IV Simposio

GETHI

Monográfico de Tumores cutáneos infrecuentes

Sarcoma de Kaposi y Angiosarcoma

Ander Mayor Ibarguren

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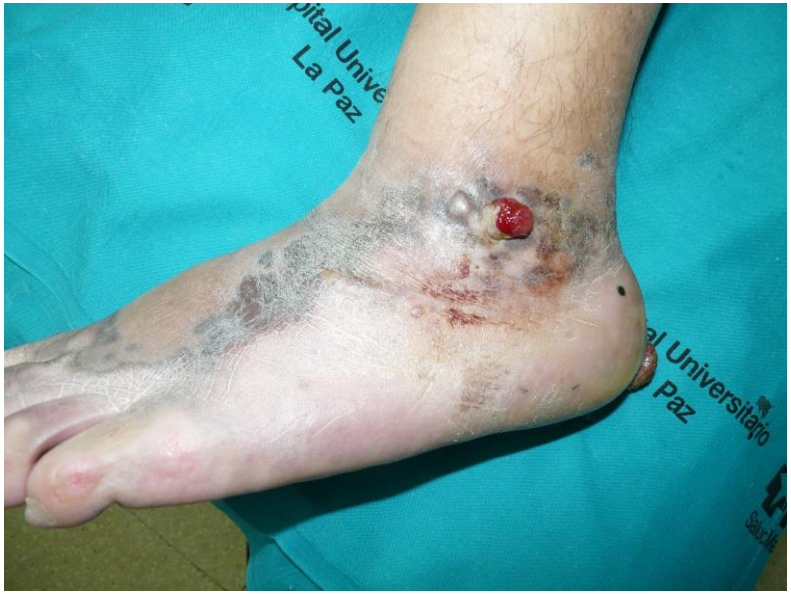
Organizado por: Grupo Gethi – Grupo Español de Tumores Huérfanos e Infrecuentes

CENTRO INTEGRAL ONCOLÓGICO hm CIOCC



Sarcoma de Kaposi

Moritz Kaposi
1872
“sarcoma idiopático pigmentado de la piel”.

Robert Chesley - ks portraits with harddick & superman spandex # 1
(a total of 6 images) photo © Mark I Chester
from the series Diary of a Thought Criminal, 1989

NYtimes

RARE CANCER SEEN
IN 41 HOMOSEXUALS

Outbreak Occurs Among Men
in New York and California
—8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the

SIDA
1989

Identification of Herpesvirus-Like DNA Sequences in AIDS-Associated Kaposi's Sarcoma

Yuan Chang,* Ethel Cesarman,† Melissa S. Pessin, Frank Lee, Janice Culpepper, Daniel M. Knowles,† Patrick S. Moore

Representational difference analysis was used to isolate unique sequences present in more than 90 percent of Kaposi's sarcoma (KS) tissues obtained from patients with acquired immunodeficiency syndrome (AIDS). These sequences were not present in tissue DNA from non-AIDS patients, but were present in 15 percent of non-KS tissue DNA samples from AIDS patients. The sequences are homologous to, but distinct from, capsid and tegument protein genes of the Gammaherpesvirinae, herpesvirus saimiri and Epstein-Barr virus. These KS-associated herpesvirus-like (KSHV) sequences appear to define a new human herpesvirus.

Science. 1994 Dec 16;266(5192):1865-9

Professorin Dr. Yuan Chang; © Joshua Franzos

Professor Dr. Patrick S. Moore; © Joshua Franzos

Yuan Chang and Patrick Moore win prize for the discovery of two cancer viruses

East and Southern Africa (2017)

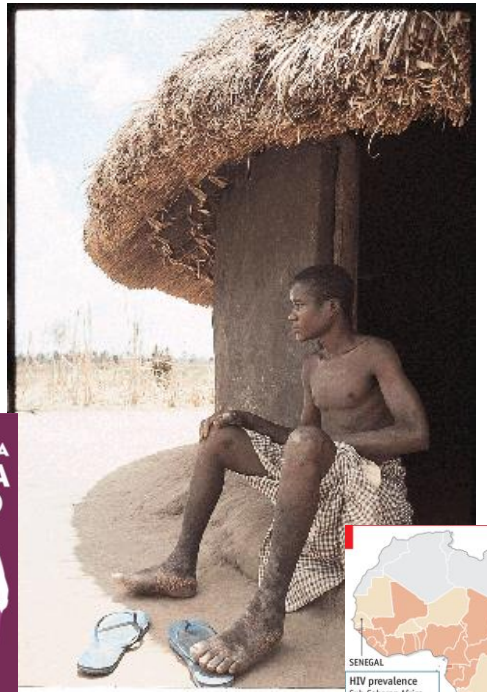
19.6m people living with HIV
6.8% adult HIV prevalence (ages 15-49)
800,000 new HIV infections
380,000 AIDS-related deaths
66% adults on antiretroviral treatment*
59% children on antiretroviral treatment*
*All adults/children living with HIV

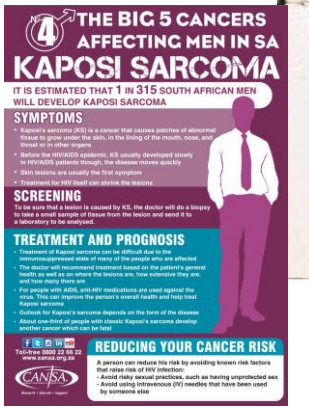
Source: UNAIDS Data 2018

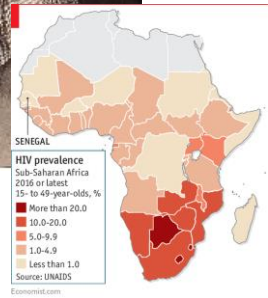
Sub-Saharan Africa (2013)

24.7 million people living with HIV
4.7% adult HIV prevalence
1.5 million new HIV infections
1.1 million AIDS-related deaths
39% adults on antiretroviral treatment

Source: UNAIDS Gap Report 2014

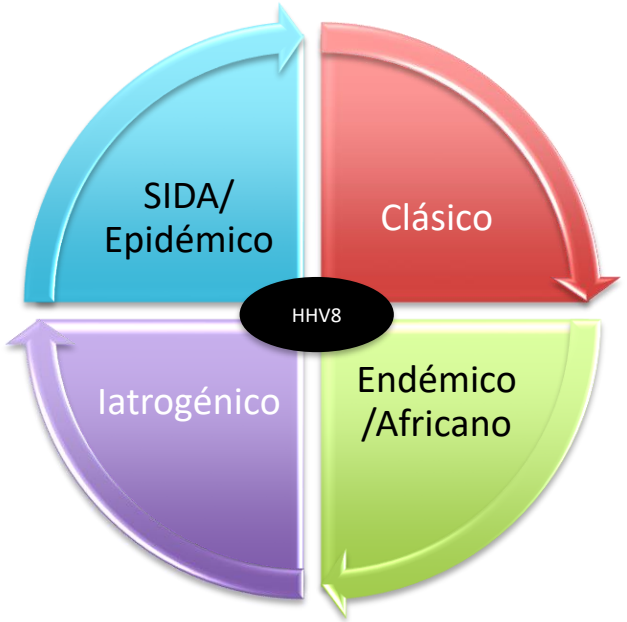






Sarcoma de Kaposi

- Trastorno angioproliferativo causado necesariamente por la infección del **HHV-8**.
- Clasificación:



Sarcoma de Kaposi

Variante	Clásico	SIDA/VIH	Iatrogénico	Endémico
Población	• Cuenca Mediterránea-región centroeuropea • Población Turca/Eurasia al norte de china • H:M = 3:1	HSH VIH+ Niveles CD4 < 200 IRIS	• Trasplantados de órganos sólido • Terapia Inmunosupresora	África ecuatorial y subsahariana
Edad	>60 años (<4-8% casos <60)	20-50años	< 60 años	• Adultos jóvenes • Niños*
Incidencia	• 1672 casos/año UE • 10500 casos con dx previo en Europa en 2008.	Hasta un 25% previo era TARGA	RR: 150-200 de un tx de órgano sólido	¿? Actualmente difícil de diferenciarlo del epidémico
Clínica	Lesiones cutáneas en EEII. Ocasionalmente GI y linfática Curso crónico-indolente	Lesiones multifocales Afectación mucosas Visceral Px variable	Cutánea Afectacion GI riesgo sangrado+ Afectacion Visceral: Tx hepático > corazón > renal Px Variable	• Nodular benigna • Localmente agresiva, invadiendo partes blandas y hueso • Florida diseminada (cutánea y visceral) • *Linfadenopática rápidamente progresiva con afectación visceral

Sarcoma de Kaposi

International Journal of Dermatology

Review

Epidemiology of Kaposi sarcoma: review and description of the nonepidemic variant

Ramya Vangipuram[1,2], MD, and Stephen K. Tyring[1,2], MD, PhD

Table 1 Epidemiology of Kaposi sarcoma

Variant	Risk group	Clinical presentation	Prognosis
Classic	Elderly (60–70s) males of Mediterranean, eastern European, South American descent	Cutaneous, GI involvement, occasional lymph node and other organ involvement	Chronic course
Endemic (African)	Young – middle-aged sub-Saharan African males	Four subtypes: **(1)** benign nodular **(2)** locally aggressive, invading soft tissue and bone **(3)** florid disseminated, with skin and visceral involvement	Variable – indolent to locally invasive to aggressive and fatal (especially the lymphadenopathic variant)
	Children (1–3) – lymphadenopathic variant	**(4)** lymphadenopathic, rapidly disseminating to lymph nodes and visceral organs (29)	
Iatrogenic	Solid-organ transplant recipients Patients on immunosuppresion	Cutaneous, risk of GI hemorrhage	Variable – indolent to aggressive; resolves with cessation of immunotherapy
Epidemic (HIV-associated)	HIV positive	Multifocal cutaneous lesions, mucosal, visceral	Variable – chronic to rapidly progressive, requiring highly active antiretroviral therapy and/or chemotherapy
Nonepidemic	Middle-aged (40–50s), MSM	Cutaneous, with rare mucocutaneous involvement	Indolent

GI, gastrointestinal; HIV, human immunodeficiency virus; MSM, men who have sex with men.

Table 2 Reports of nonepidemic Kaposi sarcoma in the literature

Authors (year)	Number of patients, age(s), location of KS
Marquart et al. (1986)	*N* = 1, 44, penis
Garcia-Muret et al. (1990)	*N* = 1, 42, disseminated: cutaneous and GI tract
Friedman-Kien et al. (1990)	*N* = 6, 32–62 (mean age 45), lower extremity and penis
Kua et al. (2004)	*N* = 1, 52, buccal mucosa
Lanternier et al. (2008)	*N* = 28, 35–83 (mean age 55), face, trunk, upper extremity, genitalia, lower extremity, genitalia
Potthoff et al. (2010)	*N* = 1, 53, trunk, lower extremity
Rashidgamat et al. (2014)	*N* = 8, 36–65 (mean age 53), upper extremity, lower extremity, penis
Hinojosa et al. (2017)	*N* = 1, 55, face, lower extremity

Sarcoma de Kaposi- Posibles nuevas "variantes epidemiológicas"

International Journal of Dermatology

Review

Epidemiology of Kaposi sarcoma: review and description of the nonepidemic variant

Ramya Vangipuram[1,2], MD, and Stephen K. Tyring[1,2], MD, PhD

Variante No Epidémica

- SK en HSH HIV neg.
- KS tipo clásico con edad relativamente jóvenes para clásico (40-50)
- Curso indolente
- Cutánea y mucosas

Table 2 Reports of nonepidemic Kaposi sarcoma in the literature

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Kaposi's sarcoma in HIV negative men who have sex with men: an emerging problem

Ander Mayor-Ibarguren, Kieron Leslie and Toby Maurer

UCSF Dermatology department

O

To review the prevalence of uninfected HIV MSM patients among the classical KS patients seen in a tertiary referral center located in San Francisco in the last 5 years.

M

We reviewed the patients diagnosed with classical Kaposi's sarcoma from January 1st 2010 to October 31st 2015 in a tertiary referring centre set in San Francisco.

