

SARCOMA DE EWING Y SARCOMAS EMERGENTES EWING -LIKE



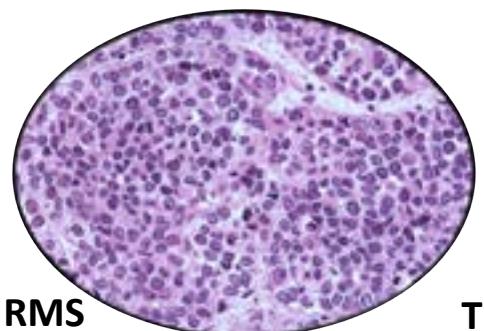
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Hospital de Niños • •
Dr. Luis Calvo Mackenna
Hospital Autogestionado de Alta Complejidad Fundado en 1942

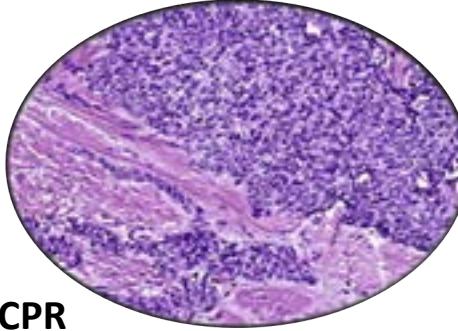


INTRODUCCIÓN

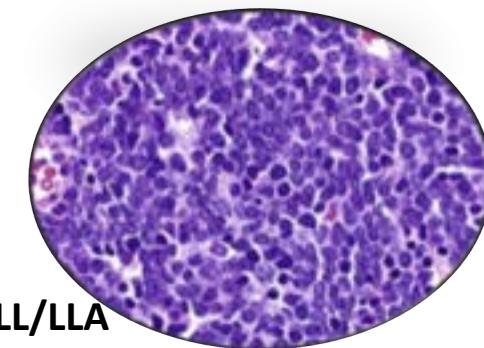
TUMORES DE CÉLULAS PEQUEÑAS, REDONDAS Y AZULES



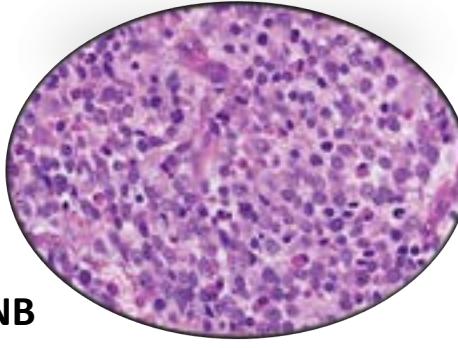
RMS



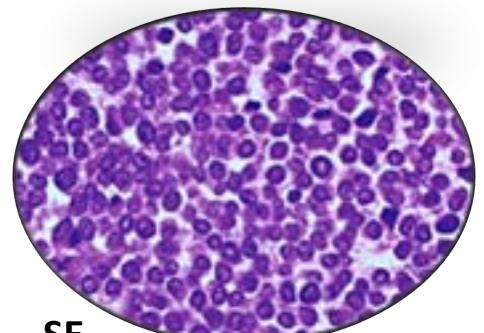
TDCPR



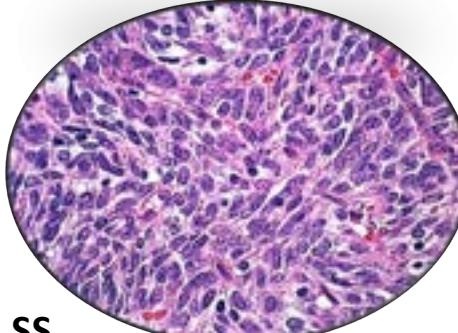
LL/LLA



NB



SE



SS

CONSIDERACIONES GENERALES:

- ❖ Neoplasias de apariencia primitiva, altamente agresivas.
- ❖ Nulo o mínimos criterios morfológicos de diferenciación.
- ❖ Niños, adolescentes y adultos jóvenes.
- ❖ Presentan diversas estirpes biológicas.
- ❖ Tamaño y forma es un término relativo.

TUMORES DE CÉLULAS PEQUEÑAS, REDONDAS Y AZULES

Pediatria

- Linfoma/Leucemia Linfoblástica.
- Neuroblastoma.
- Rabdomiosarcoma.
- **SARCOMA DE EWING.**
- Meduloblastoma.
- Tumor de Wilms.
- Hepatoblastoma.
- OS células pequeñas.
- TDCPR
- Cordoma pobremente diferenciado.
- Condrosarcoma mesenquimal.
- Tumores Germinales.
- Sialoblastoma.
- Pancreatoblastoma.
- Blastoma pleuropulmonar.
- Sarcoma sinovial.
- Tumor rabdoide.
- Sarcoma indiferenciado.
- **SARCOMAS EWING LIKE (BCOR-CCNB3, CIC-DUX 4)**
- Tu neuroectodérmico melanótico
- Otros



TABLE 2. Key Changes and Updates in the 2013 WHO Classification of Tumors of Bone

Tumor Category		Major Changes and Updates
Chondrogenic	Classification changes	New entity: osteochondromyxoma (associated with Carney complex) included. Atypical cartilaginous tumor introduced as synonym for grade 1 chondrosarcoma.
	New genetics	<i>IDH1/2</i> mutations in enchondroma, periosteal chondroma and chondrosarcoma. <i>HEY1-NCOA2</i> fusion gene in mesenchymal chondrosarcoma.
Osteogenic	Classification changes	Osteoma separated from osteoid osteoma.
	New genetics	Amplification of <i>MDM2</i> and <i>CDK4</i> in low-grade central and paraosteal osteosarcomas, and less often in conventional osteosarcoma.
Fibrogenic	Classification changes	Fibrosarcoma strictly defined to exclude cases demonstrating any recognizable line of differentiation other than fibroblastic
Ewing sarcoma		Classification changes New genetics
PNET removed as a synonym for Ewing sarcoma. A subset of undifferentiated round cell (non-Ewing) sarcomas harbor <i>CIC-DUX4</i> or <i>BCOR-CCNB3</i> fusion genes.		
Notochordal	Classification changes	Benign notochordal cell tumor added.
	New genetics	Copy number gain of brachury in chordoma.
Vascular	Classification changes	Epithelioid hemangioma added as a new entity and distinguished from hemangioma. Epithelioid hemangioendothelioma now included.
	New genetics	Recurrent fusion genes in epithelioid hemangioendothelioma: <i>WWTR1-CAMTA1</i> and <i>YAP1-TFE3</i> .
Myogenic, lipogenic, and epithelial	Classification changes	Leiomyoma and schwannoma removed.
Tumors of undefined neoplastic nature	Classification changes	Chondromesenchymal hamartoma is new designation for tumors previously classified as chest wall hamartoma.
	New genetics	<i>USP6</i> gene rearrangement in 70% of primary aneurysmal bone cyst, usually due to <i>t(16;17)(q22;p13)</i> , and not present in secondary aneurysmal bone cyst.
Undifferentiated high-grade pleomorphic sarcoma	Classification changes	This new category recognizes pleomorphic sarcomas that cannot be classified into any of the other categories.

WHO Classification of Tumours of Soft Tissue and Bone

Edited by Christopher D.M. Fletcher, Julia A. Bridge, Paulina C.R. Gospodarowicz, Franklin Mertens



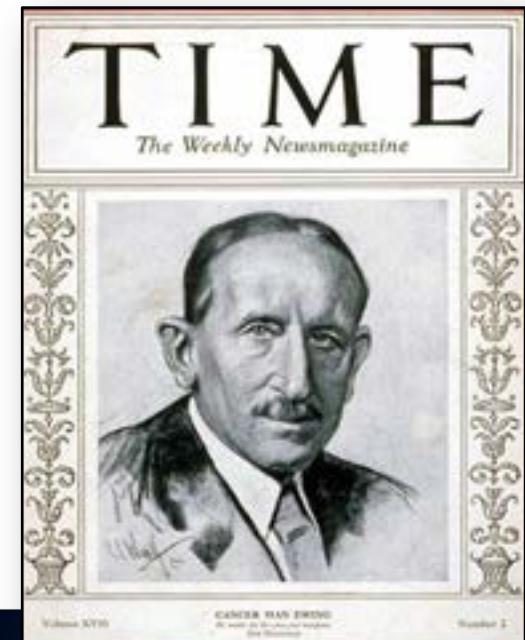
SARCOMA DE EWING

DEFINICIÓN (OMS, 2013)

Sarcoma de células pequeñas y redondas que muestra hallazgos moleculares patognomónicos y diversos grados de diferenciación neuroectodérmica por microscopía de luz, electrónica, o inmunohistoquímica.



