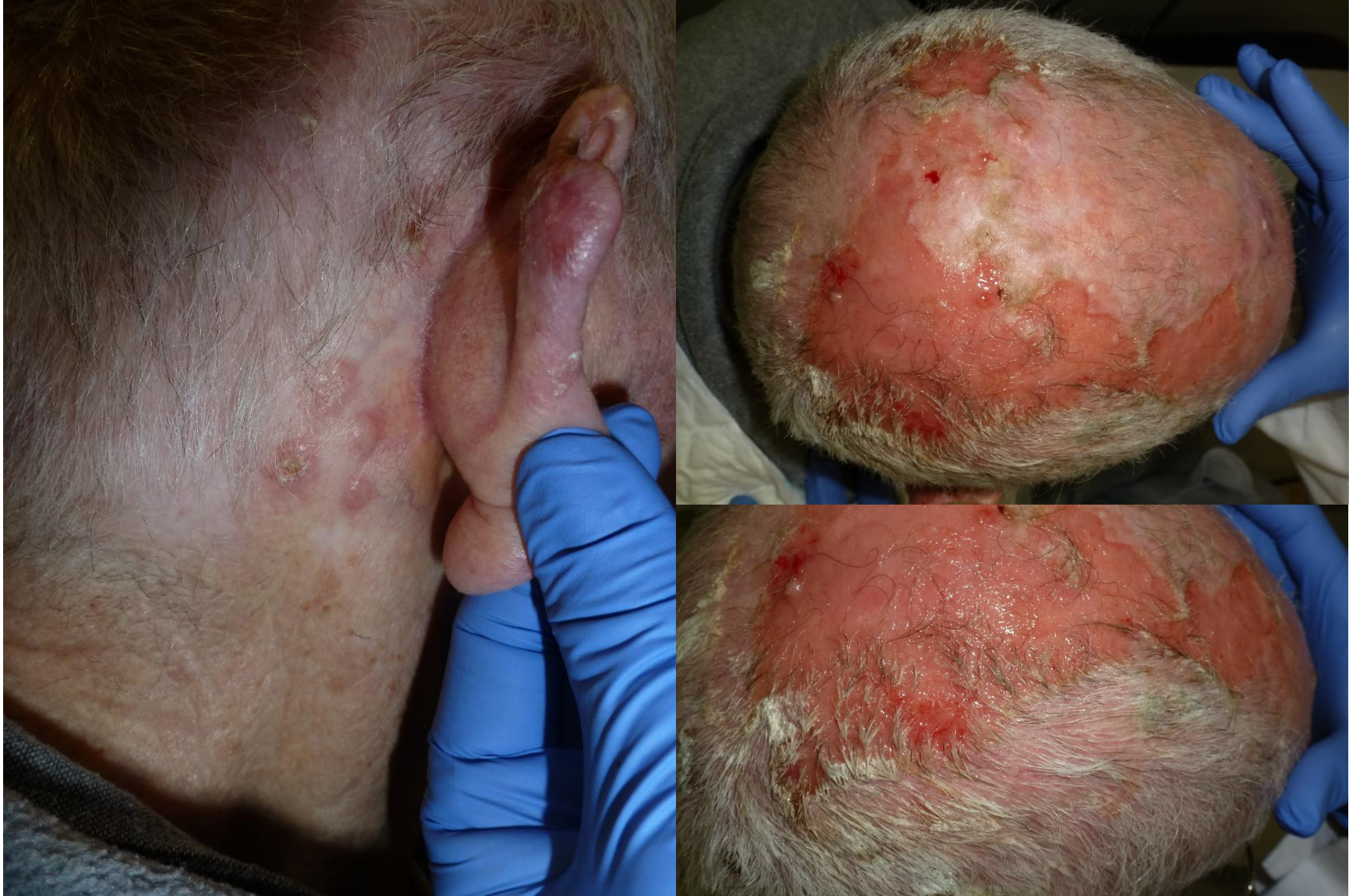
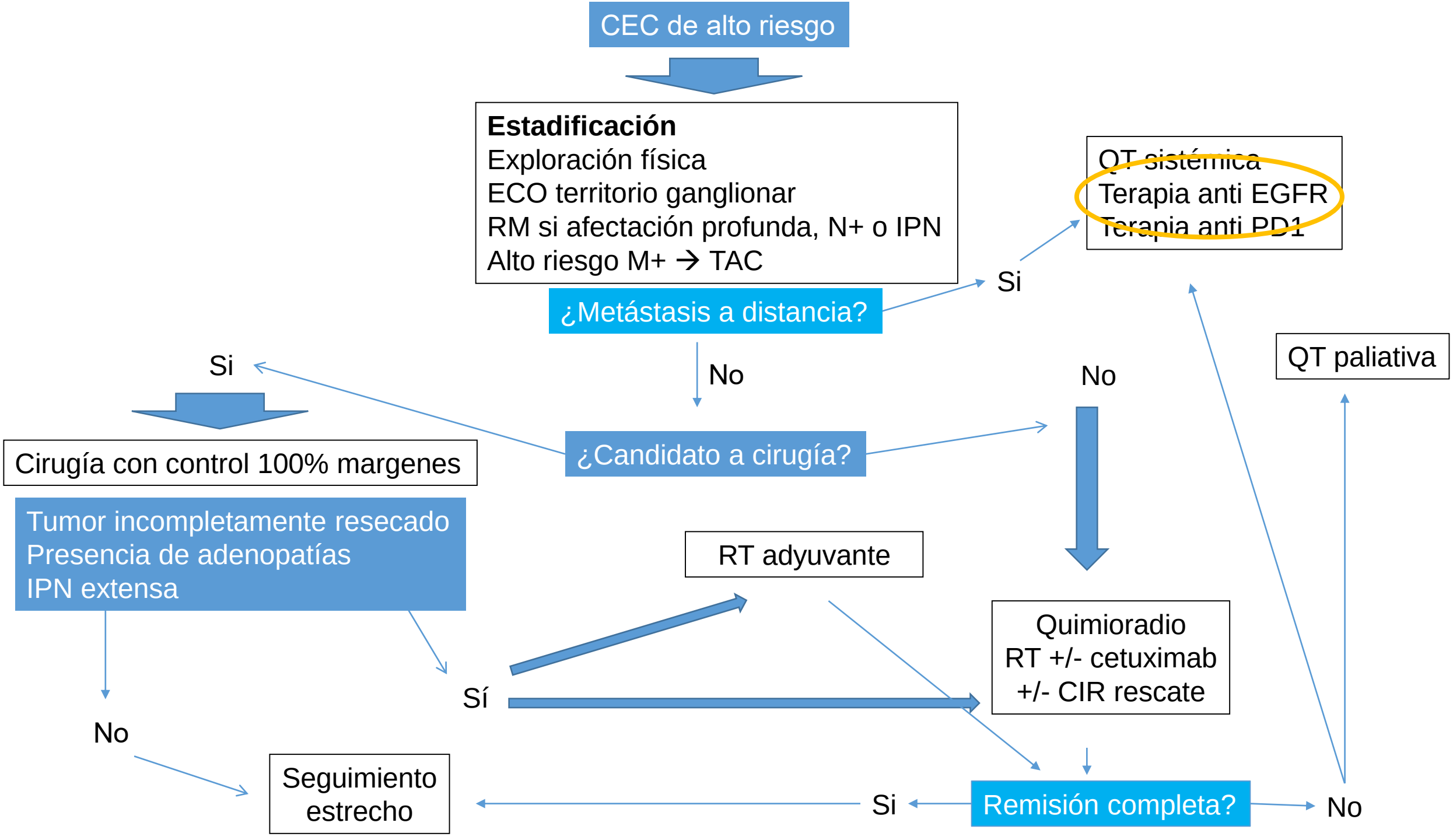
Remisión completa?
No