R

Total KS seen	41
Classical KS (non HIV, No Iatrogenic)	25
MSM <60 yo	11 (26.82%) * (44%)** (34.37%)***
Median Age of onset	50 yo (36-60)

- *: of Total KS
- ** : of Clasiccal KS
- *** : of New KS diagnosis

Kaposi's sarcoma in HIV negative men who have sex with men: an emerging problem

Ander Mayor-Ibarguren, Kieron Leslie and Toby Maurer

UCSF Dermatology department

Results

- Idiopathic CD4 lymphopenia was ruled out in 6 out of 11 patients, though this underlying condition is highly unlikely in the rest of the series.
- HIV infection was strictly ruled out.
- Median age of onset was 50 years old (36-60).
- Presentation was similar to classic KS in terms of course (more indolent), except for the youngest of patients who required systemic chemotherapy due to multiple relapsing and lymphedema.
- Type of lesions: nodules and patches.
- Distribution of lesions:

Location	n/N (%)
Lower extremities	5/11 (45.5%)
Foot (sole-dorsum)	4/11 (36.6%)
Upper extremities	3/11 (27.3%)
Trunk	1/11 (9%)
Mucosal	1/11 (9%)

Kaposi's sarcoma in HIV negative men who have sex with men: an emerging problem

Ander Mayor-Ibarguren, Kieron Leslie and Toby Maurer

UCSF Dermatology department

Results

- Overall Survival 100% (6 years follow-up)
- Treatments and Response :

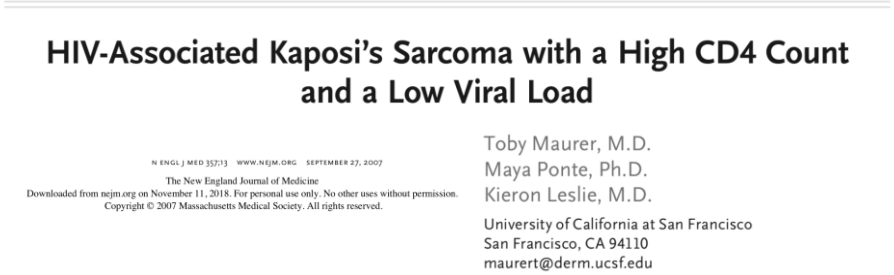
Treatment	n/N	Response
Criotherapy	2/11	Partial.
IL Vinblastine	1/11	Failure
Radiotherapy	1/11	Failure
Lyposomal Doxorrubicin	1/11	Complete
Retinoid	1/11	No resoponse. No progression.
Exicsion	6/11	Complete.
Monitoring	2/11	No progression.

* Youngest of patients. Multiple Lesions. Multiple relapses. Lypmhedema.

** Treatment of Choice for single and small lesions.

** * Refused treatment. No progression.

Sarcoma de Kaposi- Posibles nuevas "variantes epidemiológicas"



HIV-Associated Kaposi's Sarcoma with a High CD4 Count and a Low Viral Load

N ENGL J MED 357;13 WWW.NEJM.ORG SEPTEMBER 27, 2007
The New England Journal of Medicine

Toby Maurer, M.D.
Maya Ponte, Ph.D.
Kieron Leslie, M.D.
University of California at San Francisco
San Francisco, CA 94110
maurert@derm.ucsf.edu

Immunosenescence is associated with presence of Kaposi's sarcoma in antiretroviral treated HIV infection

Patrick Unemori[a], Kieron S. Leslie[a], Peter W. Hunt[b], Elizabeth Sinclair[c], Lorrie Epling[c], Ronald Mitsuyasu[d], Rita B. Effros[d], Jeffrey Dock[d], Sheila G. Dollard[e], Steven G. Deeks[b], Jeffrey N. Martin[f], and Toby A. Maurer[a]

SK en paciente VIH+ con CV baja/indetectable y niveles CD4 altos.

Posible relación "inmunosenescencia acelerada": Casos vs controles

- > CD4 CD57+ CD28-
- > CD8 CD57+ CD28-
- Menor proporción CD4 naive y CD 8 naive
- Mayor expresión CCR5 en CD4 y CD8

Sarcoma de Kaposi- Posibles nuevas "variantes epidemiológicas"

Case report

Kaposi's sarcoma associated with idiopathic CD4+ lymphocytopenia: case report

© Masson, Paris, 2001. Gastroenterol Clin Biol 2001;25:707-710

CAS CLINIQUE

Sarcome de Kaposi digestif primitif avec lymphocytopénie CD4 idiopathique, VIH négatif, HHV8 positif

Abdelkhalek BEN REJEB (1), Nabil EBDELLI (2), Mohamed Riadh BOUALI (2), Aïda GOUCHA (1), Fathi BOUGRINE (1), Faouzi KHEDIRI (2), George DELSOL (3)

(1) Service d'Anatomie Pathologique, (2) Service de Gastroentérologie, Hôpital Militaire, Mont Fleury, Tunis, Tunisie ; (3) Service d'Anatomie Pathologique, Hôpital Purpan, CHU, Toulouse.

- SK en ptes con linfocitopenia CD4 idiopática.
- Ptes HIV neg.
- Escasos casos reportados en la literatura

Sarcoma de Kaposi- Posibles nuevas “variantes epidemiológicas”

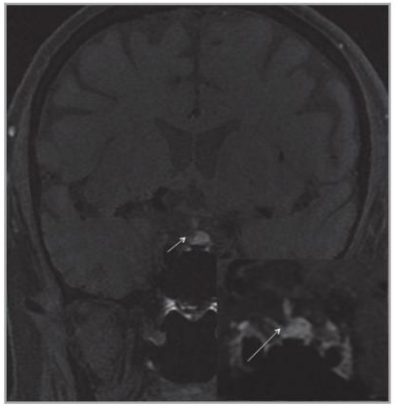
CASE REPORT

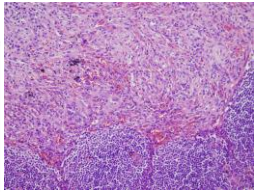
BJD
British Journal of Dermatology

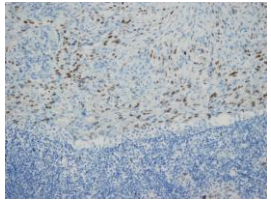
Kaposi sarcoma secondary to endogenous adrenocorticotropic hormone-dependent Cushing syndrome

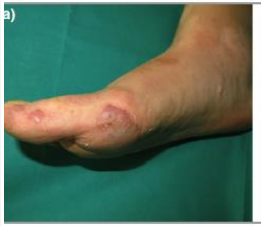
A. Mayor-Ibarguren,[1] M.C. Roldán-Puchalt,[2] T. Sancho-Bueso,[3] C. Pérez-López,[4] J. Álvarez-Linera,[5] R. Frutos,[6] C. Álvarez-Escolá,[2] R. Regojo-Zapata,[7] M.J. Beato-Merino,[7] P. Herranz-Pinto[1] and B. Lecumberri[2]

[1]Department of Dermatology, [2]Department of Endocrinology, [3]Department of Internal Medicine, [4]Department of Neurosurgery, [6]Department of Radiology and [7]Department of Pathology, La Paz Hospital, Paseo de la Castellana 261, Madrid, Spain
[5]Department of Radiology, Hospital Ruber Internacional, Madrid, Spain









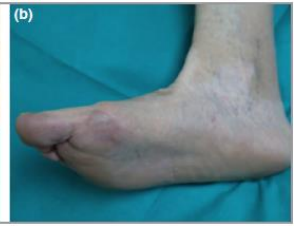
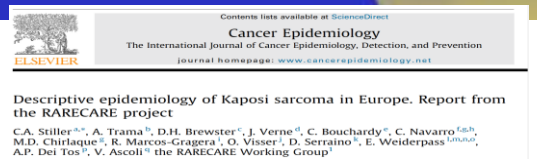


Table 1 Clinical aspects of reported cases of Kaposi sarcoma (KS) associated with endogenous Cushing syndrome (CS) (all HIV-negative)

Patient	1	2	3	4
Reference	Yetkin 2009[9]	Jeng 2011[10]	Bala 2014[11]	Our case
Sex	Female	Male	Female	Male
Age (years)	43	54	60	67
Ethnicity	Not reported	Hispanic	Not reported	White
CS symptoms and signs of progression	HBP (5 years). Fatigue, hirsutism and facial swelling (4 months). Moon face and skin atrophy with bruises detected at presentation. Hypokalaemia	Fatigue and proximal muscle weakness (1 year). Polyuria, DM and hypokalaemia (5 months). Swelling/redness of lower extremities (1 month). Central fat deposition detected at presentation	Central obesity, moon face, muscle atrophy and weakness, asthenia, emotional disturbance and refractory HBP (progressive over 6 years). Polyuria, exertional dyspnoea and DM (weeks). Facial hirsutism, buffalo hump and skin atrophy with bruises detected at presentation	Rapidly progressive severe lower-limb oedema, nocturia and polydipsia (2 weeks). Mild face plethora and dorsal hump, hyperglycaemia, HBP and hypokalaemia detected at presentation
CS aetiology	Ectopic ACTH-secreting hypothalamic 1·5-cm adenoma (base of third ventricle). IPSS central-to-peripheral ACTH ratio 5·2	ACTH-secreting pituitary 1·6-cm adenoma. IPSS central-to-peripheral ACTH ratio 5·72	Benign cortisol-secreting 3·5-cm right adrenocortical tumour (no evidence of malignancy, Weiss score 0)	ACTH-secreting right pituitary 5-mm microadenoma. IPSS central-to-peripheral prolactin-adjusted ACTH ratio (right and left): basal 3·30 and 3·18; 10 min after CRH injection 14·61 and 9·80
KS presentation	Several purple nonblanching nodules and plaques (0·5–2 cm) on abdomen, lower extremities, toes of both feet and eyelids. Detected after CS diagnosis, increased rapidly in a few days	Numerous raised nonblanching purple plaques (0·5–2 cm) on lower extremities. Detected 1 month before presentation	Multiple bilateral pulmonary nodules (confirmed by thoracoscopic wedge resection). No skin lesions. No involvement of the gastrointestinal tract or other organs	Multiple violaceous plaques on both feet and right arm. Subtle feet lesions detectable at presentation. Mediastinic lymph nodes (right pulmonary ligament)
CS treatment	Transcranial surgery (right trans-sylvian approach) and successful resection of the hypothalamic adenoma. Postsurgical adrenal insufficiency	Two consecutive unsuccessful trans-sphenoidal surgeries. Bilateral adrenalectomy (left adrenal not fully removed). Postsurgical normocortisolaemia after adrenalectomy	Right laparoscopic adrenalectomy. Postsurgical adrenal insufficiency	Metyrapone 750 mg per day. Trans-sphenoidal surgical resection (endoscopic endonasal approach). Postsurgical persistent hypercortisolism, well controlled with metyrapone 250 mg per day
KS course	One month after transcranial surgery, all cutaneous lesions had disappeared spontaneously	Four months after adrenalectomy, KS was treated with combination chemotherapy: four cycles of liposomal doxorubicin 20 mg m^{-2} and paclitaxel 25 mg m^{-2} every 2 weeks over a 4-month period	Complete disappearance of pulmonary KS lesions 3 months after adrenalectomy	Complete disappearance of lesions after normocortisolism achievement. Metyrapone was stopped one year after surgery
Comments	Multiple KS cutaneous lesions in a young woman that resolved after hypercortisolism disappearance supports the aetiological relationship	The age of the patient, location of the cutaneous lesions and the need for chemotherapy despite controlling the immunosuppressive condition might suggest a classical KS. Still, the temporary relationship strongly suggests a CS-related KS	The involution of advanced pulmonary KS after adrenalectomy supports the aetiological relationship between ECS and KS	The involution of KS after medical and surgical treatment of CS strongly supports the aetiological relationship between ECS and KS. No systemic treatment for KS was necessary despite mediastinal lymph involvement

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; CS, Cushing syndrome; DM, diabetes mellitus; ECS, endogenous CS; HBP, high blood pressure; IPSS, inferior petrosal sinus sampling.