- ❖ Descrito por **JAMES EWING** en 1921 (ENDOTELIOMA DIFUSO DEL HUESO)
- ❖ Afecta **hueso (80%) y tejidos blandos (20%)**.
- ❖ Principalmente **población pediátrica y adultos jóvenes**.
- ❖ **20%** de metástasis al diagnóstico



EPIDEMIOLOGIA

- ❖ 6-8% Tu malignos primarios óseos.
- ❖ 2º tu maligno óseo primario en niños y adolescentes, 3º en adultos.
- ❖ 1,5 casos/ millón.
- ❖ Predominantemente a **NIÑOS, ADOLESCENTES Y ADULTOS JÓVENES.**
- ❖ 80% en < 20 años, máxima incidencia en **2da DÉCADA DE LA VIDA.**
- ❖ Leve predilección en sexo masculino (1.4:1)
- ❖ Mayor en caucásicos, bajo en afrodescendientes y asiáticos.

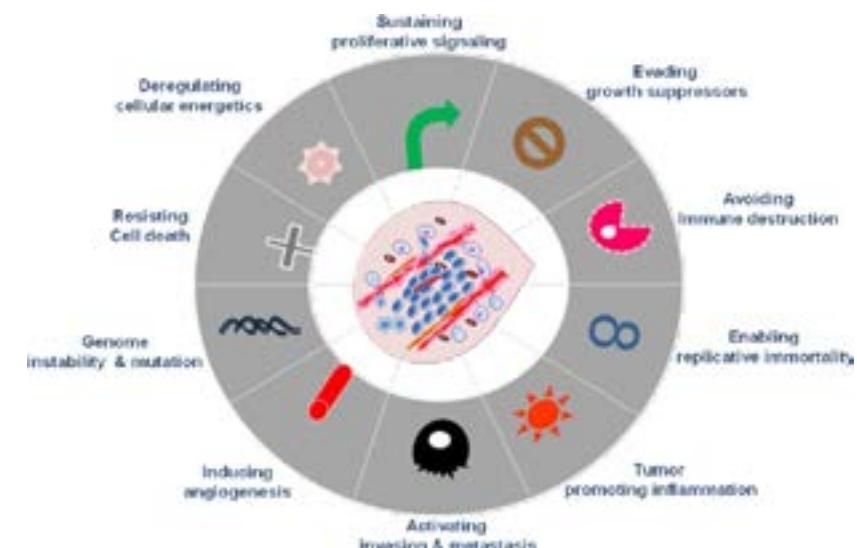


PATOGENIA

Tumor genéticamente bien caracterizado, su principal característica es la presencia de una translocación específica, da a lugar a genes y proteínas de fusión químéricas que promueven la oncogénesis.

CONSIDERACIONES

- ❖ Baja asociación a Síndromes genéticos.
- ❖ Casos aislados de presentación familiar.
- ❖ No se ha descrito como malignización de tumores óseos benignos.
- ❖ No parece relacionarse con hueso en crecimiento.
- ❖ No se ha asociado a factores medioambientales ni infecciosos.



CÉLULA DE ORIGEN



Casi 100 años después de su primera descripción, el origen es aún incierto

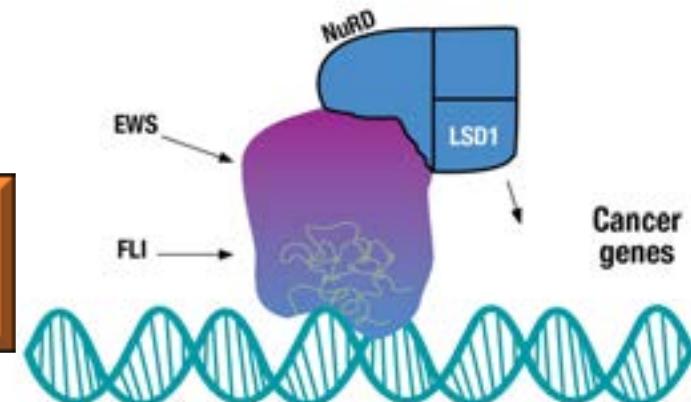
Table 1: The various proposed cell of origin

Cell of origin	Proposed by	Year
Endothelial origin	James	1921
Hematopoietic origin	Kadsin and Bensch	1971
Fibroblastic	Dickman <i>et al.</i>	1982
Neural crest origin	Cavazzana <i>et al.</i>	1988
Mesenchymal progenitor/stem cells	Castillero-trejo <i>et al.</i>	2005
Neural derived MSC or from a neural Crest cell	Elizabeth C. Toomey	2010

MSC: Mesenchymal stem cell

GENÉTICA

Translocación cromosómica que involucra un gen de familia FET y uno de la familia de factores de transcripción ETS.



Proteínas de fusión químéricas

Factores de transcripción aberrantes

- ❖ 85% t(11;22)(q24;q12), fusiona Gen EWSR1 y FLI 1.
- ❖ Gen de fusión EWSR1-FLI1

Promueven la oncogénesis desregulando cientos de genes

- Prolif y dif celular
- Ciclo celular
- Angiogénesis
- Migración
- Apoptosis

GENÉTICA

<i>FET</i> part	<i>ETS</i> part	Fusion gene	Chromosomal translocation	Frequency
<i>FUS</i>	<i>FEV</i> <i>ERG</i>	<i>FUS–FEV</i> <i>FUS–ERG</i>	<i>t(2;16)(q35;p11)</i> <i>t(16;21)(p11;q22)</i>	<1% <1%
<i>EWSR1</i>	<i>FLI1</i> <i>ERG</i>	<i>EWSR1–FLI1</i> <i>EWSR1–ERG</i>	<i>t(11;22)(q24;q12)</i> <i>t(21;22)(q22;q12)</i>	≈85% ≈10%
	<i>ETV1</i> <i>ETV4</i> <i>FEV</i> <i>ETV5 (?)</i>	<i>EWSR1–ETV1</i> <i>EWSR1–ETV4</i> <i>EWSR1–FEV</i> <i>EWSR1–ETV5</i>	<i>t(7;22)(p22;q12)</i> <i>t(17;22)(q21;q12)</i> <i>t(2;22)(q33;q12)</i> ?	<1% <1% <1% ?
<i>TAF15</i>	?	?	?	?

CLÍNICA

- Aumento de volumen.
- Fx. en hueso patológico (raro).
- Síntomas compresivos.
- Síntomas B en casos avanzados
- Dolor
- Signos inflamatorios locales.
- Fiebre