Quimioterapia paliativa en CEC avanzado

- Pacientes de edad avanzada
- Enfermedad metastásica o no tratable
- Co-morbilidades (función renal que imposibilita Pt)
- Posiblemente **capecitabina como primera línea en este contexto**
- Utilidad de la **electroquimioterapia** en enfermedad cutánea avanzada

Stratigos et al. / European Journal of Cancer 51 (2015) 1989–2007

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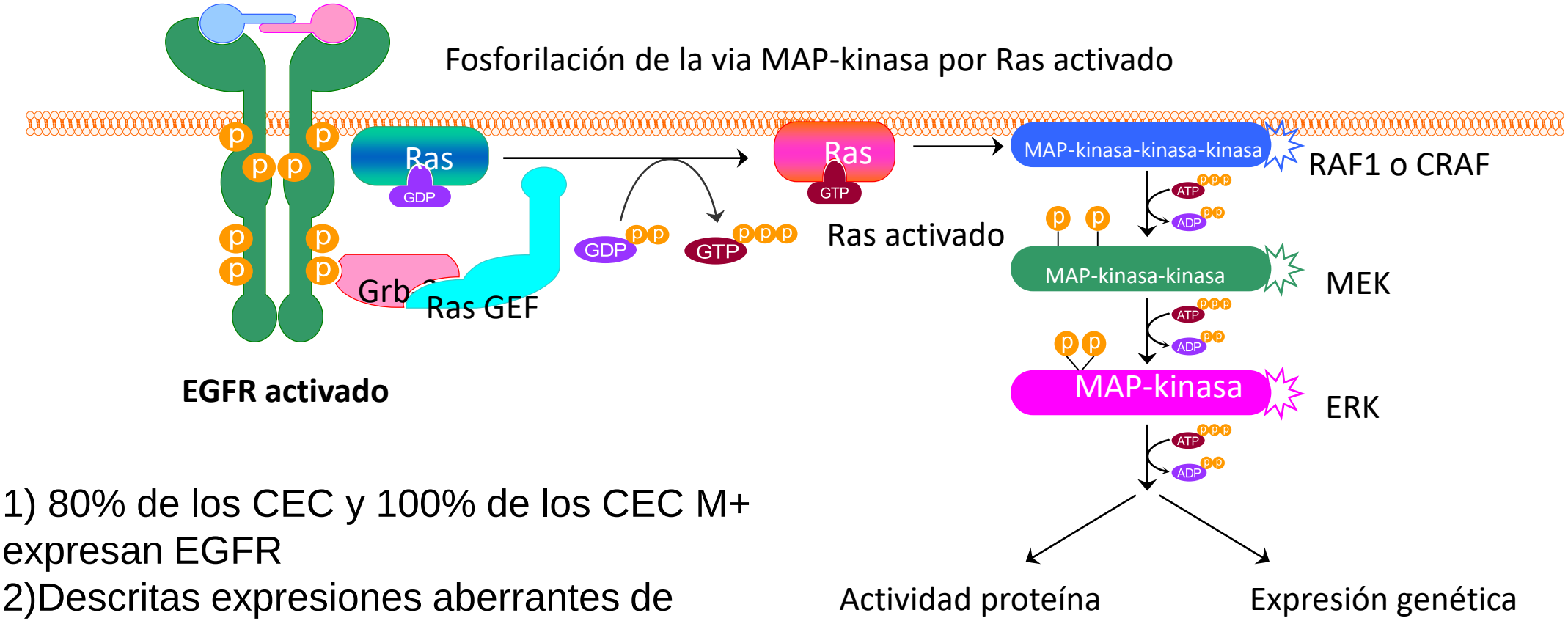
No