Sarcoma de Kaposi- Epidemiología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Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Descriptive epidemiology of Kaposi sarcoma in Europe. Report from the RARECARE project

C.A. Stiller[a,*], A. Trama[b], D.H. Brewster[c], J. Verne[d], C. Bouchardy[e], C. Navarro[f,g,h], M.D. Chirlaque[g], R. Marcos-Gragera[i], O. Visser[j], D. Serraino[k], E. Weiderpass[l,m,n,o], A.P. Dei Tos[p], V. Ascoli[q] the RARECARE Working Group[†]

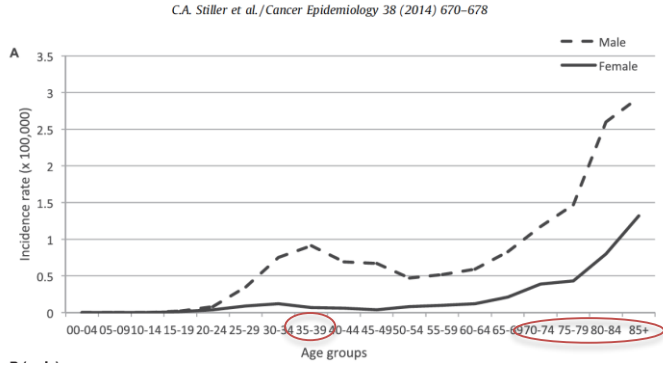
- Estudio RARECARE 1995-2002
- Incidencia : 0'3 casos/100000 habitantes (o'8 Sur Europa).
- H: M = 3:1

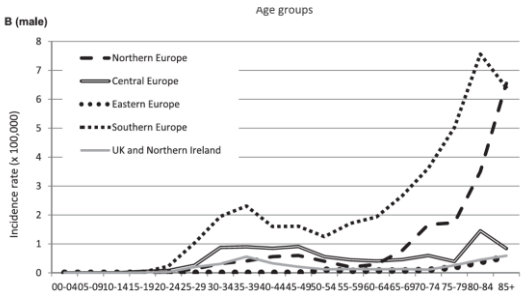
- Pico incidencia (s/t H):

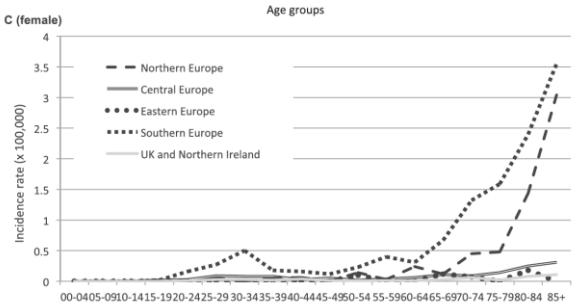
a) 35-39a (se piensa q VIH+)

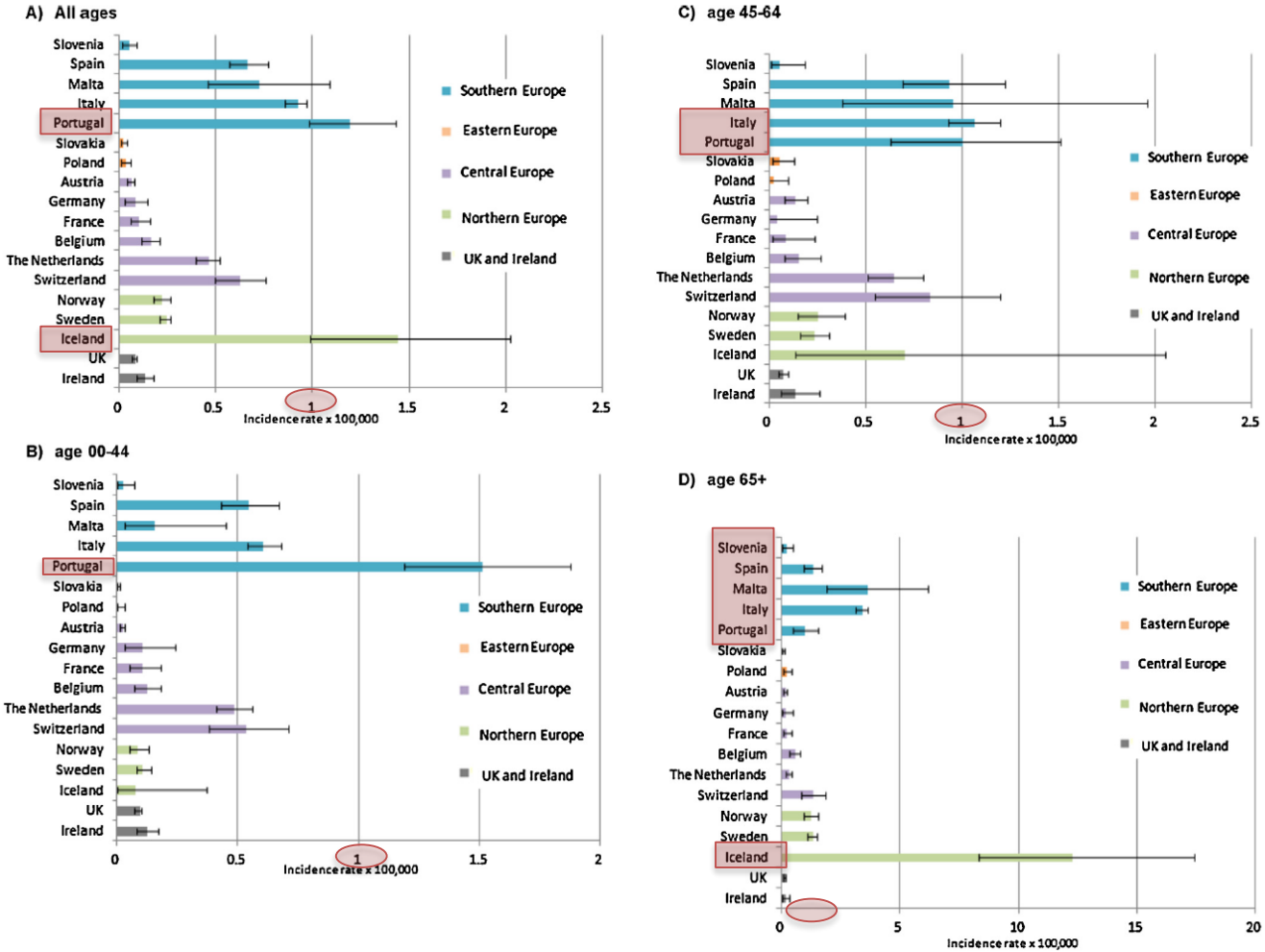
b) >70a

No datos VIH, Tx








A) All ages
Slovenia
Spain
Malta
Italy
Portugal
Slovakia
Poland
Austria
Germany
France
Belgium
The Netherlands
Switzerland
Norway
Sweden
Iceland
UK
Ireland
Southern Europe
Eastern Europe
Central Europe
Northern Europe
UK and Ireland
0
0.5
1
1.5
2
2.5
Incidence rate x 100,000
B) age 00-44
Slovenia
Spain
Malta
Italy
Portugal
Slovakia
Poland
Austria
Germany
France
Belgium
The Netherlands
Switzerland
Norway
Sweden
Iceland
UK
Ireland
Southern Europe
Eastern Europe
Central Europe
Northern Europe
UK and Ireland
0
0.5
1
1.5
2
Incidence rate x 100,000
C) age 45-64
Slovenia
Spain
Malta
Italy
Portugal
Slovakia
Poland
Austria
Germany
France
Belgium
The Netherlands
Switzerland
Norway
Sweden
Iceland
UK
Ireland
Southern Europe
Eastern Europe
Central Europe
Northern Europe
UK and Ireland
0
0.5
1
1.5
2
2.5
Incidence rate x 100,000
D) age 65+
Slovenia
Spain
Malta
Italy
Portugal
Slovakia
Poland
Austria
Germany
France
Belgium
The Netherlands
Switzerland
Norway
Sweden
Iceland
UK
Ireland
Southern Europe
Eastern Europe
Central Europe
Northern Europe
UK and Ireland
0
5
10
15
20
Incidence rate x 100,000

Sarcoma de Kaposi- Epidemiología

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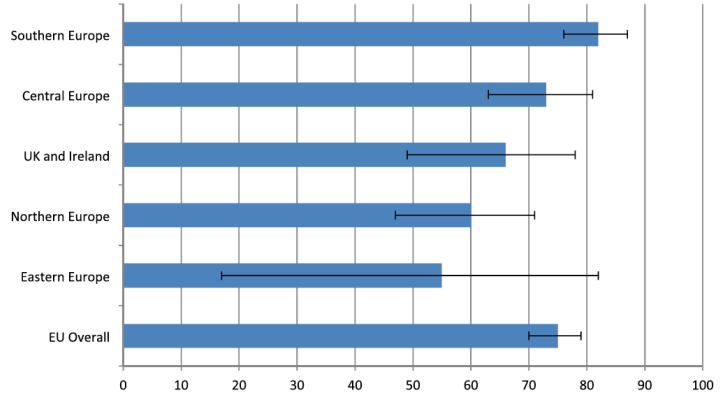


Fig. 3. Five-year relative survival of Kaposi sarcoma by EU Regions. Period survival analysis 2000–2002. Error bars are 95% CI.

TARGA

Table 5
Kaposi sarcoma in Europe. Five-year relative survival from 1991 to 2002.

	N (1987–2002)	% survival (95% CI)			
		1991–1993	1994–1996	1997–1999	2000–2002
Kaposi sarcoma					
00–44 years	1147	17 (13–22)	19 (15–24)	67 (59–74)	71 (62–78)
45–64 years	572	25 (18–33)	39 (30–48)	70 (59–79)	72 (61–81)
65+ years	852	74 (58–85)	71 (57–82)	73 (58–83)	66 (53–76)

- SPV 5años 75% en ptes >65años (SK clásico)
- SPV 5 años en ptes <65 años cambia drásticamente a partir 1997 (SK asociado SIDA)

Sarcoma de Kaposi- mortalidad SK clasico

British Journal of Cancer (2009) 101, 1085 – 1090

www.bjcancer.com

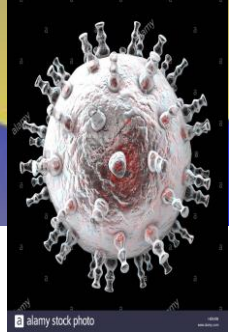
Cause-specific mortality in classic Kaposi's sarcoma: a population-based study in Italy (1995–2002)

V Ascoli*,[1], G Minelli[2], M Kanieff[2], R Crialesi[3], L Frova[3] and S Conti[2]

[1]Dipartimento di Medicina Sperimentale, Università La Sapienza, Viale Regina Elena 324, 00161 Rome, Italy; [2]Ufficio di Statistica, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy; [3]Servizio Sanità e Assistenza, ISTAT, Viale Liegi 13, 00198 Rome, Italy

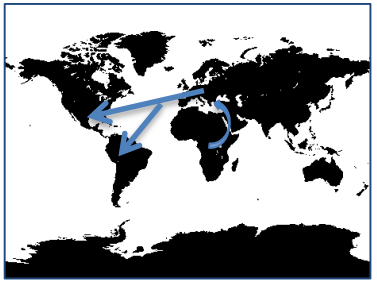
12.2% SK
21.9% otras neoplasias
65.9% otras causas.

65% Varones media edad 82años
35% Mujeres media edad 82años



Sarcoma de Kaposi- VHH8

- VHH8 o KSHV; virus oncogénico causa necesaria para el desarrollo de enfermedades relacionadas (SK, PEL, Enf. Castleman)



- Se trata de un herpes virus, de la subfamilia gammavirus (VEB). 4 subtipos:

B: África. Presente en hombres modernos África.

D: Europa del Este y Asia

A and C: Europa, Norte Asia y América.

A: Variante progresiva. Mas frecuente ptes HIV + en Brasil. C HIV negativo.

C: Variante lentamente progresiva

- Mecanismo de infección no esclarecido

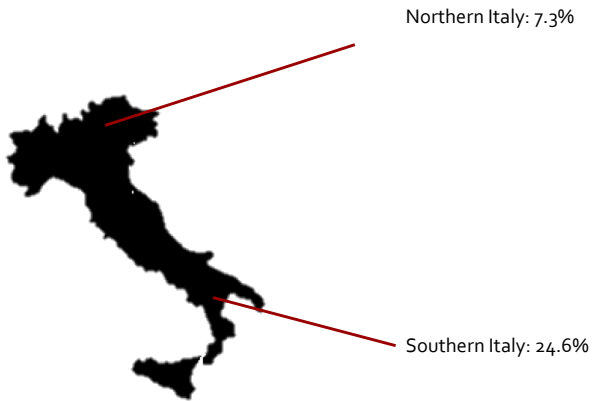
Infección variable en el mundo y dentro de cada región: asociación con incidencia de los tumores relacionados

S. Li et al. Kaposi's sarcoma-associated Herpes virus : Epidemiology and Molecular Biology. Adv Exp Med Biol. 2017;1018:91-127. doi: 10.1007/978-981-10-5765-6_7.

Non-endemic=<10%

Intermidiate-endemic: 10-25% Mediterranean area

High-level endemic: Uganda: 62% HIV-negative men w/o KS[3]



Variabilidad alta

USA: Población general <5%.

The New England Journal of Medicine

SEXUAL TRANSMISSION AND THE NATURAL HISTORY OF HUMAN HERPESVIRUS 8 INFECTION

JEFFREY N. MARTIN, M.D., M.P.H., DONALD E. GANEM, M.D., DENNIS H. OSMOND, PH.D., KIMBERLY A. PAGE-SHAFER, PH.D., DON MACRAE, B.S., AND DEAN H. KEDES, M.D., PH.D.

CONCISE COMMUNICATION

Correlates of Prevalent and Incident Kaposi's Sarcoma–Associated Herpesvirus Infection in Men Who Have Sex with Men

Corey Casper,[1] Anna Wald,[1,2,3] John Pauk,[1] Stephen R. Tabet,[1] Lawrence Corey,[1,3,4] and Connie L. Celum[1]

Departments of [1]Medicine, [2]Epidemiology, and [3]Laboratory Medicine, University of Washington, and [4]Program in Infectious Disease, Fred Hutchinson Cancer Research Center, Seattle, Washington

MSM population:

Variabilidad alta

25-60% in HIV infected patients
20-30% in HIV-uninfected patients.