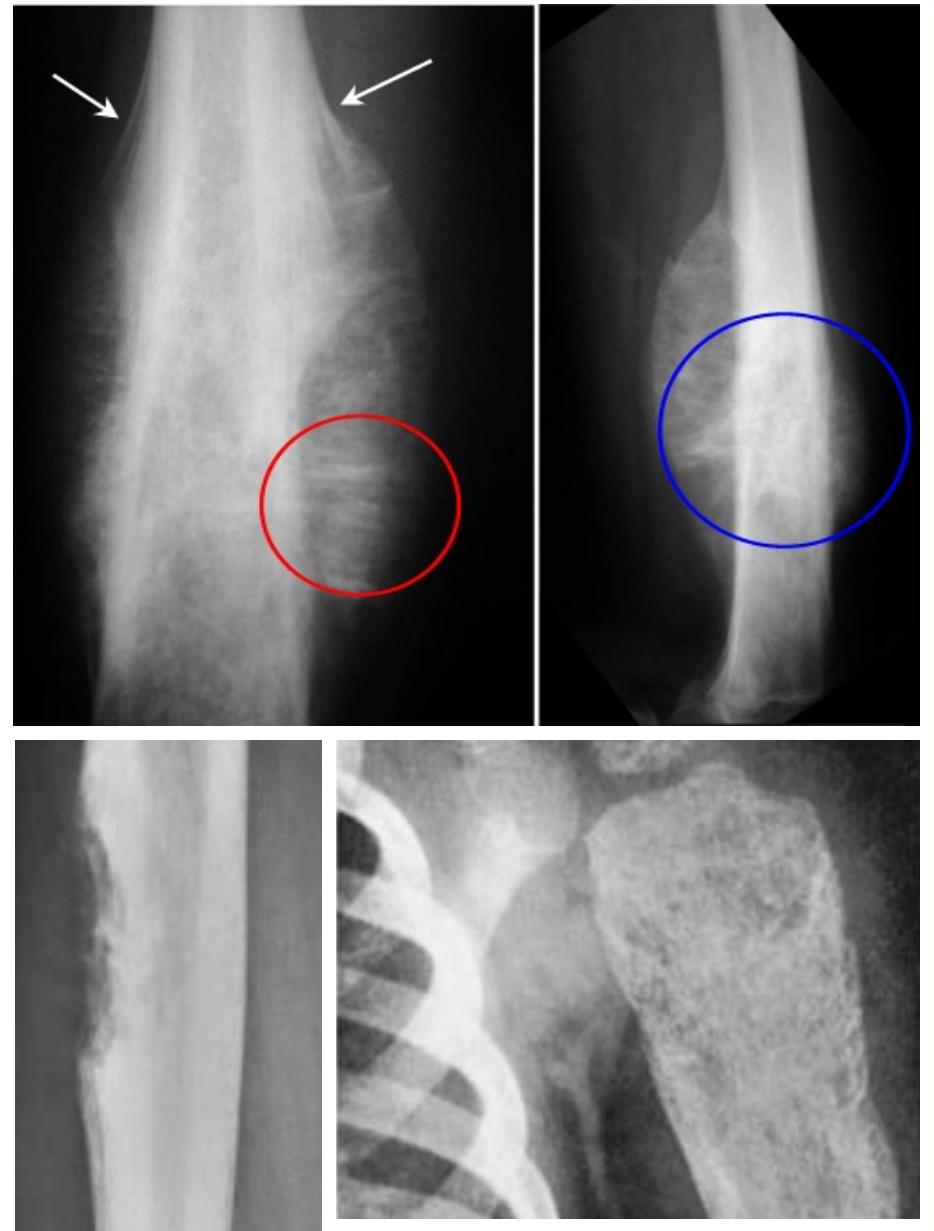
LABORATORIO

- VHS elevada
- Leucocitosis



IMAGENOLOGÍA

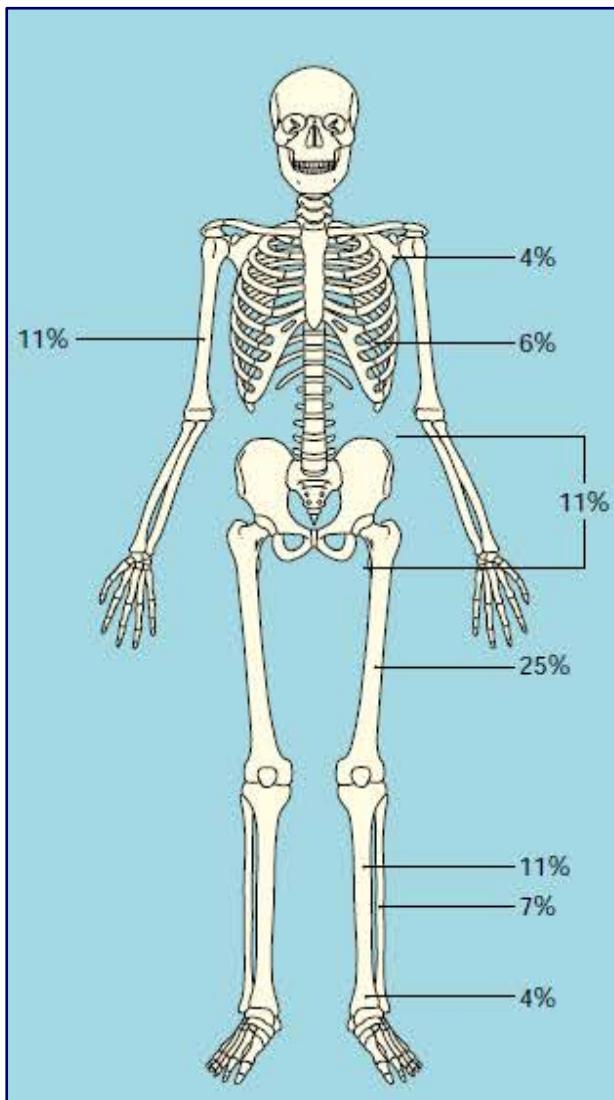
- Variable.
- Mal definida, patrón apolillado, permeativo
- Reacción perióstica (sol naciente, codman).
- Desde predominio lítico a patrón esclerótico
- Lesión poco definida de partes blandas
- Lesión de partes blandas y erosión cortical adyacente
- Imita cualquier sarcoma óseo, osteomielitis o Histiocitosis de Langerhans