Razonamiento para el tratamiento Anti EGFR



1) 80% de los CEC y 100% de los CEC M+ expresan EGFR
2)Descritas expresiones aberrantes de EGFR en células tumorales,
3) Baja frecuencia de mutaciones activadoras de RAS;
4)incremento de copias del gen EGFR en CEC

VOLUME 29 · NUMBER 25 · SEPTEMBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Cetuximab As First-Line Single-Drug Therapy in Patients With Unresectable Squamous Cell Carcinoma of the Skin

Eve Maubec, Peter Petrow, Isabelle Scheer-Senyarich, Pierre Duvillard, Ludovic Lacroix, Julien Gelly, Agnès Certain, Xavier Duval, Béatrice Crickx, Valérie Buffard, Nicole Basset-Seguin, Pierre Saez, Anne-Bénédicte Duval-Modeste, Henri Adamski, Sandrine Mansard, Florent Grange, Anne Dompmartin, Sandrine Faivre, France Mentré, and Marie-Françoise Avril

Eve Maubec, Isabelle Scheer-Senyarich, Julien Gelly, Agnès Certain, Xavier Duval, Béatrice Crickx, and France Mentré, Assistance Publique-Hopitaux de Paris (APHP), Université Paris Diderot, Hôpital Bichat; Nicole Basset-Seguin, APHP, Université Paris Diderot, Hôpital Saint Louis; Peter Petrow, Institut Curie; Marie-Françoise Avril, APHP, Université Paris Descartes, Hôpital Cochin, Paris; Peter Petrow, Association des Centres Radiologie et de l'Imagerie Medicale, Compiègne; Pierre Duvillard and Ludovic Lacroix, Institut Gustave Roussy, Villejuif; Valérie Buffard, APHP, Université Paris XII Val de Marne, Hôpital Henri Mondor, Créteil; Pierre Saez, Hôpital Louis Pasteur, Chartres; Anne-Bénédicte Duval-Modeste, Hôpital Charles Nicole, Rouen; Henri Adamski, Centre Hospitalier Universitaire de Pontchaillou, Rennes; Sandrine Mansard, Centre Hospitalier Universitaire Estaing, Clermont-Ferrand; Florent Grange, Centre Hospitalier Universitaire Robert Debré, Reims; Anne Dompmartin, Centre Hospitalier Universitaire de Caen, Caen; Pierre Saez, Hôpital Emile Muller, Mulhouse; and Sandrine Faivre, APHP, Université Paris Diderot, Hôpital Beaujon, Clichy, France.

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ABSTRACT

Purpose
To evaluate the efficacy and safety of cetuximab, a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR), as a first-line monotherapy in patients with unresectable squamous cell carcinoma of the skin (SCCS).

Patients and Methods
Thirty-six patients received cetuximab (initial dose of 400 mg/m^2 followed by subsequent weekly doses of 250 mg/m^2) for at least 6 weeks with a 48-week follow-up. The primary end point was the disease control rate (DCR) at 6 weeks (according to Response Evaluation Criteria in Solid Tumors [RECIST] criteria). Secondary end points included best response rate, overall survival, progression-free survival (PFS), and toxicity assessment. Association of treatment efficacy with *RAS* mutations or FcγR genotypes was investigated.

Results
Median age of the study population was 79 years. DCR at 6 weeks was obtained in 25 of 36 patients (69%; 95% CI, 52% to 84%) of the intention-to-treat population. The best responses were eight partial responses and two complete responses. There were no cetuximab-related deaths. There were three related serious adverse events: two grade 4 infusion reactions and one grade 3 interstitial pneumopathy. Grade 1 to 2 acne-like rash occurred in 78% of patients and was associated with prolonged PFS. One *HRAS* mutation was identified. Combined FcγRIIa-131H/H and/or FcγRIIIa-158V/V polymorphisms were not associated with the clinical outcomes.

Conclusion
As a first-line treatment in patients with unresectable SCCS, cetuximab achieved 69% DCR. A randomized phase III trial is warranted to confirm that cetuximab may be considered as a therapeutic option especially in elderly patients. The low frequency of *RAS* mutations in SCCS makes SCCS tumors attractive for EGFR inhibition.

J Clin Oncol 29:3419-3426. © 2011 by American Society of Clinical Oncology

36 pacientes
Cetuximab:
Initial dose: 400 mg/m2
250 mg/m2 /wk x 6-wk

ORR 34%:
8 PR
2 CR

Cancer Therapy: Clinical

Clinical Cancer Research

A Phase II Study of Gefitinib for Aggressive Cutaneous Squamous Cell Carcinoma of the Head and Neck

Carol M. Lewis[1], Bonnie S. Glisson[2], Lei Feng[3], Fiona Wan[1], Ximing Tang[2], Ignacio I. Wistuba[4], Adel K. El-Naggar[4], David I. Rosenthal[5], Mark S. Chambers[1], Robert A. Lustig[6], and Randal S. Weber[1]

Abstract

Purpose: To determine the disease control rate and toxicity of treating patients with aggressive cutaneous squamous cell carcinoma (CSCC) with neoadjuvant gefitinib.

Experimental Design: A prospective phase II clinical trial evaluating neoadjuvant gefitinib given prior to standard treatment with surgery and/or radiotherapy. Patients with stable disease after one cycle received escalated doses. Patients who responded were given gefitinib during radiation therapy, as well as maintenance therapy after definitive treatment. We analyzed the correlation between epidermal growth factor receptor (EGFR) expression, mutation status, and gene copy number on available tissue samples and clinical response.