Sarcoma de Kaposi- VHH8

Fuente biológica:

Saliva	Semen	Mujeres	Tracto digestivo
• 50 ptes HSH infectados por HHV-8 sin SK, se detectaba en el **39%** el virus en saliva el 35% de los días vs 1% en región anal y genital. • Ptes con SK se detectó HHV-8 en **saliva (39%) vs 12% semen**. El numero de copias Saliva (33000) vs plasma (300) vs semen (40). • 44 HSH Seattle: 61% positividad HHV-8 Saliva. • 1/3 de trabajadores sexuales en Kenia • 1/4 de madres de pacientes con anemia perniciosa en Uganda.	• Eliminación intermitente y menor numero de copias que en saliva • Reservorio prostático: se ha encontrado postitividad HHV-8 en tejido próstata de ptes con SK.	Tracto Genitourinario • Infrecuente • Frotis cervicovaginal mujeres HIV: (0'33%-7%) Leche materna • Infrecuente • Positividad baja en mujeres de Zambia y Sudáfrica	• Infrecuente • 1.4% ptes HSH HHV-8 +

Sarcoma de Kaposi- VHH8

Transmisión

Sexual	No sexual	Transfusión sanguínea	Tx órgano solido
• En ptes HSH asociación entre positividad seroconversión y el numero de parejas sexuales e historia de ITS • Seroprevalencia mayor entre mujeres y hombres que atienden clínicas ITS vs donantes de sangre	• Niños en Africa HHV-8 + y desarrollan SK antes pubertad. • Seropositividad mayor entre familiares cercanos en regiones endémicas (transmisión horizontal)	• Riesgo de seroconversión 2,8% en Uganda • No evidencia en USA y Europa • (transfusiones no leucorreducidas– viremia inusual en ptes HHV-8 +)	• 220 ptes tx renales: Aumento de seroconversión HHV-8 de 6% a 18% en un año 5 de estos 6 ptes el donante era HHV-8+ • Evidencia de transmisión KS

Saliva explicaría transmisión sexual y horizontal

Sarcoma de Kaposi VHH8

Seroprevalence of Kaposi's Sarcoma-Associated Herpesvirus Among Men Who Have Sex With Men in Japan

Harutaka Katano,[1]* Yoshiyuki Yokomaku,[2] Hitomi Fukumoto,[1] Takayuki Kanno,[1] Tomoyuki Nakayama,[2] Akitomo Shingae,[3] Wataru Sugiura,[2,4] Seiichi Ichikawa,[3] and Akira Yasuoka[5]

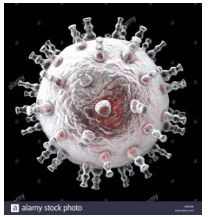
[1]Department of Pathology, National Institute of Infectious Diseases, Tokyo, Japan
[2]Department of Infectious Diseases and Immunology, Clinical Research Center, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan
[3]Department of Communicable Disease Epidemiology and Control, Nagoya City University, School of Nursing, Mizuho-cho, Mizuho-ku, Nagoya, Japan
[4]Department of AIDS Research, Nagoya University Graduate School of Medicine, Nagoya, Japan
[5]Nagasaki University Infection Control and Education Center, Nagasaki University Hospital, Nagasaki, Japan

TABLE II. Multivariate Model of Predictors of Kaposi's Sarcoma-Associated Herpesvirus (KSHV) Seropositivity in Sexual Behaviors

Question	Answer	KSHV+	Total	%	AOR (95% CI)*	*P*
Sexual orientation	Homosexual	25	196	12.76	Reference	
	Bisexual	2	34	5.88	0.431 (0.088–2.117)	0.300
Possibility of HIV infection	No	14	144	9.70	Reference	
	Yes	13	86	15.10	1.867 (0.767–4.544)	0.169
Sexual behaviors in last 6 months	No	2	10	20.00	Reference	
	Yes	25	216	11.60	0.356 (0.59–2.144)	0.260
Performance of insertive anal sex with main partner	Not wearing condom	4	30	13.30	Reference	
	Sometimes wearing condom	4	39	10.30	1.077 (0.141–8.224)	0.943
	While wearing condom	6	56	10.70	0.737 (0.095–5.724)	0.771
Receipt of anal sex with main partner	Partner not wearing condom	3	29	10.30	Reference	
	Partner sometimes wearing condom	2	30	6.70	1.467(0.123–17.574)	0.762
	Partner wearing condom	8	50	16.00	3.676 (0.365–36.975)	0.269
Performance of insertive anal sex with casual partner(s)	Not wearing condom	5	20	25.00	Reference	
	Sometimes wearing condom	1	31	3.20	0.117 (0.008–1.786)	0.123
	While wearing condom	8	68	11.80	0.346 (0.049–2.419)	0.285
Receipt of anal sex with casual partner(s)	Partner not wearing condom	4	14	28.60	Reference	
	Partner sometimes wearing condom	1	31	3.20	0.093 (0.005–1.699)	0.109
	Partner wearing condom	10	48	20.80	0.737 (0.085–6.400)	0.782

*AOR, adjusted odds ratio; CI, confidence interval.

Sarcoma de Kaposi- VHH8



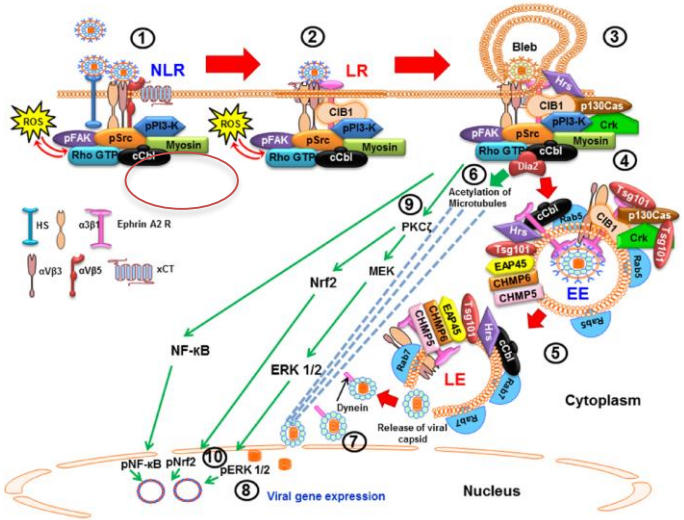
Infección

- HHV-8 **amplio tropismo celular: Linf B**, células endoteliales, macrófagos y células epiteliales.

- Glicoproteina B y K8.1 adhesión a la célula
- Glicoproteinas gH y gL criticas para invasión celular

- Se une a diversas moléculas:
  - heparan sulfato
  - Integrinas
  - DC-SIGN
  - xCT

- **Ephrin A2 R: interactua con receptor de andrógenos en células endoteliales.**



Sarcoma de Kaposi- VHH8

Fase latente- fase lítica

- Orf50: región génica que induce fase lítica
- Citoquinas y cofactores: oncostatina M, factor de crecimiento hepatocito, IFN-gamma, vitamina D3, hipoxia
- Citoquinas inflamatorias asociadas VIH
- miRNA que reduzcan actividad NFkB
- Interacción con TLR-7 y TLR-8

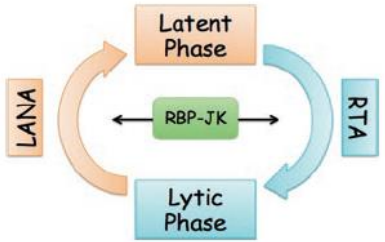


Fig. 7.2 Model for the switch of the latent phase and lytic phase. The model for the switch of the latent phase and lytic phase: LANA and RTA control the switch between latency and lytic reactivation through targeting of the RBP-Jκ effector protein

S. Li et al. Kaposi's sarcoma-associated Herpes virus : Epidemiology and Molecular Biology. Adv Exp Med Biol. 2017;1018:91-127. doi: 10.1007/978-981-10-5765-6_7.

Sarcoma de Kaposi

Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma–associated herpesvirus

Young-Kwon Hong[1], Kimberly Foreman[2], Jay W Shin[1], Satoshi Hirakawa[1], Christine L Curry[2], David R Sage[3], Towia Libermann[4], Bruce J Dezube[3], Joyce D Fingeroth[3] & Michael Detmar[1]

Kaposi sarcoma is considered a neoplasm of lymphatic endothelium infected with Kaposi sarcoma–associated herpesvirus. It is characterized by the expression of lymphatic lineage–specific genes by Kaposi sarcoma tumor cells. Here we show that infection of differentiated blood vascular endothelial cells with Kaposi sarcoma–associated herpesvirus leads to their lymphatic reprogramming; induction of ~70% of the main lymphatic lineage–specific genes, including *PROX1*, a master regulator of lymphatic development; and downregulation of blood vascular genes.

Published online 27 June 2004; doi:10.1038/ng1383

NATURE GENETICS VOLUME 36 | NUMBER 7 | JULY 2004

Published in final edited form as:
Cancer Res. 2012 November 15; 72(22): 5833–5842. doi:10.1158/0008-5472.CAN-12-1229.

Lymphatic Reprogramming by Kaposi Sarcoma Herpes Virus Promotes the Oncogenic Activity of the Virus-Encoded G-protein Coupled Receptor

Berenice Aguilar[1,4], Inho Choi[1,4], Dongwon Choi[1], Hee Kyoung Chung[1], Sunju Lee[1], Jaehyuk Yoo[1], Yong Suk Lee[1], Yong Sun Maeng[1], Ha Neul Lee[1], Eunkyung Park[1], Kyu Eui Kim[1], Nam Yoon Kim[1], Jae Myung Baik[1], Jae U. Jung[2], Chester J. Koh[3], and Young-Kwon Hong[1]

[1] Department of Surgery and Department of Biochemistry and Molecular Biology, Norris

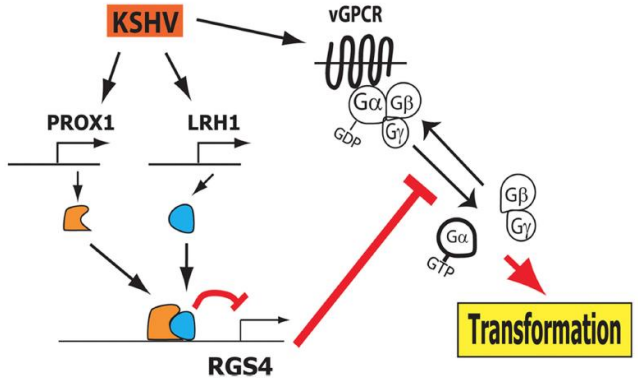


Figure 7. Working hypothesis of PROX1/LRH1-mediated inhibition of RGS4 expression to protect vGPCR activity for KS tumorigenesis
Acting as aGTPase-activating protein (GAP)of cellular GPCRs, RGS4 can also antagonize KSHV viral GPCR activity. In order to ensure the maximum activity of vGPCR, KSHV-mediated upregulation of a nuclear receptor LRH1 and its interacting coregulator PROX1 leads to cooperative suppression of the expression of RGS4, a newly identified inhibitor of vGPCR.

Sarcoma de Kaposi- Factores de riesgo

FR		
VHH-8	Cepa “A” asociado a mayor carga viral y anticuerpos líticos y latentes del virus vs Cepa “C”	
Genes inmunomoduladores	Haplotipos del receptor beta IL-8 e IL-13. Genes que codifican para STAT4 (relacionado con IFN-y) Variantes en promotores de IL-6 e IL-4	
IS (AIDS + Tx)	Niveles Linfocitos T Niveles Linfocitos T CD4 Niveles Linfocitos B Aplicación Corticoides tópicos	Corticoides sistémicos Inmunosenescencia.
Activación inmune	Relación con niveles de neopterina y b2-microglobulina, CXVL-10, sIL-1RII, sIL-2RA y CCL-3	Asma y pacientes alérgicos (uso CT?)