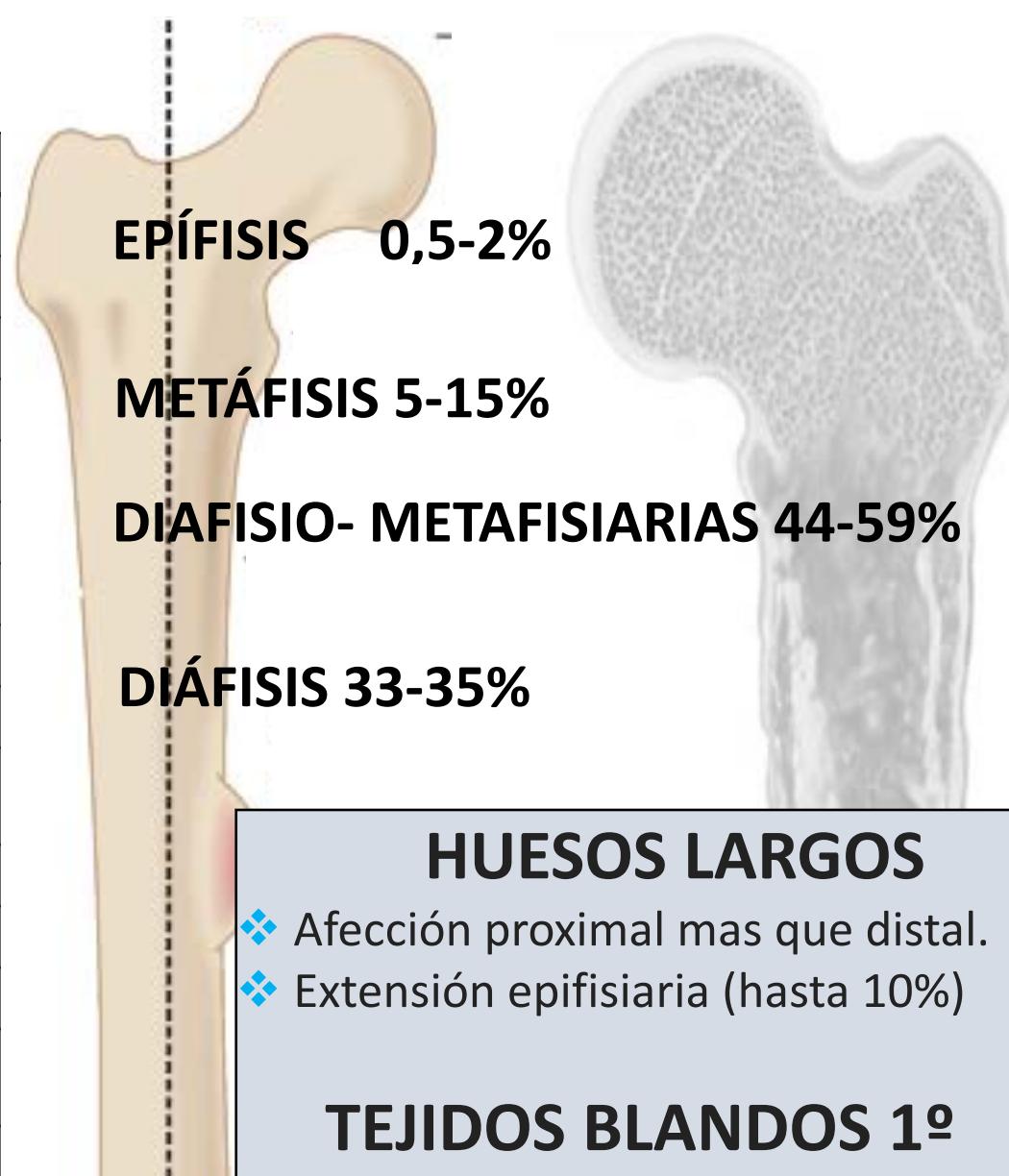


**SARCOMA DE EWING Y
OSTEOMIELITIS
CLINICA, LABORATORIO,
IMAGENOLOGÍA, INCLUSO HISTOLOGIA
PUEDEN SER SIMILARES**

LOCALIZACIÓN



Sitio	%
Fémur	20-25
Ilion	12
Tibia	8-11
Humero	11
Fíbula	7-9
Costilla	8
Sacro	6
Columna	4-6
Escápula	4-5
Pie o mano	3
Radio	3-5
Maxilar	1-2
Clavícula	2
Huesos faciales	0,5
Esternón	0,2

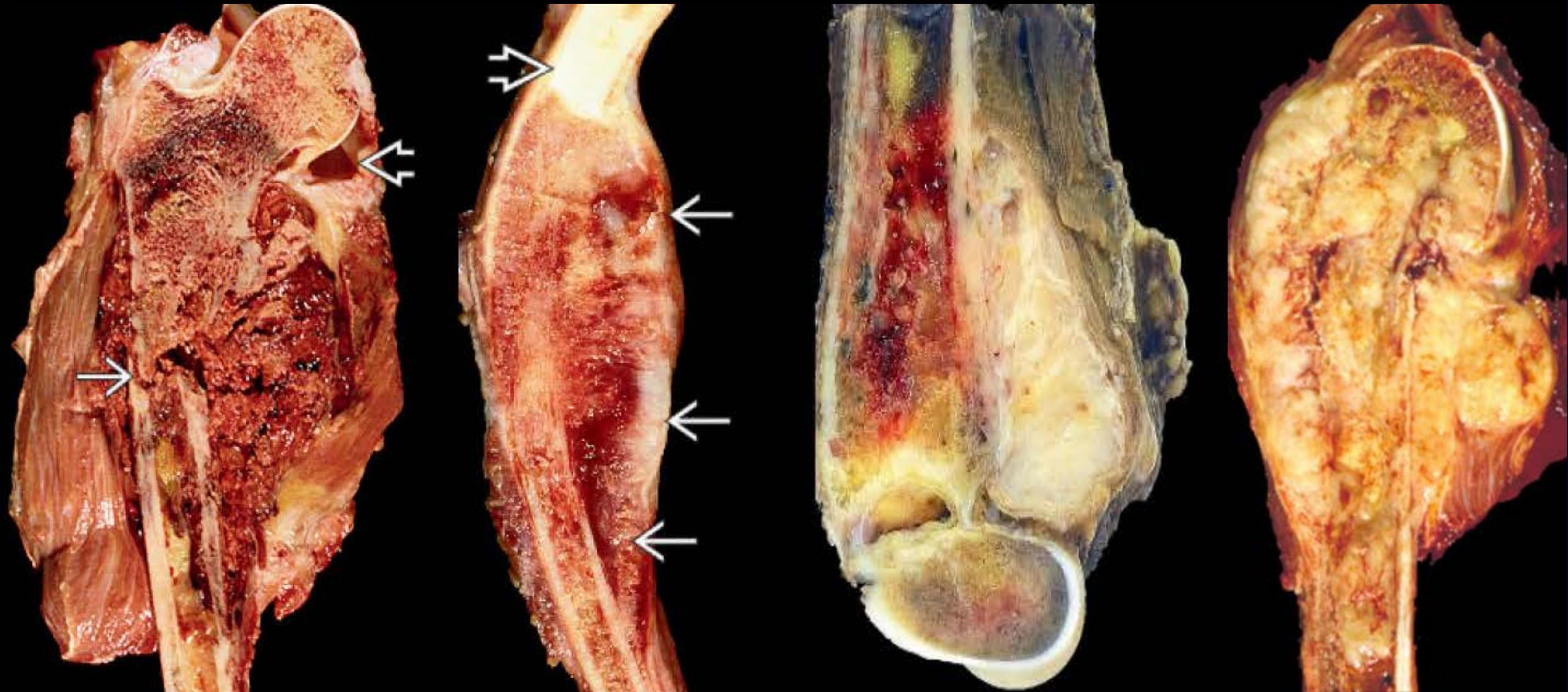


MACROSCOPÍA

- ❖ Raro ver un tumor sin tratamiento previo.
- ❖ Lesión sólida blanquecina grisácea o amarillentas.
- ❖ Aspecto de carne de pescado
- ❖ Bordes infiltrativos.
- ❖ Adelgazamiento o destrucción cortical.
- ❖ Hemorragia y necrosis.
- ❖ A veces zonas quísticas.
- ❖ Márgenes intramedulares mal definidos