Results: Twenty-three patients were accrued and 22 patients were evaluable for response prior to definitive local treatment; complete responses were attained by 18.2% of patients and partial responses by 27.3%. Grades 2 to 3 toxicities were observed in 59.1% of patients experiencing class-specific effects during induction therapy. After induction, 11.8% underwent surgery alone, 17.6% had definitive radiation, 11.8% were treated with radiation and concurrent gefitinib, and 47% had surgery with postoperative radiation and concurrent gefitinib. Median follow-up for the censored observations was 32 months. Two-year overall, disease-specific, and progression-free survival rates were 72.1%, 72.1%, and 63.6%, respectively. No EGFR-activating mutations were identified in tumor samples available from 10 patients. No associations between EGFR correlative studies and patient outcomes were identified.

Conclusions: Gefitinib, in the neoadjuvant setting, was active and well tolerated in patients with aggressive CSCC and did not interfere with definitive treatment. In view of the 18% complete response rate we observed, EGFR tyrosine kinase inhibitors should be further explored in the treatment of aggressive CSCC. *Clin Cancer Res; 18(5); 1435–46. ©2012 AACR.*

Gefitinib neoadyuvante en 23 pacientes

ORR 45%

18% CR

27% PR

Supervivencia libre de progression del 64% a los 32 meses

Tumores mas pequeños

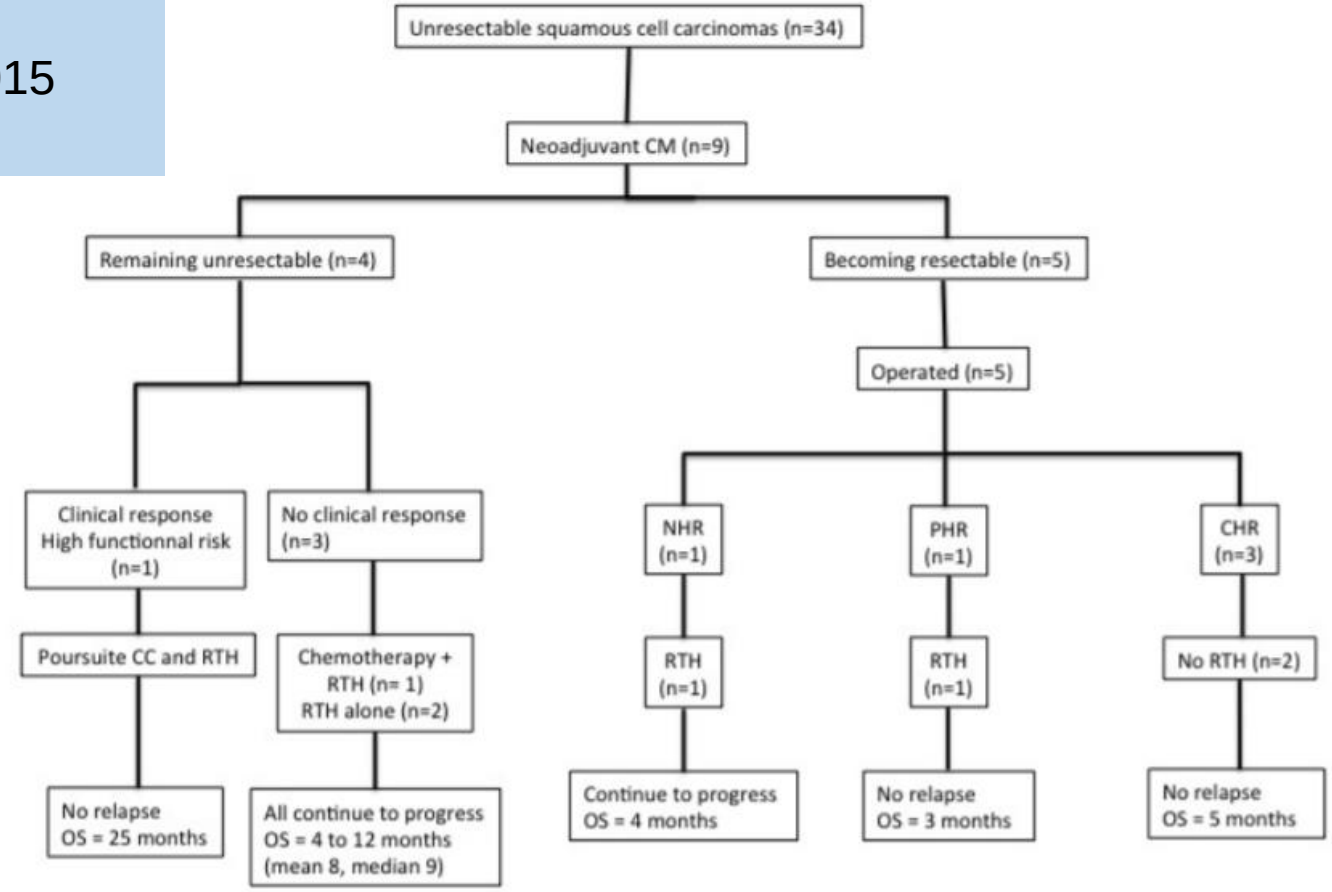
Reigneau M.: Efficacy of neoadjuvant cetuximab alone or with platinum salt for the treatment of unresectable advanced nonmetastatic cutaneous squamous cell carcinomas.