Sarcoma de Kaposi- Factore de riesgo

FR	
Sexo	Más frecuente en varones en todas sus variantes.
Asociación con otras neoplasias	• Hasta 20 veces incremento de riesgo de desarrollar neoplasias hematológicas (Linfoma no hodking, linfoma hodking, leucemia) • Israel: Linfoma hodking OR=7.5 / LNH OR= 5.3 / Leucemia cronia OR=10. (S/T en inmigrantes de Union Soviética y Polonia
Anemia	
Exposición a suelo volcánico / suelo luvisol	• Riesgo de SK 2 veces mayor en la población cerca del monte Vesubio vs alrededores • Luvisol: tipo de suelo dentro de zona con suaves pendientes y llanuras en climas donde se definen notablemente estaciones secas y húmedas. Ricos en Hierro y sales de aluminio.
Exposición a ciertos atrópodos	

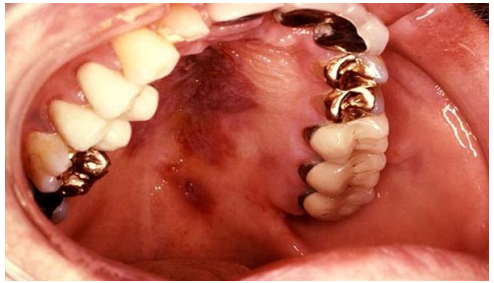
Sarcoma de Kaposi- Factores de riesgo

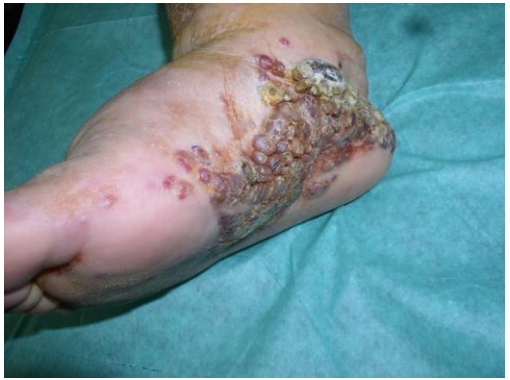
FR	
Tabaco	**Factor protector en diversos estudios. Efecto acumulativo (mayor protección 40paq/año que 10 paq/año**
Edema crónico de miembros inferiores	
Diabetes mellitus	

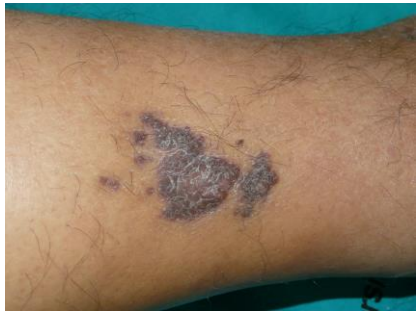
Sarcoma de Kaposi- Clínica

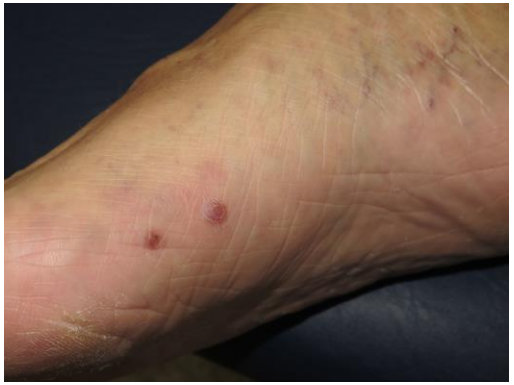
Afectación cutánea:

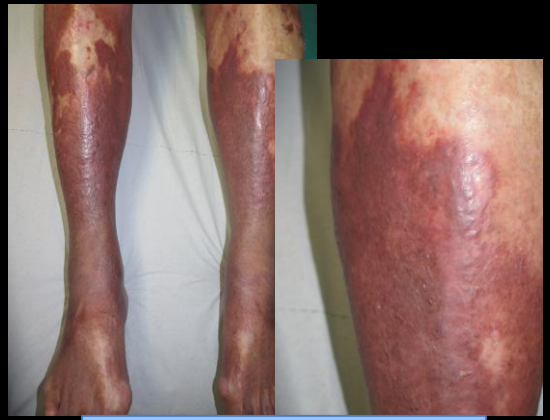
- Parches, placas o nódulos (únicos o múltiples) eritematovioláceos
- Localizaciones típicas:
  - EEII
  - Mucosa oral, glande
- Puede asociar linfedema
- Dx clínico, se recomienda confirmar con bp





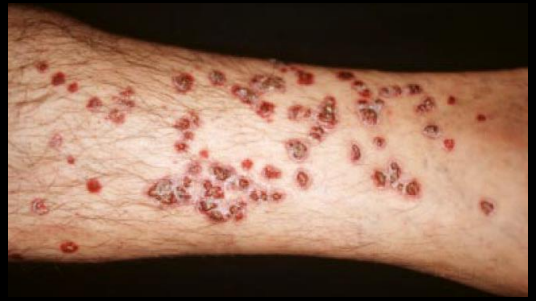






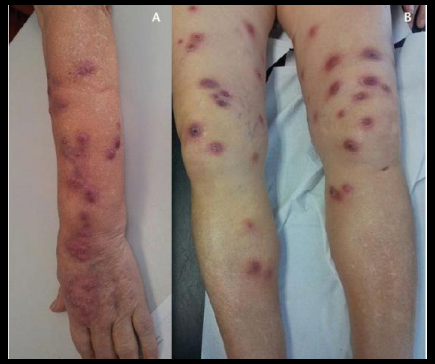
Pseudokaposi

Rodriguez G Angiomatosis Bacilar Rev Biomed 2002

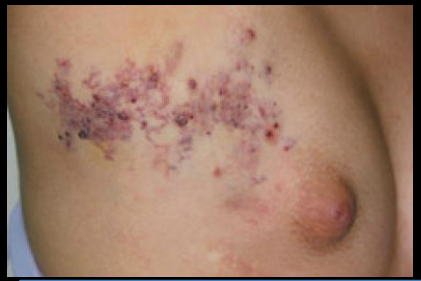


Angiomatosis bacilar

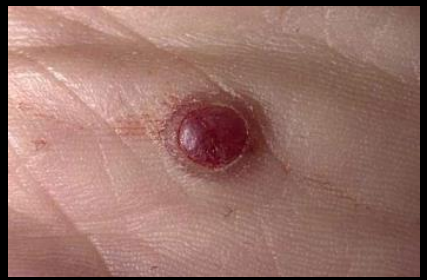
Colás Oros CE et al. Emergencias 2015;27:135



Micobacteriosis atípica

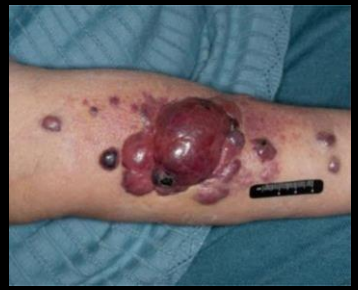


Linfangiomatosis

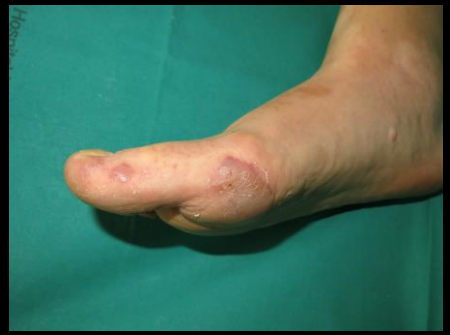


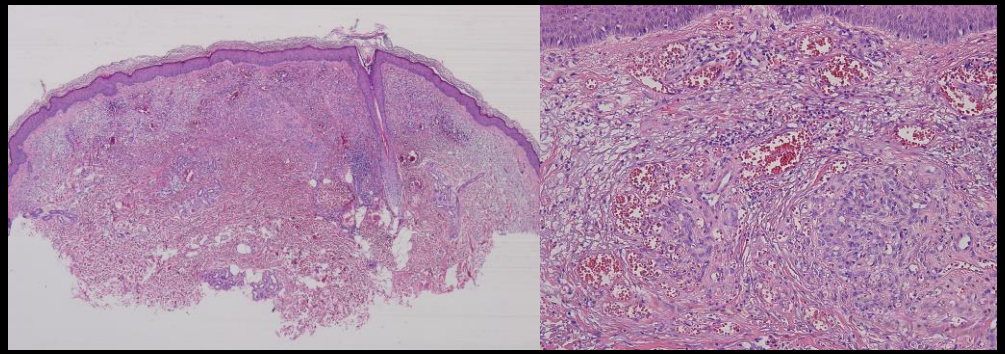
Granuloma Piógeno

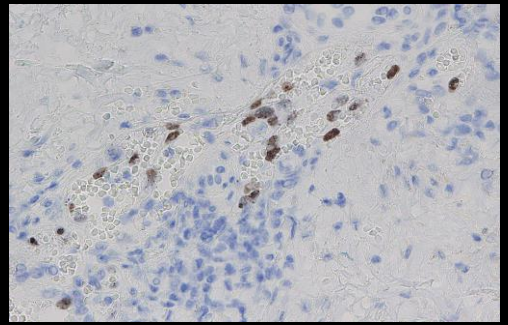
Wagner MJ Endothelial cell malignancies: new insights from the laboratory and clinic NPJ 2017

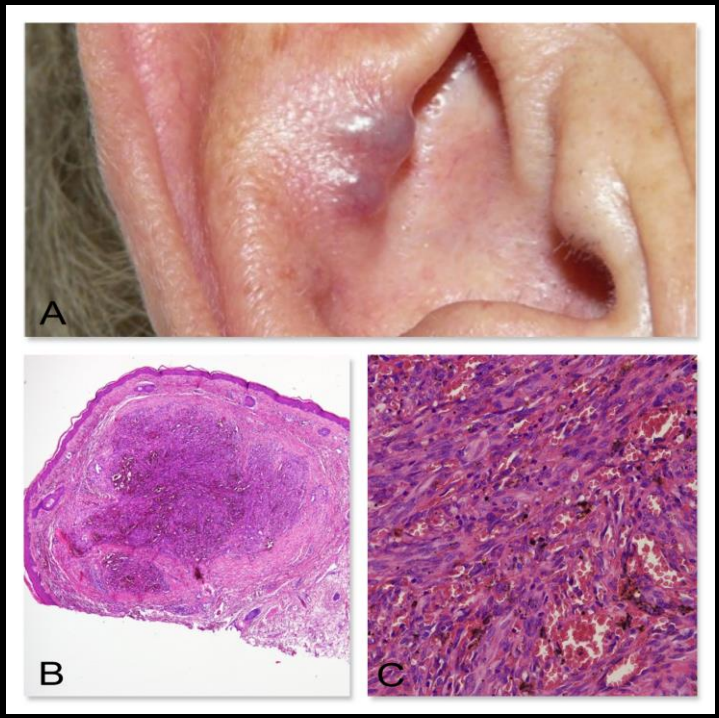


Angiosarcoma







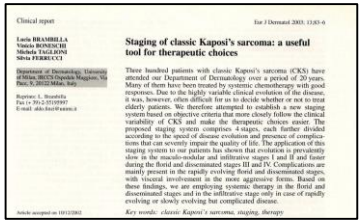


Positividad VHH8:
Especifico

Sarcoma de Kaposi-Estadificación

SK clásico

- Dado el curso indolente no esta esclarecido el papel de evaluación a distancia de la enfermedad. Guiarse según anamnesis.
- No estatificación ultima versión AJCC.
- Grupo Italiano propone un sistema 2003



Clinical report

Eur J Dermatol 2003; 13:83–6

Lucia BRAMBILLA
Vittorio BONESCHI
Michela TAGLIONI
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Staging of classic Kaposi's sarcoma: a useful tool for therapeutic choices

Three hundred patients with classic Kaposi's sarcoma (CKS) have attended our Department of Dermatology over a period of 20 years. Many of them have been treated by systemic chemotherapy with good responses. Due to the highly variable clinical evolution of the disease, it was, however, often difficult for us to decide whether or not to treat elderly patients. We therefore attempted to establish a new staging system based on objective criteria that more closely follow the clinical variability of CKS and make the therapeutic choices easier. The proposed staging system comprises 4 stages, each further divided according to the speed of disease evolution and presence of complications that can severely impair the quality of life. The application of this staging system to our patients has shown that evolution is prevalently slow in the maculo-nodular and infiltrative stages I and II and faster during the florid and disseminated stages III and IV. Complications are mainly present in the rapidly evolving florid and disseminated stages, with visceral involvement in the more aggressive forms. Based on these findings, we are employing systemic therapy in the florid and disseminated stages and in the infiltrative stage only in case of rapidly evolving or slowly evolving but complicated disease.

Key words: classic Kaposi's sarcoma, staging, therapy

Article accepted on 10/12/2002

Table I. *Mediterranean Kaposi's sarcoma staging*

Stage	Skin lesions	Localization	Behaviour	Evolution	Complications*
I - Maculo-nodular (± v)	Nodules and/or macules	Lower limbs	Non aggressive	Slow (A) Rapid (B)	• Lymphedema • Lymphorrea
II - Infiltrative (± v)	Plaques	Lower limbs	Locally aggressive	Slow (A) Rapid (B)	• Hemorrhage • Pain
III - Florid (± v)	Angiomatous nodules and plaques	Limbs, lower prevalent	Locally aggressive	Slow (A) Rapid (B)	• Functional impairment
IV - Disseminated (± v)	Angiomatous nodules and plaques	Limbs, trunk, head	Disseminated aggressive	Rapid (B)	• Ulceration

v: visceral involvement (pharyngo-oral cavity, gastroenteric tract, lymph nodes, bone marrow, lungs).
Rapid: increase in total number of nodules/plaques or in total area of plaques in the three months following an examination.
** All of them prevalent in stage III and IV, lymphedema and lymphorrea often observed in stage II, lymphedema and hemorrhage sometimes present in stage I.*

Table III. *Applied therapeutic choices according to mediterranean Kaposi sarcoma staging*

Stage	Therapy
I A-B/Bc	Elastic stocking and/or intralesional chemotherapy
II A	Elastic stocking; intralesional chemotherapy only for nodules
II Ac-B/Bc III A/Ac-B/Bc IV A/Ac-B/Bc Visceral involvement (any stage)	Systemic and intralesional chemotherapy, elastic stocking

Sarcoma de Kaposi-Estadificación

SK VIH y por extensión al asociado al IS

- Solicitar Rx Torax; si afectación broncoscopia o TC
- Solicitar sangre oculta en heces; si positivo estudio endoscópico

- Sistema de claisficación pronostica previo a la época TARGA

Tabla 2 Estadificación propuesta por el *AIDS Clinical Trials Group Oncology Committee*

	Buen pronóstico (0)	Mal pronóstico (1)
Tumor	Tumor confinado a la piel o a ganglios o mínima afectación oral	Tumor asociado a edema o ulceración Afectación oral grave SK digestivo SK visceral (no ganglionar)
Inmunidad Enfermedad sistémica	CD4 $\geq$ 200/μl Sin enfermedades oportunistas o muguet Sin síntomas B Índice de Karnofsky $\geq$ 70	CD4 < 200/μl Infecciones oportunistas o muguet Síntomas B[a] Indice de Karnofsky < 70 Otras enfermedades relacionadas con el VIH (p.ej., enfermedad neurológica o linfoma)

SK: sarcoma de Kaposi; VIH: virus de la inmunodeficiencia humana.
[a] Fiebre prolongada, sudoración nocturna, pérdida de peso de más del 10% o diarrea de más de 15 días de duración.