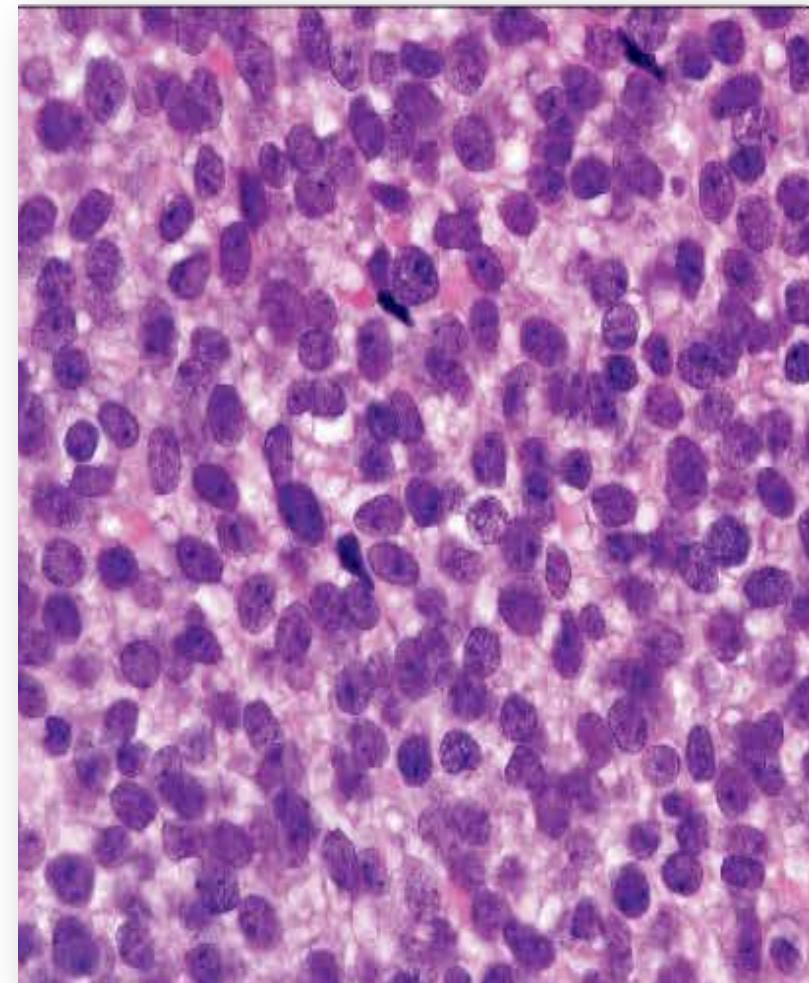
MACROSCOPÍA



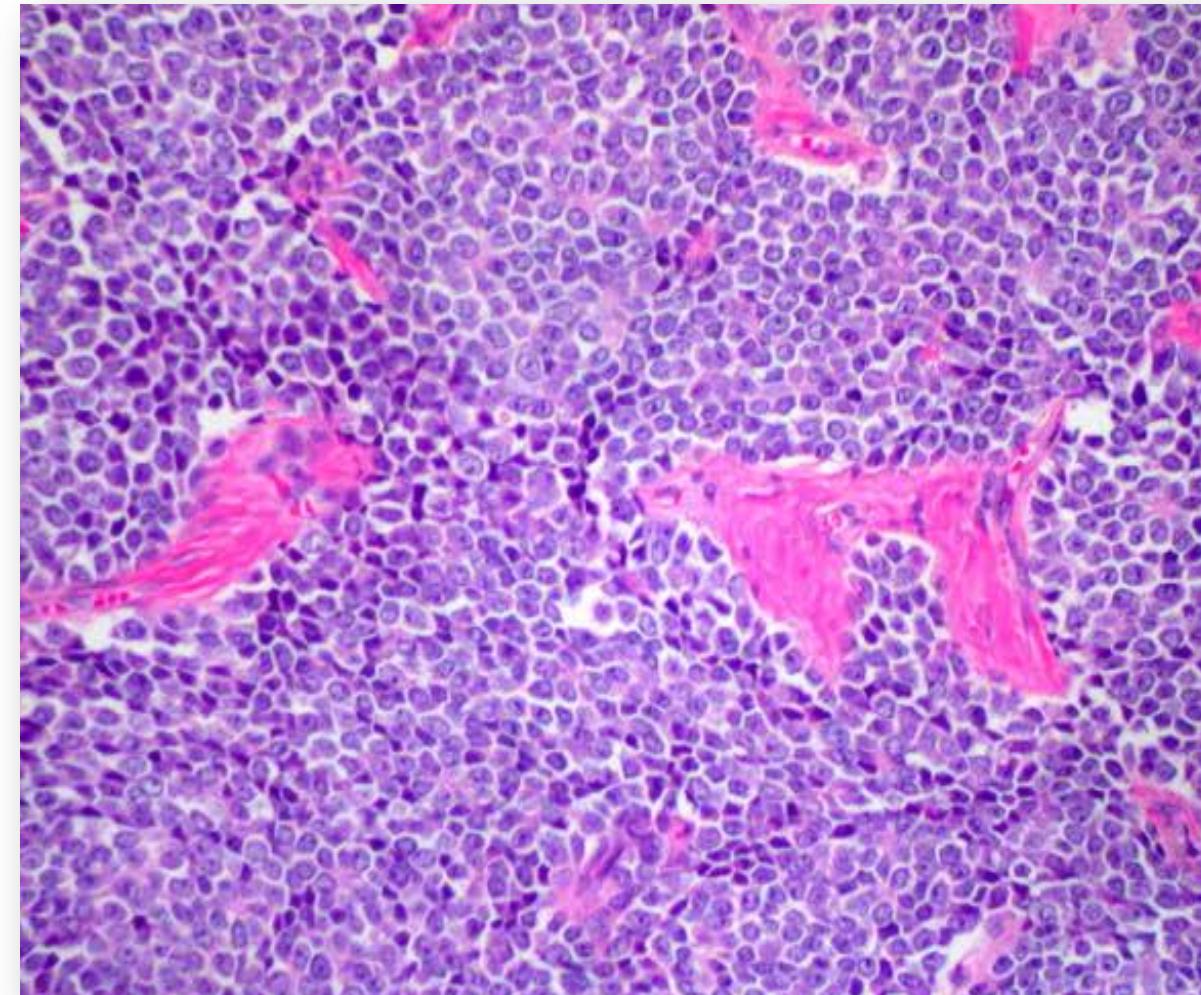
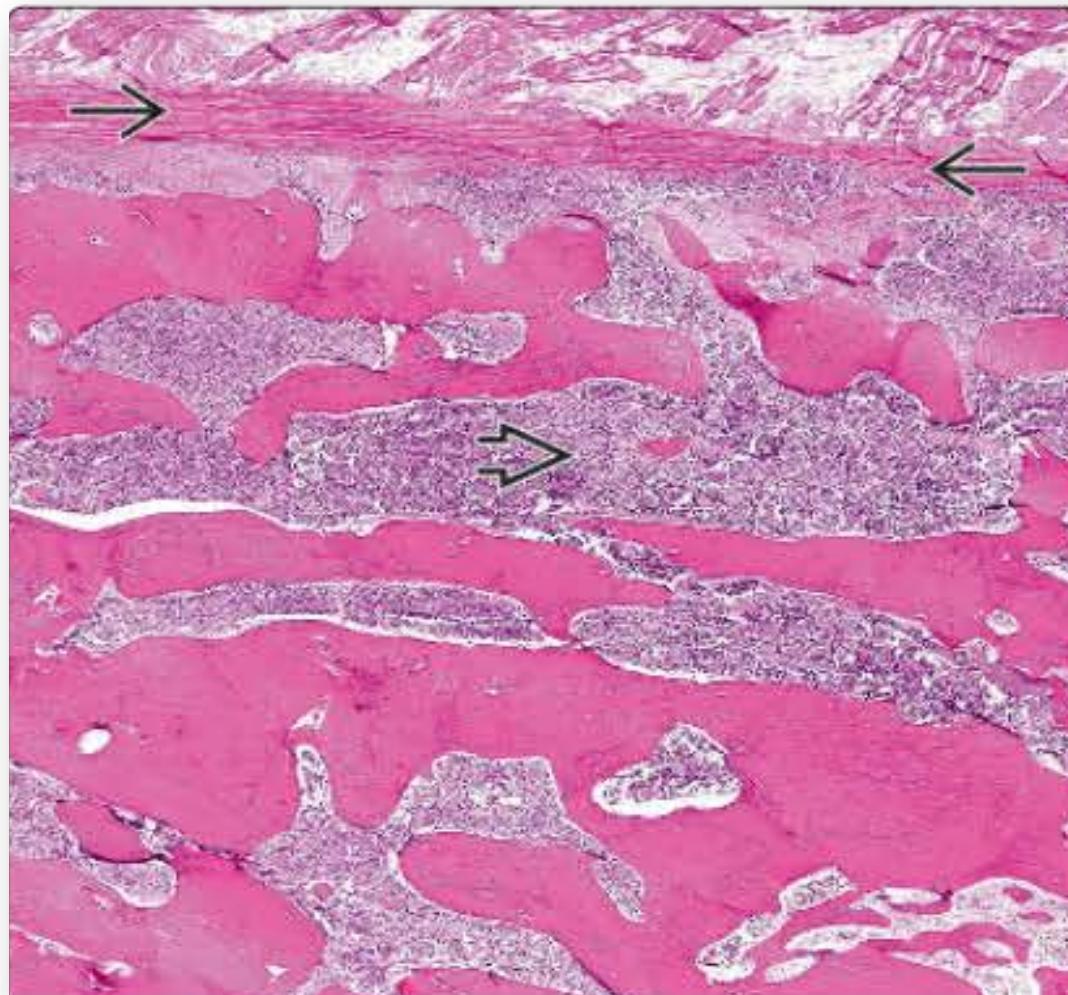
HISTOLOGÍA