Br J Dermatol. 2015 Aug;173(2):527-34. Epub 2015 Aug 8

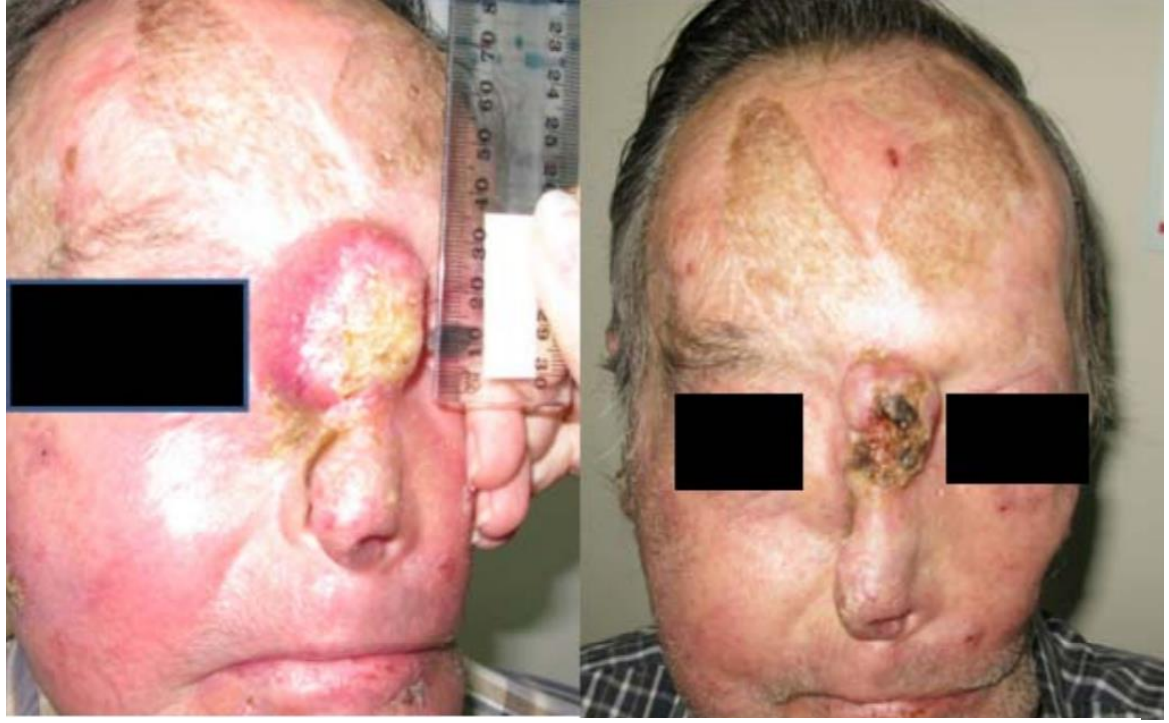
-Cetuximab neoadyuvante

-**ORR del 54**% (2 RC, 4 RP)

-Mejor tasa de respuesta cuando asocia platino a cetuximab



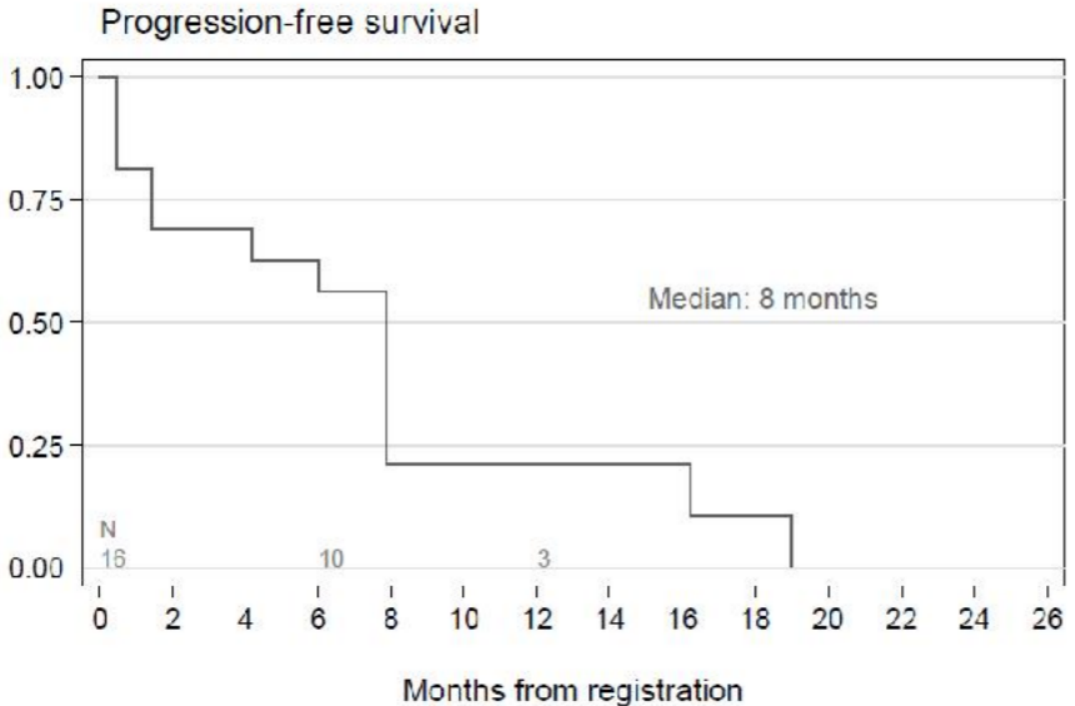
Foote MC
Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma.
Ann Oncol. 2014 Oct;25(10):2047-52.