Requena C et al. Sarcoma de Kaposi y angiosarcoma cutáneo: directrices para el diagnóstico y tratamiento. Actas Dermosifiliogr. 2018 https://doi.org/10.1016/j.ad.2018.06.013

Sarcoma de Kaposi- Tratamiento

SK clásico

Lesiones aisladas

1. Observación + Compresión elástica en caso linfedema
2. RT local (BR 85%, RC 58%, mejoría síntomas 58%)
3. Cirugía: Lesiones acrales / molestas
4. Crioterapia
5. TIL:
    1. Vinblistina 0'2mg/ml c/2sem
    2. Vincristina (0,03-0,08mg)
    3. IFN alfa 3-5 MUI 3 v/sem x 4-5sem
6. Tópicos:
    1. Alitretinoina 0'1% gel (Lesiones maculosas)
    2. Imiquimod 5% 3 v/sem x 24 sem
    3. Rapamicina tópica

7. ElectroQT


REVIEW

Treatments for classic Kaposi sarcoma: A systematic review of the literature

Elodie Régnier-Rosencher, MD,[a] Bernard Guillot, MD,[b] and Nicolas Dupin, MD[a]
Paris and Montpellier, France

Sarcoma de Kaposi- Tratamiento

SK clásico

Enfermedad diseminada

1. Doxorrubicina pegilada liposomal (20mg/m2 cada 3 semanas):
    1. De elección, salvo cardiopatía
    2. RP (+ del 50%)o RC en 70% ptes mantenidas 25meses.
    3. Mantener 1-2ciclos tras alcanzar respuesta
    4. Buena tolerancia en general, escasos efectos grados 3-4.

2. Vinblastina (3mg/m2/semanal iv o 6mg/m2/2sem/iv)
    1. Respuestas entre el 50-90%

3. Paclitaxel (100mg/sem iv)
4. Bleomicina (15U/sem x 3 semanas y después cada 3sem/i.m)
5. Etopósido oral (100mg/día 3-5 días en semana)

Sarcoma de Kaposi- Tratamiento

SK VIH

Enfermedad aislada

1. Iniciar TARGA +/- terapia local.

Enfermedad diseminada

- Iniciar TARGA + Doxorrubicina liposomal
- Paclitaxel

- No respuesta 3 meses
- Enf cutánea diseminada >15-25 lesiones
- Aparición SK en SRI
- Afectación visceral

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

AIDS-Related Kaposi Sarcoma

Version 1.2019 — October 19, 2018

NCCN.org

Requena C et al. Sarcoma de Kaposi y angiosarcoma cutáneo: directrices para el diagnóstico y tratamiento. Actas Dermosifiliogr. 2018 https://doi.org/10.1016/j.ad.2018.06.013

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

AIDS-Related Kaposi Sarcoma

Version 1.2019 — October 19, 2018

NCCN.org

SYSTEMIC THERAPY[a]

First-line systemic therapy options

- Liposomal doxorubicin[1,b] (preferred)
  - 20 mg/m² IV every 3 weeks
- Paclitaxel[2]
  - 100 mg/m² IV every 2 weeks (premedication with dexamethasone 10 mg at time of administration is acceptable for prevention of hypersensitivity reaction)

Relapsed/refractory systemic therapy[c] options (advanced cutaneous, oral, visceral, or nodal disease)

If tolerated and durable response (≥3 months) to first-line systemic therapy → Repeat of first-line systemic therapy or Alternate first-line systemic therapy → Progression

If no response to first-line systemic therapy → Alternate first-line systemic therapy[d] → Progression

- Subsequent systemic therapy options for relapsed/refractory therapy
  - Preferred regimen:
    - ◊ Pomalidomide[3]
      - – 5 mg/d orally for 21 days of each 28-day cycle
  - Other regimens (in alphabetical order):
    - ◊ Bevacizumab[4]
      - – 15 mg/kg IV on days 1 and 8 and then every 3 weeks
    - ◊ Etoposide[5]
      - – 50 mg/d orally for 7 days of each 21-day cycle
    - ◊ Gemcitabine[6]
      - – 1000 mg IV every 2 weeks
    - ◊ Imatinib[7]
      - – 400 mg/d orally
    - ◊ Interferon alfa-2b[8]
      - – 1 million International Units SC daily
    - ◊ Nab-paclitaxel[9]
      - – 100 mg IV days 1, 8, and 15 of each 28-day cycle
    - ◊ Thalidomide[10]
      - – 200 mg/d orally (starting dose, titrated to effect and tolerability)
    - ◊ Vinorelbine[11]
      - – 30 mg/m² every 2 weeks

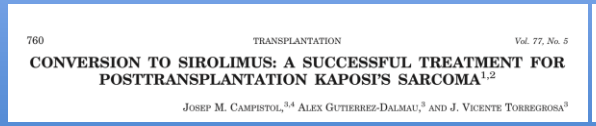
Sarcoma de Kaposi- Tratamiento

SK iatrogénico

1. Disminuir o suspender IS

La disminución de la IS puede llevar a RC del 17% en ptes tx con SK mucocutaneo y visceral

2- Sustituir Cspa por Sirolimus


760 TRANSPLANTATION Vol. 77, No. 5

CONVERSION TO SIROLIMUS: A SUCCESSFUL TREATMENT FOR POSTTRANSPLANTATION KAPOSI'S SARCOMA[1,2]

JOSEP M. CAMPISTOL,[3,4] ALEX GUTIERREZ-DALMAU,[3] AND J. VICENTE TORREGROSA[3]


EDITORIALS

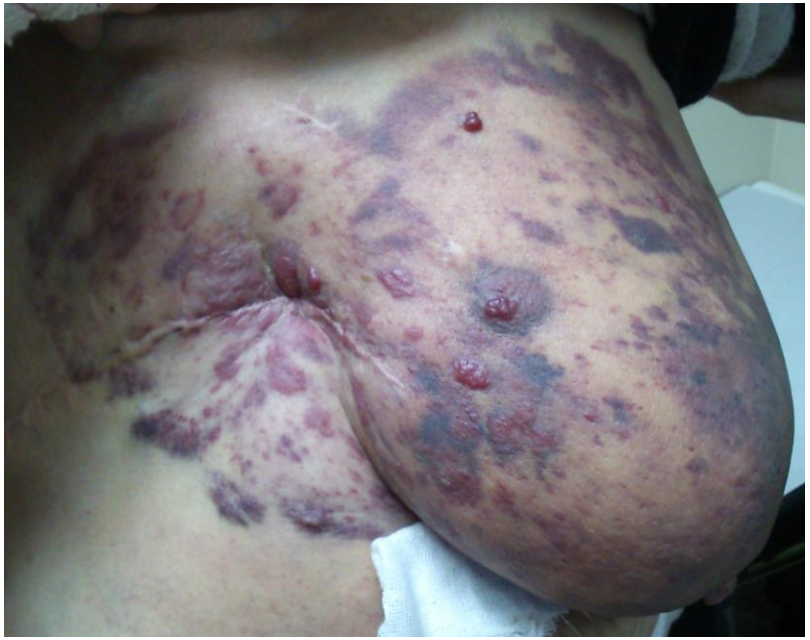
Immunosuppressive Drugs and the Risk of Cancer after Organ Transplantation

Jacques Dantal, M.D., Ph.D., and Jean-Paul Soulillou, M.D.

3- Manejarlo como Kaposi asociado a VIH

SK- ClinicalTrials.gov

Pomalidomida (CC-4047)	Derivado de la talidomida.
Lenalidomida	
EphB4-HSA	Proteína de fusión inhibe angiogénesis
Nivolumab e Ipilimumab	
Everolimus	
Selumetinib	Inhibidor MEK1 y MEK2
halofuginone hydrobromide ointment	Quinazolinona alcaloide inhibidor de Metaloproteinasas
IL-12	
Nivolumab intralesional	
Bevazicumab	



Angiosarcoma

Angiosarcoma

- Representan el 1-2% de todos los sarcomas, aunque la mitad son al menos cutáneos.
- Es una de las neoplasias cutáneas con peor px:
  - Spv 5 años 10%-50%
  - SEER 133 AS 1973-2007: Spv 5ª 34% vs 14% a 10a

- 3 variantes clínicas:
  - Wilson Jones : Idiopáticos de cara y cuero cabelludo
  - Secundarios:
    - Stewart-Treves: En áreas de linfedema brazos de pacientes mastectomizadas de manera radical vs otras localizaciones y causas de linfedema
    - Areas de piel irradiada, s/t en contexto Ca Mama

Angiosarcoma- Epidemiología

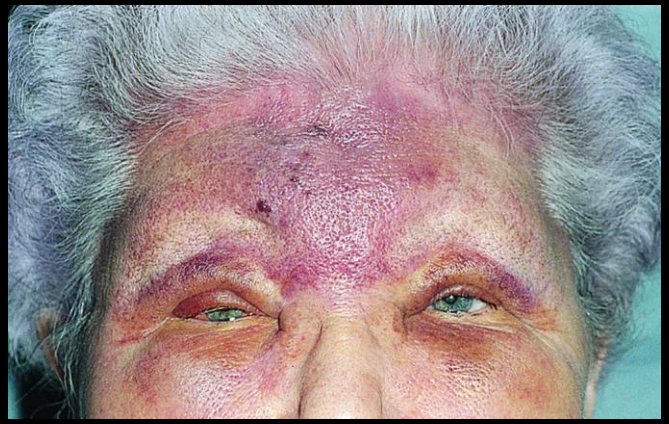
- I angiosarcoma 0’4 casos/millón habitantes USA
- Cutaneos 35-60%. I 0’2 casos /millón habitantes

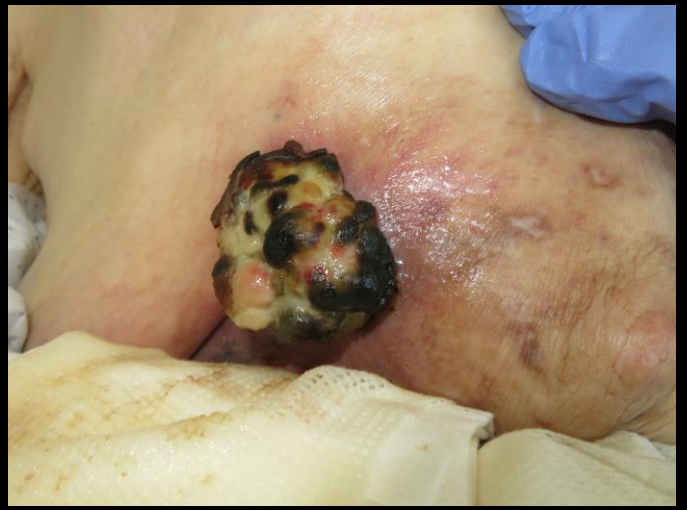
- Edad media dx 73años.