SE CLÁSICO

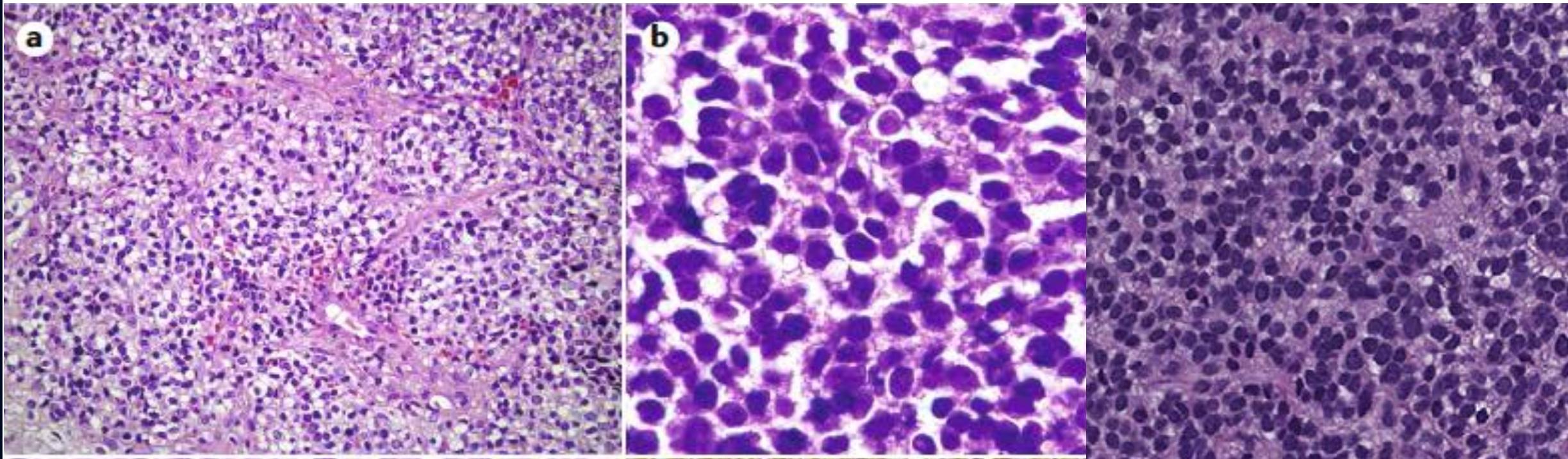
- ❖ Patrón sólido en sábanas, nidos, discreta lobulación.
- ❖ Células uniformes redondas u ovales, pequeñas (1-2 linf).
- ❖ Núcleos ovales con cromatina fina y nucléolos discretos.
- ❖ Indentaciones nucleares
- ❖ Escaso citoplasma, eosinófilo o claro (PAS+)
- ❖ Membrana poco discernible
- ❖ Mitosis variable (escasas o abundantes).
- ❖ Necrosis
- ❖ Infiltrado linfoide ausente y vasculatura discreta.
- ❖ Escaso estroma, a/v septos fibrosos adyacentes.



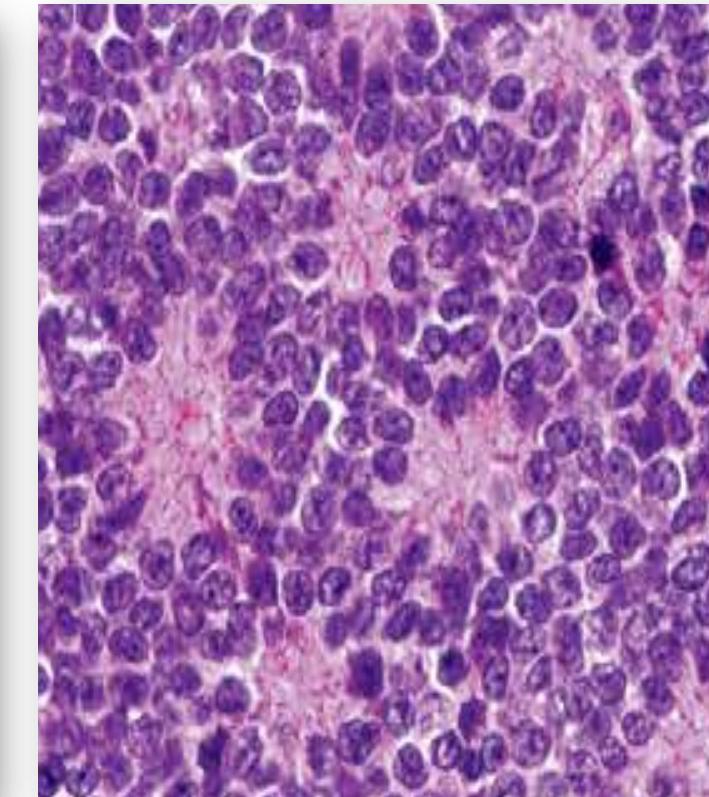
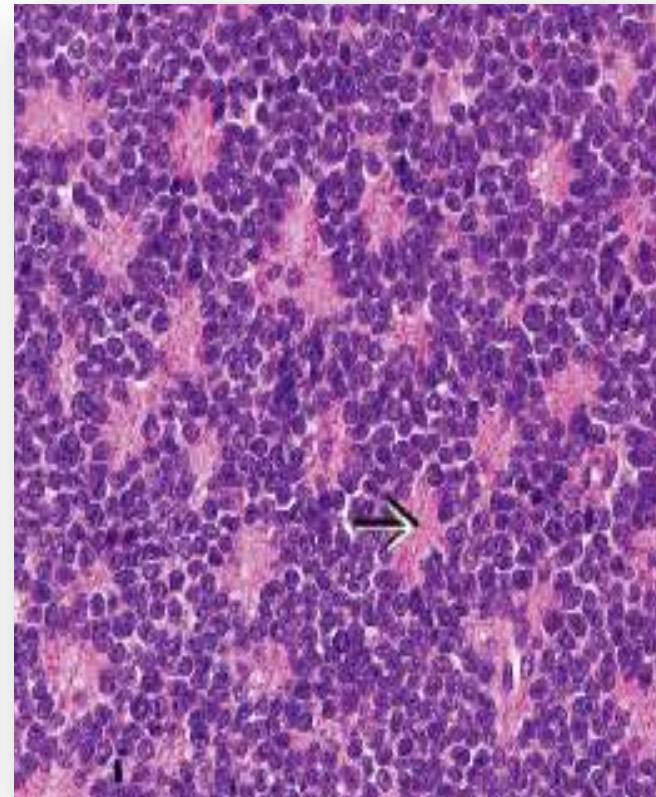
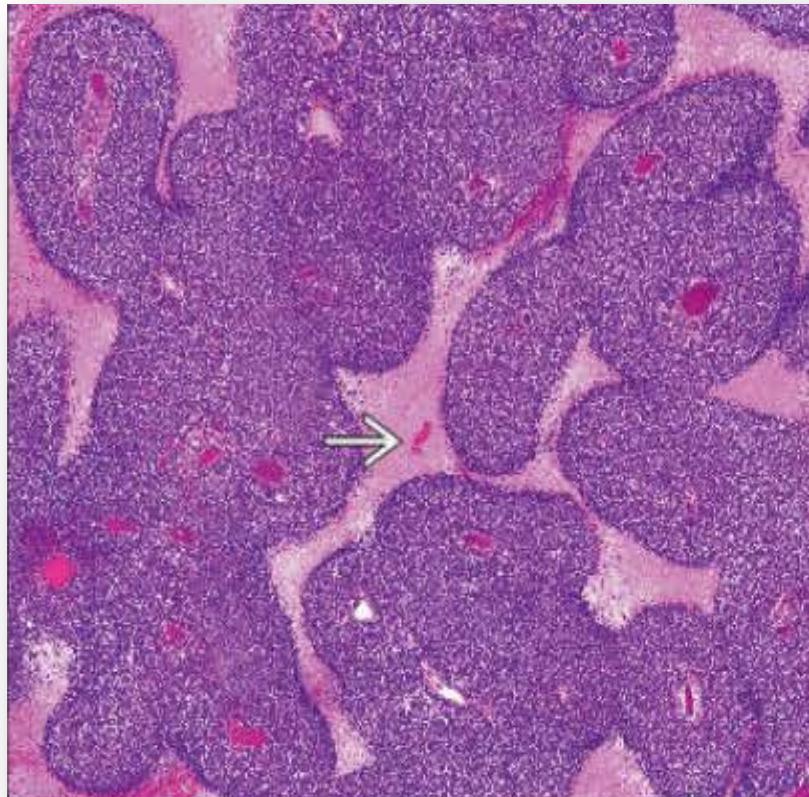
HISTOLOGÍA