16 pacientes con enfermedad local o regional avanzada

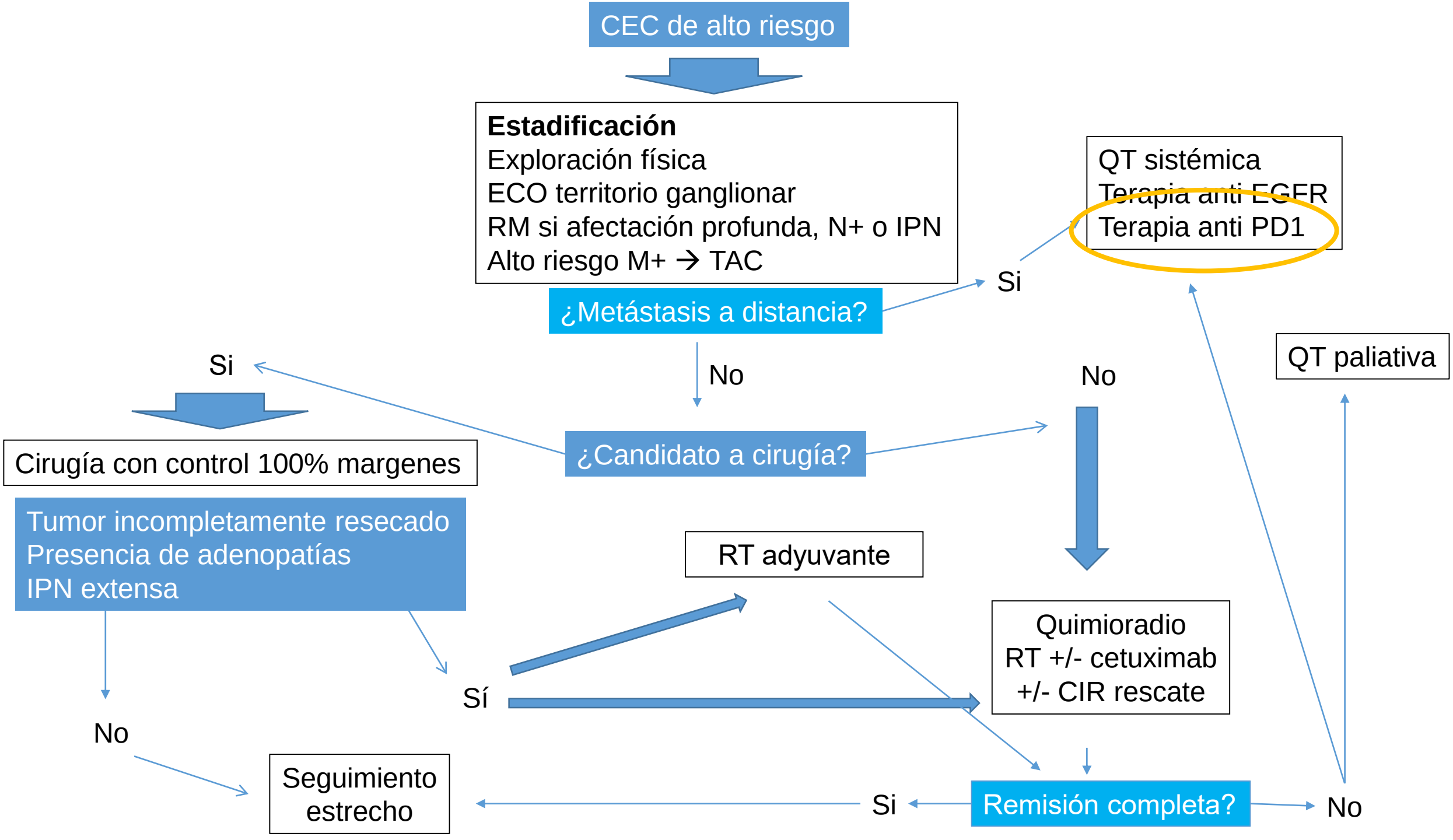
ORR 31% (2 RC, 3 RP)

Supervivencia libre de progresión 8 meses



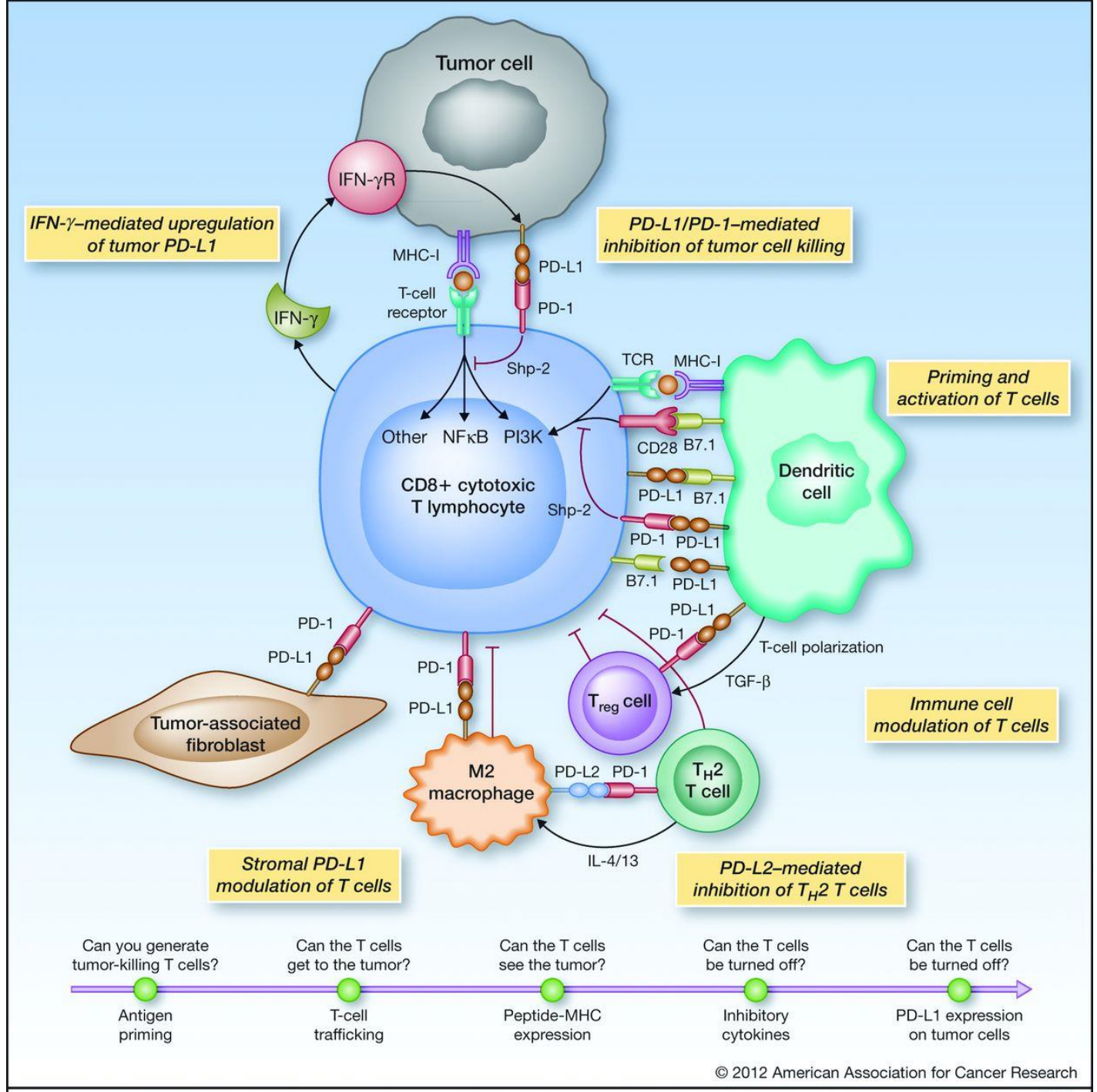
Estrategia anti-EGFR en carcinoma epidermoide cutáneo avanzado