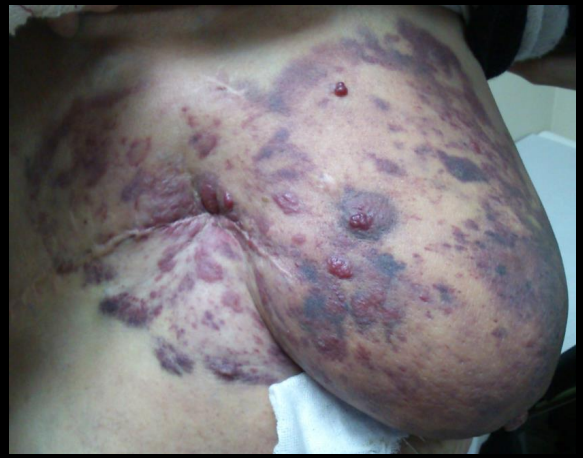
- Raza caucásica

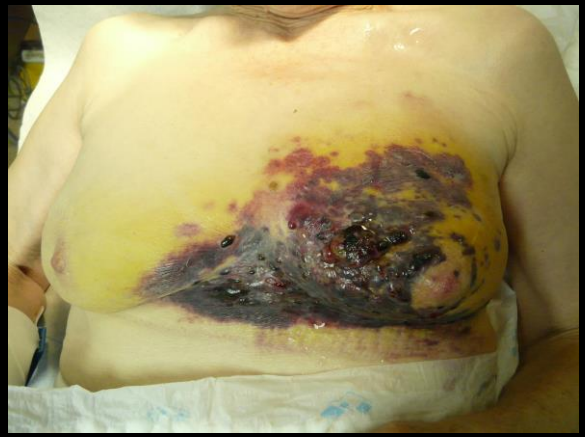
- Sexo:
  - H: Wilson Jones (ratio 2:1)
  - M: postradioterapia

Callen et al. 2000



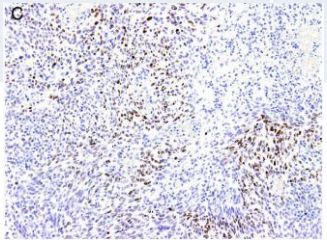






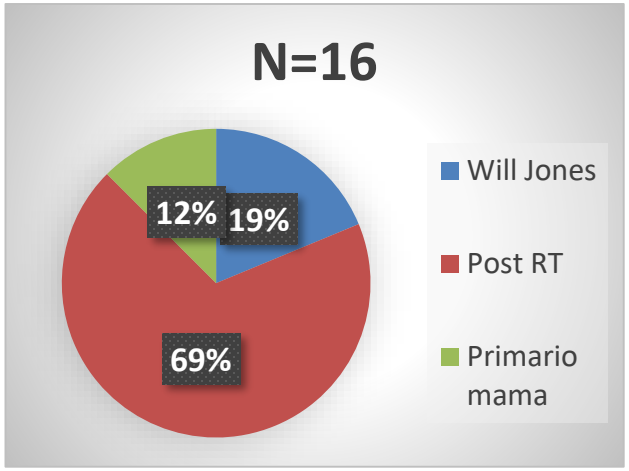
Angiosarcoma- Variantes clínicas

	Wilson Jones	Stewart-treves (Postmastectomia) / Linfedema	Postradioterapia
I	Variante + frecuente cAS <0'1% de tumores mal. Ca y Cu	5% de los AS	• 0,05-0,14% • Su incidencia esta en aumento
Localización	Frente y cuero cabelludo Cabeza y cuello (62%)	Extremidades > pared torácica /abdominal	Pectoral > otras
Clínica	Macula eritematosa➔ edema➔ placa➔ nódulos /ulceración **Carácter multicentrico**	Maculas eritematosas-aspecto hematoma o nódulos violáceos sobre áreas linfedema	Maculas eritematosas-aspecto hematoma o nódulos violáceos sobre áreas radiadas
Tiempo crecimiento/ latencia	Rápido cto	1-30 años Crecimiento rápido	5 años mama 10 años otras localizaciones Media 23,3 años si Rt procesos benignos



Amplificación/sobrexpresión MYC 50-100% de los casos secundarios

Angiosarcoma- Nuestra experiencia en los últimos 10 años

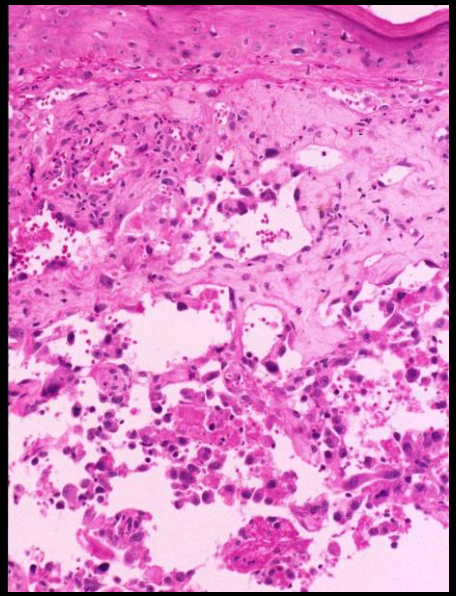


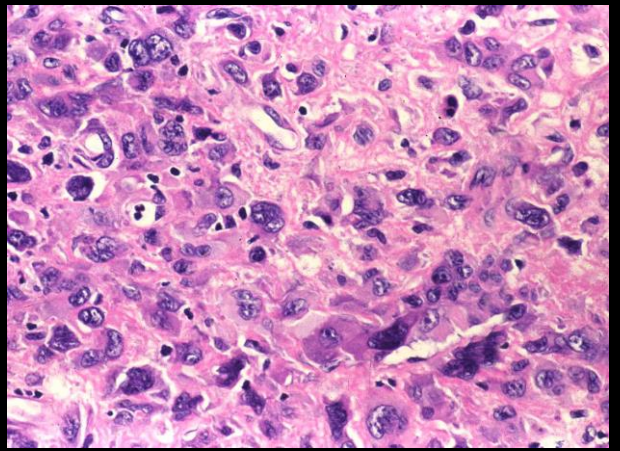
Mediana edad: 56años (26años- 83años)
Sexo M: 14 H: 2
4 perdida seguimiento
De los 12 restantes; 11 fallecimiento.
Tratamiento primario:
- Qx.
- 2 linfadenectomia:
  - 1pte: 2/8 gglios afectos
- Qt + Rt adyuvante: 1 pte

Angiosarcoma- Patogénesis

Factores de riesgo	• Linfostasis • Radiación • Exposición solar crónica (descrito en ptes XP) • Inmunosupresión (HIV y trasplantados) • Fistulas hemodiálisis o en regiones de implantes de materiales		
Mutaciones	<u>Primario</u> • P53 • PTPRB • PLGC1 (transductor señal TK) • NUP160-SCL43A • NTSR-1 • ANKRD1 • CDKN2C • KDR	<u>Secundario</u> • **MYC** • KIT • FLT4 • RET • UNC5A • KDR	• CTLA4 • ISLR2 • ICOS • RAB17 • RASGRP3

Bien diferenciado	Pobremente diferenciado
• Canales vasculares irregulares y dilatados • Disecan a través de los haces de colágeno • Canales anastomosados • Células endoteliales escasa atipia • Alguna con núcleo grande hipercromático con prominencia a la luz vascular, que a veces se agripan formando pequeñas papilas	• Estructuras vasculares irregulares • Celulas endoteliales pleomóficas, (poligonal o fusiformes) • Numerosas mitosis. • Vaculas citoplasmáticas : dx diferencial en áreas solidas con carcinoma, fribroxantoma atípico o melanoma • En ocasiones infiltrado linfoide abundante
• IHQ: Pos: Factor VIII, Ulex europaeus, trombomodulina, **CD34, CD31**, **ERG**, **VEGFR-3, podoplanina**, **WT1**	





Angiosarcoma- Estadificación

- Entre un 10-30% de los casos pueden tener enfermedad a distancia.
- Pulmón > ganglios (rara vez masas bulky)
- Se recomienda realizar TAC toraco abdominal
  - Cervical : AS de Ca
  - Pélvico: AS RT área abdominopelvico
- No estadio clínico especifico TNM AJCC- Adopta el genérico para sarcomas de partes blandas
- Principales fx px Wilson Jones:
  - T >5cm
  - Edad > o= 70ª
  - Debatido el grado hx

Journal of Surgical Oncology

A Prognostic Model for Resectable Soft Tissue and Cutaneous Angiosarcoma

ANDREW J. SINNAMON, MD,[1] MADALYN G. NEUWIRTH, MD,[1] MATTHEW T. MCMILLAN, BA,[1] BRETT L. ECKER, MD,[1] EDMUND K. BARTLETT, MD,[1] PAUL J. ZHANG, MD,[2] RACHEL R. KELZ, MD, MSCE,[1] DOUGLAS L. FRAKER, MD,[1] ROBERT E. ROSES, MD,[1] AND GIORGOS C. KARAKOUSIS, MD[1]*

[1]*Department of Surgery, University of Pennsylvania, Philadelphia, Pennsylvania*
[2]*Department of Pathology, University of Pennsylvania, Philadelphia, Pennsylvania*

TABLE I. Patient and Tumor Characteristics for Nonmetastatic Soft Tissue Angiosarcoma Patients Undergoing Resection From 2004 to 2012, n = 821

Variable	n (%)
Age (median, IQR), years	71 (58–80)
Gender	
Female	539 (65.7)
Male	282 (34.3)
Race	
White	745 (90.7)
Black	55 (6.7)
Other	21 (2.6)
Site	
Trunk	353 (43)
Head and neck	211 (25.7)
Upper extremity	38 (4.6)
Lower extremity	139 (16.9)
Unknown	80 (9.7)
Tumor size (median, IQR), cm	4.5 (2.0–7.5)
<3	254 (30.9)
3–7	315 (38.4)
>7	252 (30.7)
Depth	
Superficial	323 (39.3)
Deep	298 (36.3)
Unknown	200 (24.4)
Grade	
1	110 (13.4)
2	114 (13.9)
3	597 (72.7)
Lymph Node Status	
Negative	107 (13)
Positive	16 (2)
Not examined	698 (85)
Resection margin	
Negative	628 (76.5)
Microscopic	91 (11.1)
Macroscopic	13 (1.6)
Positive, NOS	58 (7.1)
Unknown	31 (3.8)
Chemotherapy	
None	655 (79.8)
Neoadjuvant	38 (4.6)
Adjuvant	128 (15.6)
Radiation Therapy	
None	517 (63.3)
Neoadjuvant	21 (2.6)
Adjuvant	279 (34.2)

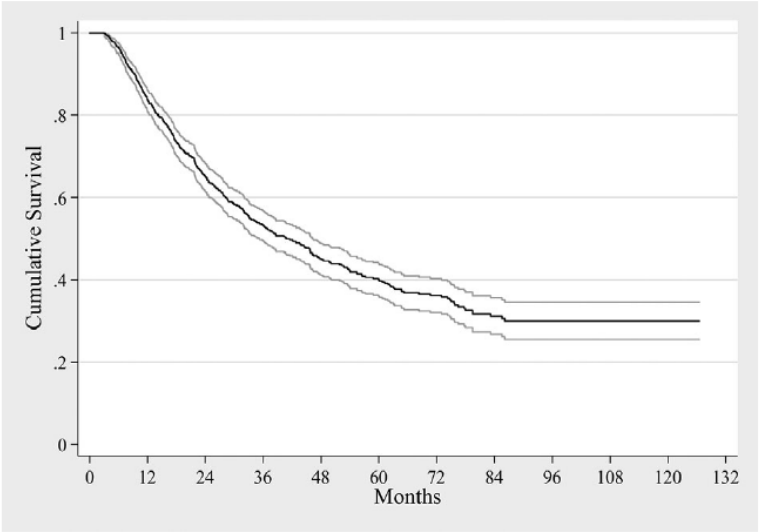
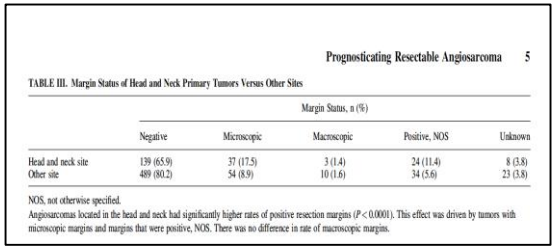


Fig. 1. Overall survival of resected localized soft tissue and cutaneous angiosarcoma, 2004–2012, n = 821. Overall 5-year survival was 39.7% (95% C.I. 35.8–43.7%) and median OS was 3.4 years (95% C.I. 2.9–3.9 yr). 95% confidence intervals are shown as lighter bars.