HISTOLOGÍA



HISTOLOGÍA

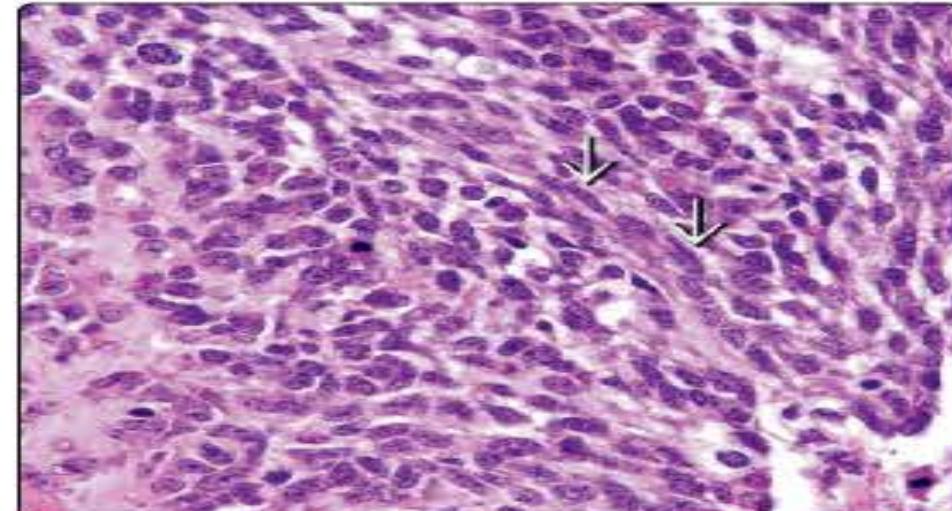
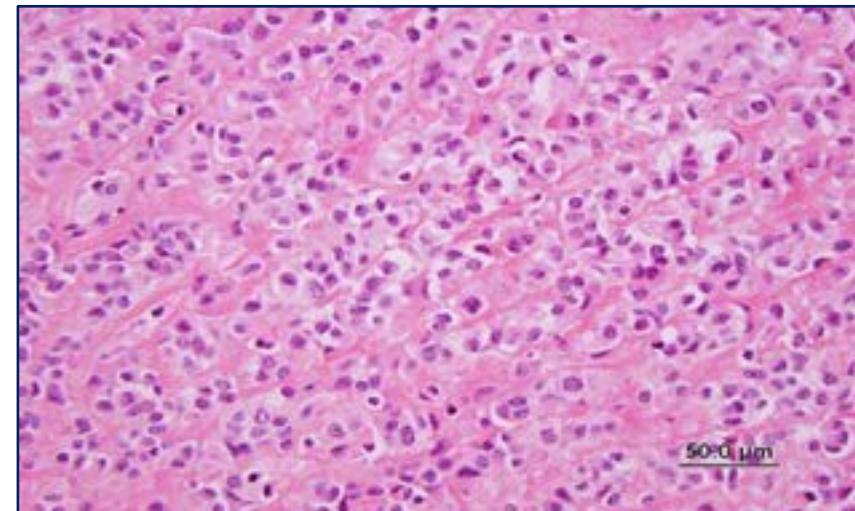
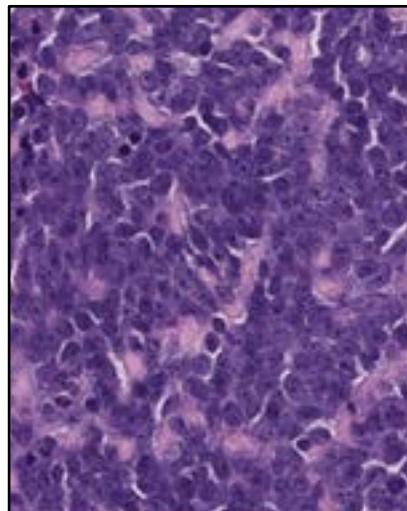
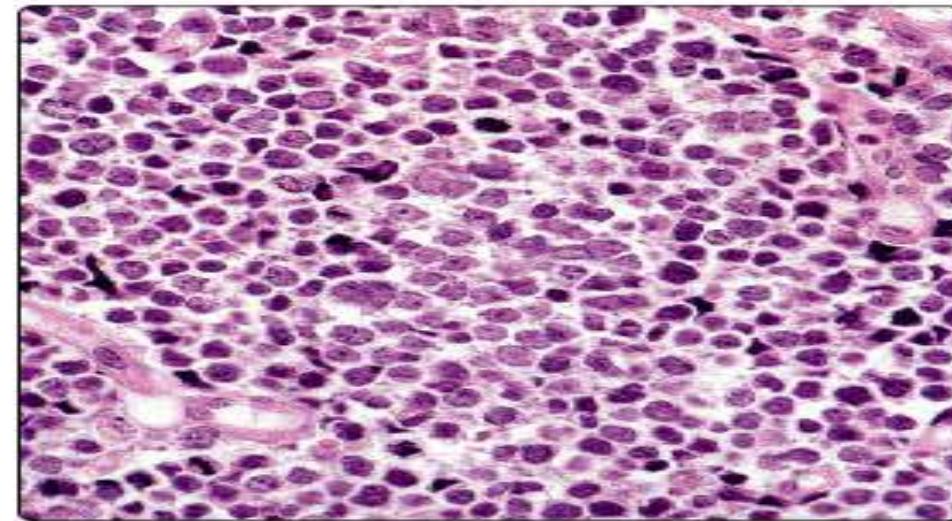


Patrón organoide y rosetas de Homer Wright (sugestivas de diferenciación neural)