- Utilizados cetuximab, panitumumab y gefitinib
- Tasa de respuesta en torno al 30%-40%
- Respuestas completas escasas < 20%
- Duraciones cortas de la respuesta
- En general, mayor eficacia con ac monoclonales que inhibidores TK


CEC de alto riesgo
Estadificación
Exploración física
ECO territorio ganglionar
RM si afectación profunda, N+ o IPN
Alto riesgo M+ → TAC
¿Metástasis a distancia?
Si
QT sistémica
Terapia anti EGFR
Terapia anti PD1
No
Si
QT paliativa
No
Cirugía con control 100% margenes
¿Candidato a cirugía?
Tumor incompletamente resecado
Presencia de adenopatías
IPN extensa
RT adyuvante
Quimioradio
RT +/- cetuximab
+/- CIR rescate
Sí
No
Seguimiento
estrecho
Si
Remisión completa?
No

CEC localmente avanzado, papel de la inmunoterapia

- El papel de la inflamación es importante en el desarrollo del CEC y es capaz de controlar el crecimiento de algunos tumores
- CEC es frecuente en inmunodeprimidos y en pacientes con exposición solar crónica
- La exposición solar crónica induce presencia de linfocitos T supresores y disminución de célula de Langerhans
- El infiltrado inflamatorio del CEC es pobre en Linfocitos T CD8 y rico en Linfocitos T reg



Inmunoterapia en el CEC avanzado

Articulo	Casos	Tratamiento	Fármaco	Resultado	Intervalo libre de progresión	Efectos adversos
Day 2017	CEC M+ pulmón e hígado	3ª línea	Ipilimumab	RP	8 meses	Hipofisitis
Winkler 2016	CEC N+	1ª línea	Pembrolizumab	RP	5 meses	--
Chang 2016	CEC localmente avanzado	2ª línea	Pembrolizumab	RP	5 meses	Astenia Artralgia
Lipson 2016	CEC localmente avanzado Trasplantado renal	2ª línea	Pembrolizumab	RP	8 meses	Rechazo órgano (riñon
Borradori 2016	CEC M+	3ª línea	Pembrolizumab	RP	7 meses	Astenia, edema cerebral
	CEC localmente avanzado	4ª línea	Pembrolizumab	EE	4 meses	--
	CEC localmente avanzado	2ª línea	Nivolumab	RP	7 meses	--
	CEC M+	4ª línea	Nivolumab	RP	6 meses	Astenia, hiponatremia

Park JC.: Immune checkpoint inhibition (ICI) in advanced cutaneous squamous cell carcinoma (cSCC): Clinical response and correlative biomarker analysis.
J Clin Oncol 36, 2018 (suppl; abstr 9564)
(Massachussets General Hospital)

- Resumen de su Experiencia con anti-PD-1 en pacientes con CEC Avanzado, con correlación con biomarcadores
- Nivolumab o Pembrolizumab, fuera de ensayo clínico **(vida real)**
- 13 pacientes (7 con factores de riesgo: LLC (3), Xeroderma (2), Marjolin (2))
- 8 pembrolizumab y 5 nivolumab.
- 9 pts (69%) QT previa o cetuximab
- Seguimento medio 16.5 meses
- **7 pts (62%) ORR** (2 RC, 5 RP)
- Supervivencia libre de progression a los 12 meses: 68%
- Toxicidad grado 3 en el 23%, con un fallecimiento por miocarditis

Park JC.: Immune checkpoint inhibition (ICI) in advanced cutaneous squamous cell carcinoma (cSCC): Clinical response and correlative biomarker analysis.
J Clin Oncol 36, 2018 (suppl; abstr 9564)
(Massachussets General Hospital)