SPV 5 a 39,7%
Mediana 3.4 años

TABLE II. Univariate and Multivariable Cox Proportional Hazards Modeling of Factors Associated With Poor Overall Survival

	Univariate hazard ratio (95% C.I.)	*P*	Multivariable hazard ratio, preoperative model (95% C.I.)	*P*	Multivariable hazard ratio, postoperative model (95% C.I.)	*P*
Age, years						
≤70	Ref		Ref			
>70	2.08 (1.71–2.53)	<0.0001	2.02 (1.62–2.52)	<0.0001	2.06 (1.67–2.54)	<0.0001
Gender						
Female	Ref					
Male	1.06 (0.88–1.29)	0.589				
Race						
White	Ref	0.004	Ref		Ref	
Black	1.78 (1.27–2.47)	0.001	1.92 (1.35–2.72)	<0.0001	2.01 (1.43–2.82)	<0.0001
Other	0.69 (0.33–1.47)	0.342	0.74 (0.29–18.9)	0.854	0.74 (0.28–1.97)	0.543
Site						
Trunk	Ref	0.0009	Ref		Ref	
Head and neck	1.65 (1.31–2.07)	<0.0001	1.44 (1.13–1.83)	0.003	1.26 (0.96–1.67)	0.075
Upper extremity	1.05 (0.66–1.69)	0.827	0.94 (0.56–1.57)	0.808	0.87 (0.51–1.46)	0.588
Lower extremity	1.27 (0.97–1.68)	0.081	1.11 (0.83–1.49)	0.499	1.07 (0.80–1.43)	0.652
Unknown	1.31 (0.94–1.82)	0.117	1.26 (0.89–1.79)	0.196	1.14 (0.81–1.59)	0.451
Tumor size, cm						
<3	Ref	<0.0001	Ref		Ref	
3–7	1.74 (1.36–2.24)	<0.0001	1.64 (1.26–2.15)	<0.0001	1.58 (1.22–2.05)	<0.0001
>7	2.36 (1.83–3.04)	<0.0001	2.37 (1.78–3.16)	<0.0001	2.24 (1.71–2.92)	<0.0001
Depth						
Superficial	Ref	0.117				
Deep	1.22 (0.98–1.52)	0.069				
Unknown	1.04 (0.81–1.33)	0.757				
Grade						
1	Ref	<0.0001	Ref		Ref	
2	1.64 (1.07–2.49)	0.022	1.21 (0.81–1.80)	0.355	1.27 (0.84–1.91)	0.260
3	2.09 (1.48–2.97)	<0.0001	1.53 (1.10–2.14)	0.013	1.50 (1.07–2.11)	0.019
Lymph Node Status						
Negative	Ref	0.054			Ref	
Positive	2.22 (1.09–4.53)	0.028			1.43 (0.78–2.62)	0.251
Not examined	1.31 (0.98–1.76)	0.071			1.28 (0.95–1.72)	0.110
Resection margin						
Negative	Ref	<0.0001			Ref	
Microscopic	1.96 (1.51–2.56)	<0.0001			1.59 (1.19–2.13)	0.002
Macroscopic	3.24 (1.78–5.93)	<0.0001			3.38 (1.38–8.31)	0.008
Positive, NOS	1.82 (1.31–2.52)	<0.0001			1.60 (1.15–2.23)	0.005
Unknown	1.26 (0.78–2.03)	0.34			1.15 (0.63–2.09)	0.649
Chemotherapy						
None	Ref	0.679				
Neoadjuvant	0.82 (0.50–1.33)	0.424				
Adjuvant	0.95 (0.73–1.23)	0.7				
Radiation Therapy						
None	Ref	0.646				
Neoadjuvant	0.77 (0.39–1.49)	0.439				
Adjuvant	0.94 (0.77–1.15)	0.575				



Prognosticating Resectable Angiosarcoma 5

TABLE III. Margin Status of Head and Neck Primary Tumors Versus Other Sites

	Margin Status, n (%)				
	Negative	Microscopic	Macroscopic	Positive, NOS	Unknown
Head and neck site	139 (65.9)	37 (17.5)	3 (1.4)	24 (11.4)	8 (3.8)
Other site	489 (80.2)	54 (8.9)	10 (1.6)	34 (5.6)	23 (3.8)

NOS, not otherwise specified.

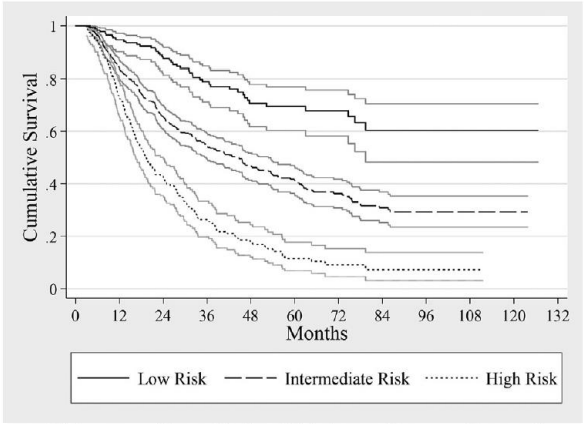
Angiosarcomas located in the head and neck had significantly higher rates of positive resection margins ($P < 0.0001$). This effect was driven by tumors with microscopic margins and margins that were positive, NOS. There was no difference in rate of macroscopic margins.

Los de Cabeza y Cuello eran los que con mayor frecuencia asociaban márgenes + microscópicos o + NOS

TABLE IV. Weighted Risk Score for Nonmetastatic Soft Tissue Angiosarcoma

Factor	Points
Age, years	
<70	0
>70	1
Race	
White/other	0
Black	1
Tumor grade	
1/2	0
3	1
Tumor size, cm	
<3	0
3–7	1
>7	2
Resection margin	
Negative	0
Microscopic/Positive NOS	1
Macroscopic	2

Scores are proportional to magnitude of hazard ratios from factors found significantly associated with poor overall survival in the multivariable model.



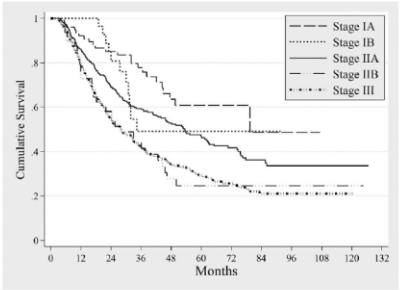
Risk	N	Median OS (yr)	HR	Cox *p*-value
Low	175	Not reached	REF	
Intermediate	461	3.7	2.60	<0.0001
High	185	1.6	5.65	<0.0001

Bajo riesgo 0-1
Riesgo medio 2-3
Alto riesgo >3

VS

6 Sinnamon et al.

AJCC 7ed



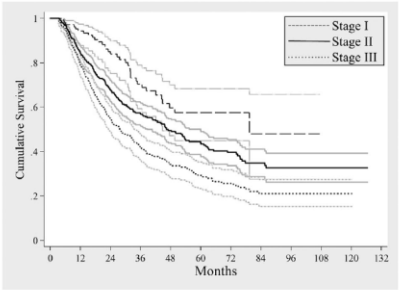
A

	N	Median OS (yr)		N	Median OS (yr)
Stage IA	79	Not Reached	**Stage IIA**	350	4.5
Stage IB	30	2.9	**Stage IIB**	48	2.4
			Stage III	314	2.3

B

	N	Median OS (yr)	HR	Cox *p*-value
Stage I	109	6.7	REF	
Stage II	398	3.9	1.73	<0.0001
Stage III	314	2.3	2.57	<0.0001

AJCC 7ed sin subestadios



A

	N	Median OS (yr)		N	Median OS (yr)
Stage IA	79	Not Reached	**Stage IIA**	350	4.5
Stage IB	30	2.9	**Stage IIB**	48	2.4
			Stage III	314	2.3

B

	N	Median OS (yr)	HR	Cox *p*-value
Stage I	109	6.7	REF	
Stage II	398	3.9	1.73	<0.0001
Stage III	314	2.3	2.57	<0.0001

Journal of Surgical Oncology

A Prognostic Model for Resectable Soft Tissue and Cutaneous Angiosarcoma

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Edad >70ª
Raza negra
Tamaño tumoral (a mayor peor) : (<3 vs 3-7cm vs > 7cm
Márgenes +
Grado 3 histológico

Angiosarcoma- Tratamiento

Cirugía única opción curativa

Tto		Comentarios
Qx	3cm margen- profundidad fascia (musculo en ocasiones) Considerar mapeo con bp previo a Cx.	Edad avanzada ptes. Dx con T > 5cm Carácter multicentrico
Qx + Rt	Parece ofrecer mejores resultados Misma dosis que Rt monoterapia salvo en casos de RT postradioterapia (menos dosis)	2 series AS Ca y Cu no metastásico • 12 ptes: Libres enf 5 • 72ptes: OS 68 % vs 32% SpvEsp 76 % vs 33% Qt neoadyuvante o adyuvante no añade beneficio

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Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp

B. Ashleigh Guadagnolo, MD, MPH[1], Gunar K. Zagars, MD[1], Dejka Araujo, MD[2], Vinod Ravi, MD[2], Thomas D. Shellenberger, DMD, MD[3], and Erich Sturgis, MD, MPH[4,5]

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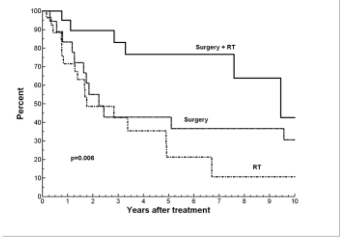

Figure 2.
Disease-specific survival by definitive local therapy

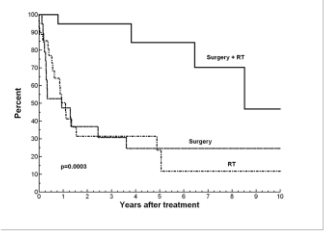

Figure 3.
Local control by definitive local therapy

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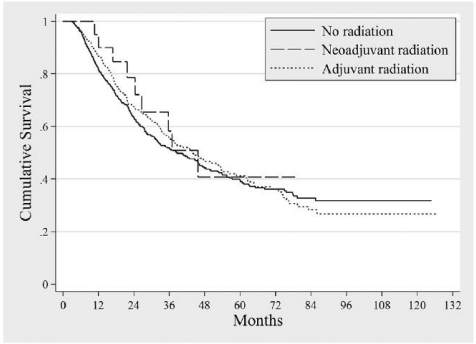
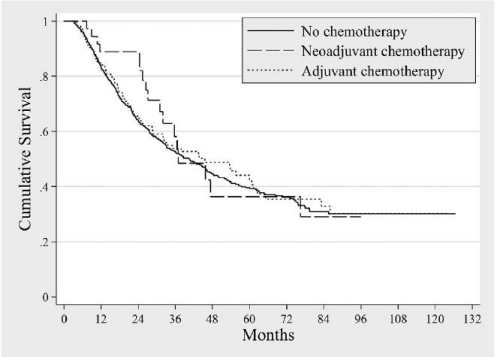


Radiotherapy	N	Median OS (yr)	log-rank *p*
None	517	3.2	REF
Neoadjuvant	21	3.8	0.428
Adjuvant	279	3.7	0.578

Fig. 3. Overall survival for angiosarcoma stratified by receipt of radiation therapy. Univariate analysis shown.



Chemotherapy	N	Median OS (yr)	log-rank *p*
None	655	3.4	REF
Neoadjuvant	38	3.1	0.422
Adjuvant	128	3.8	0.700

Fig. 2. Overall survival for angiosarcoma stratified by receipt of chemotherapy. Univariate analysis shown.

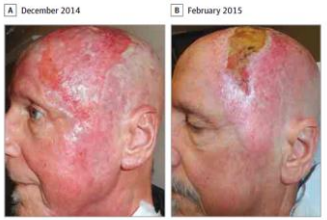
Angiosarcoma- Tratamiento

Tto		Comentarios
RT	En casos inoperables Neoadyuvante a cirugía Adyuvante a cirugia	60Gy: 20 sesiones 3Gy
QT	Casos paliativos Neoadyuvante en casos periorbitarios	Mejores resultados: Paclitaxel-Docetaxel.Doxorrubicina liposomal Pobres resultados con Sorafenib, Sunitinib y bevacizumab.
Betabloqueantes	Pueden tener algún beneficio en régimen paliativo	

Case Report/Case Series

Growth Attenuation of Cutaneous Angiosarcoma With Propranolol-Mediated β-Blockade

William Chow, DO; Clarissa N. Amaya, MS; Steven Rains, MS; Michael Chow, BS; Erin B. Dickerson, PhD; Brad A. Bryan, PhD, MBA



Progressive images of the patient during and following combination therapy with propranolol hydrochloride, paclitaxel, and radiotherapy.

Angiosarcoma- ClinicalTrials.gov

Carotixumab	Ac. Anti CD105 (endoglina)
Paclitaxel + Bevacizumab	
Paclitaxel+ Avelumab	
Eribulina	QT análogo de la hialocondrina B
Oraxol	Paclitaxel oral
Propanolol	
Pazopanib	
Regorafenib	
Trebananib	
Cixutumumab + Doxorrubicina Hydroclorhide	Anti IGF-1R
Ribociclib	Inh CDK4/6

Conclusiones

Sarcoma de Kaposi

Mejorar el registro de casos.
Mejorar estudios epidemiológicos sobre VHH-8.

Recordar la linfocitopenia CD4 idiopática y Cushing endógeno como causas infrecuentes.

Estandarizar guías de tratamiento local.

Estudios que comparen eficacia de los diversos métodos

Angiosarcoma

Incidencia muy baja. Alta mortalidad.

Fundamental dx precoz para poder asegurar tratamiento qx.

Posible beneficio RT adyuvante

Necesidad de mejoras terapéuticas para casos avanzados.

IV Simposio

GETHI

Monográfico de Tumores cutáneos infrecuentes

Sarcoma de Kaposi y Angiosarcoma

Ander Mayor Ibarguren

Dermatología HULP

andermayor@gmail.com

Organizado por: Grupo Gethi – Grupo Español de Tumores Huérfanos e Infrecuentes

GRACIAS POR SU ATENCIÓN

CENTRO INTEGRAL ONCOLÓGICO hm CIOCC