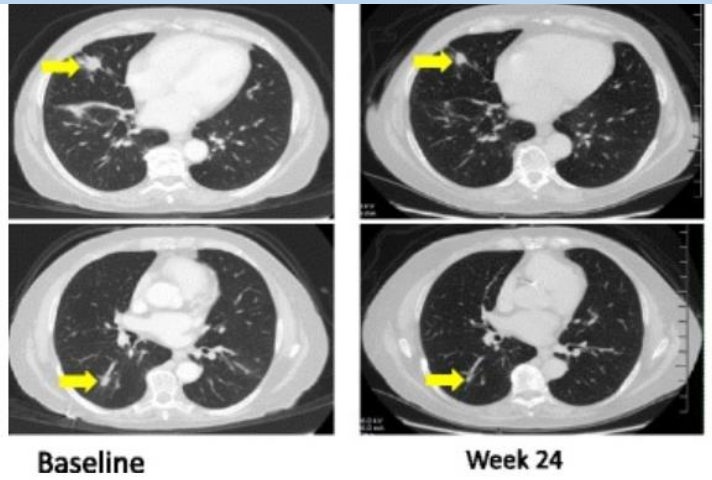
- BIOMARCADORES: Biopsia previa en 11 pts.
- CD4, CD8 y Tregs presentes en grado variable. NO ASOCIACION CON RESPUESTA
- PD-L1 expresion en el tumor y celulas inmunes presente el el 78% de los pacientes
- Expresión media de **PD-1-L en celulas del tumor** en respondedores vs no respondedores 11’5 vs 0 %. Clara relacion con la respuesta
- La expresión media PD-1-L en células inmunes del tumor no se relacionó con la respuesta
- **Conclusiones**
- Los pacientes no incluibles en ensayos clínicos responden a terapia anti-PD-1
- La expresión de PD-1-L en las células tumorales se relaciona con la respuesta.

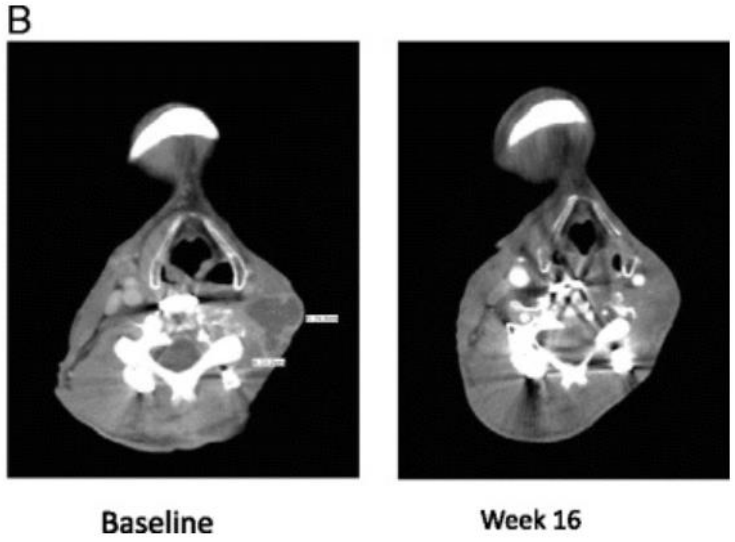
Kudchadkar M.: Phase II trial of pembrolizumab (MK-3475) in metastatic cutaneous squamous cell carcinoma (cSCC). J Clin Oncol 36, 2018 (suppl; abstr 9543). ASCO 2018. (Emory University)

- 10 pts (8V/ 2M). Edad media 68’7 . 3 de ellos habían llevado QT previa
- Pembrolizumab dosis estandar
- **ORR 40%,** 1 RC, 3 RP, 1SD, 2PD, 3NE
- Toxicidades grado 3 en 2 pacientes: Hepatitis y neumonitis

Papadopoulos KP, et al. REGN 2810: A fully human anti-PD-1 monoclonal antibody, for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma - initial safety and efficacy from expansion cohorts of phase one study (abstract 9503). ASCO 2017

- Estudio prospectivo fase I
- anti-PD-1 REGN2810 **CEMIPLIMAB**
- 26 pacientes (10 m+, 16 no operables)
- ORR 46% (2 RC, 10 RP)
- Duración respuesta 7 meses





Rischin D. et al.: Primary analysis of phase 2 results for cemiplimab, a human monoclonal anti-PD-1, in patients with metastatic cutaneous squamous cell carcinoma (mCSCC). J Clin Oncol 36, 2018 (suppl; abstr 9519). ASCO 2018 (Brigham Womans Hospital Boston, Melbourne)

- Ensayo pivotal fase II en pacientes con CEC metastásico.
- Pacientes con mCSCC (definidas como nodales o a distancia)
- Cemiplimab 3 mg/kg IV, cada dos semanas .
- Valoracion cada 8 semanas (pruebas de imagen con RECIST 1.1, criterios OMS para fotos)
- Objetivo primario ORR (RC + RP)
- Objetivo secundario duracion de respuestas (definiendo la tasa de control de estabilización de enfermedad como aquella que dura más allá de 16 semanas)

Rischin D. et al.: Primary analysis of phase 2 results for cemiplimab, a human monoclonal anti-PD-1, in patients with metastatic cutaneous squamous cell carcinoma (mCSCC). J Clin Oncol 36, 2018 (suppl; abstr 9519). ASCO 2018 (Brigham Womans Hospital Boston, Melbourne)

- 59 pacientes incluidos (54 V/ 5 M) ; (71.0 años [rango: 38–93].
- Seguimiento medio 7.9 meses
- **ORR 47.5%** (95% CI: 34.3–60.9; 4 RC y 24 RP), independientemente de tto previo. El 70% habian recibido tratamiento
- 3 pacientes respondedores progresaron durante el periodo de seguimiento
- La tasa de duracion de respuesta mas alla de 16 semanas es del 61% (95% CI: 47.4–73.5).
- Efectos adversos: los más frecuentes diarrea, fatiga y nauseas (20% pacientes).
- Efectos autoinmunes grado 3 en el 10% de los paciente