SE ATÍPICO

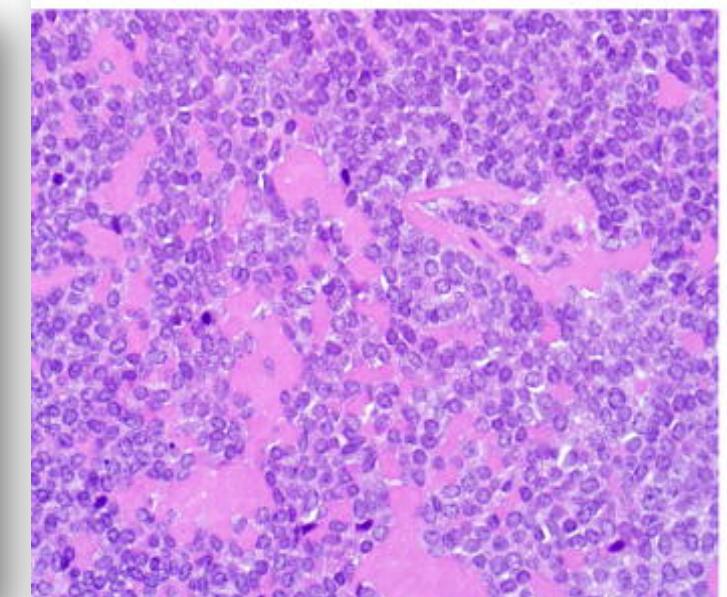
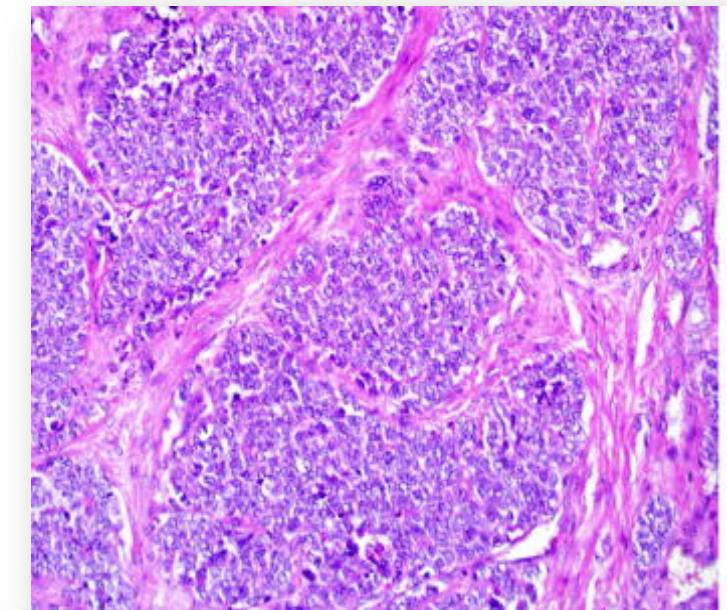
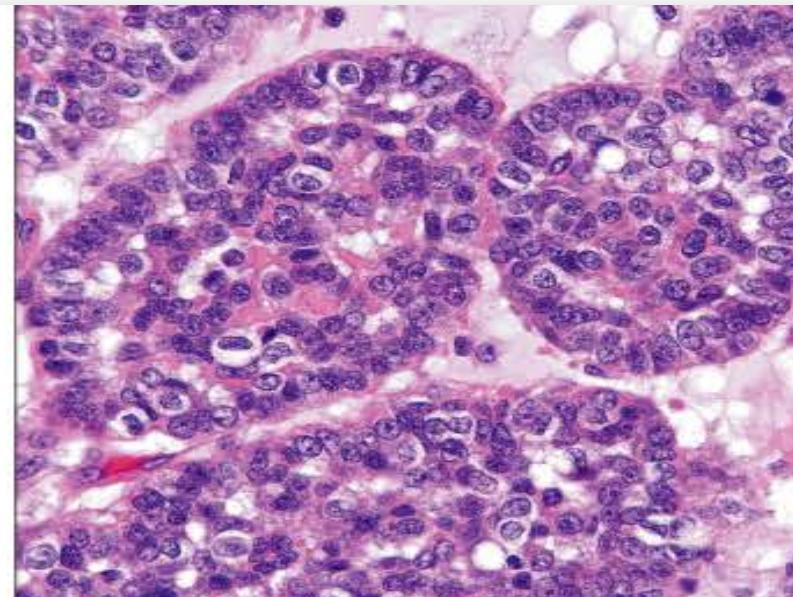
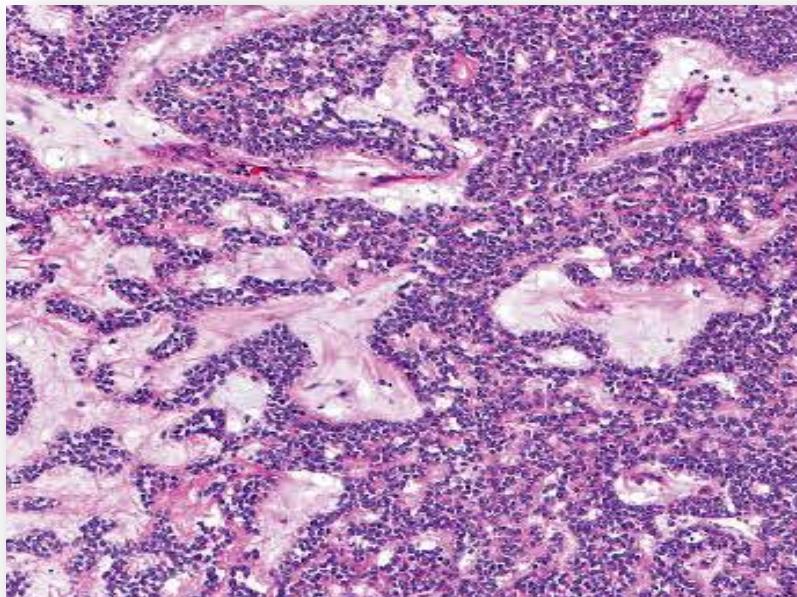
- ❖ Células de mayor tamaño, a veces fusadas.
- ❖ Mayor pleomorfismo.
- ❖ Bordes nucleares irregulares.
- ❖ Nucléolos prominentes.
- ❖ Mayor cantidad de estroma.
- ❖ Mitosis mas frecuentes.

HISTOLOGÍA



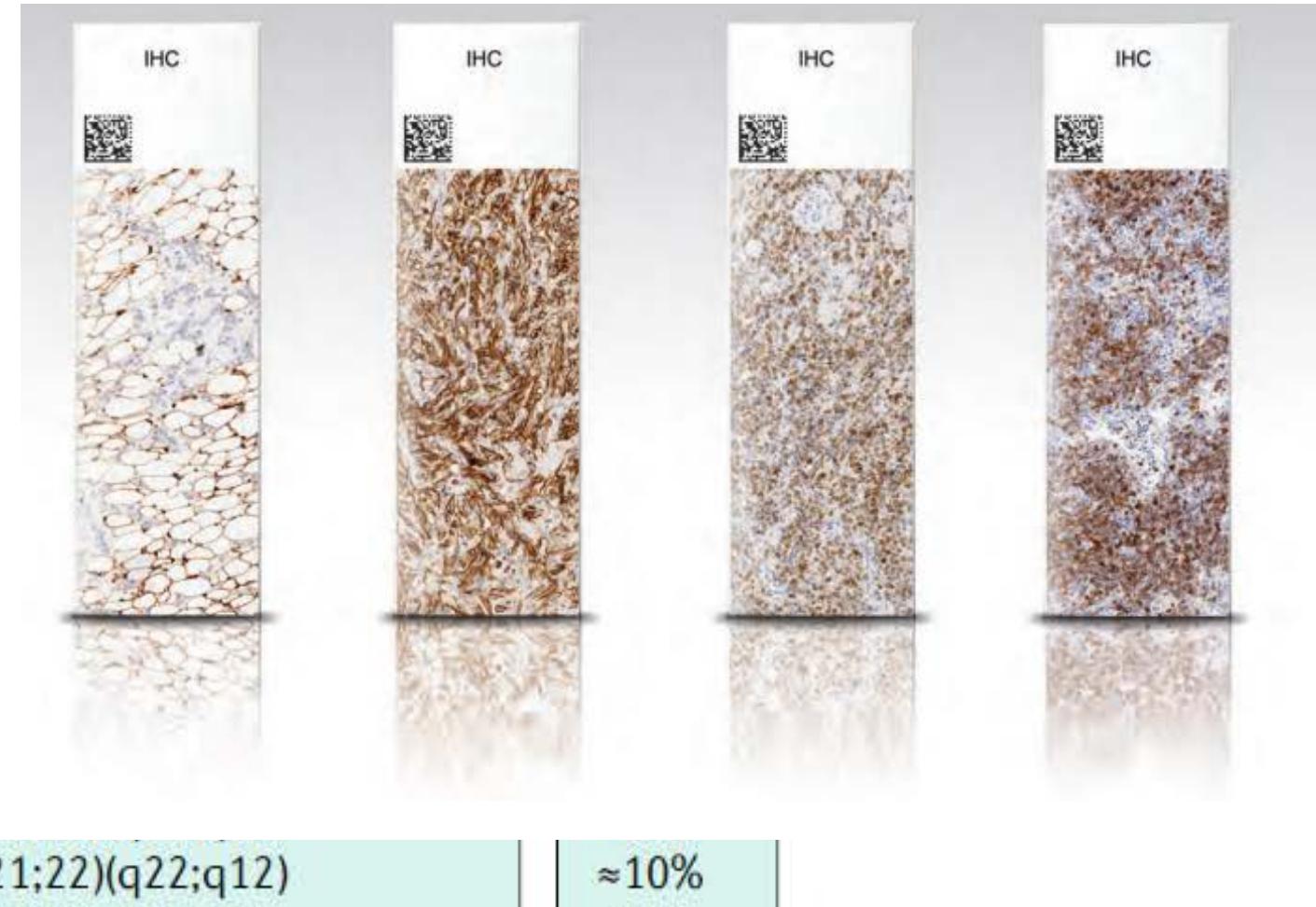
SE ADAMANTINOMA LIKE

- ❖ Raro, cabeza y cuello
- ❖ Nidos y cordones interconectados.
- ❖ Estroma colágeno.
- ❖ Células de aspecto epitelial.
- ❖ Palizadas periféricas



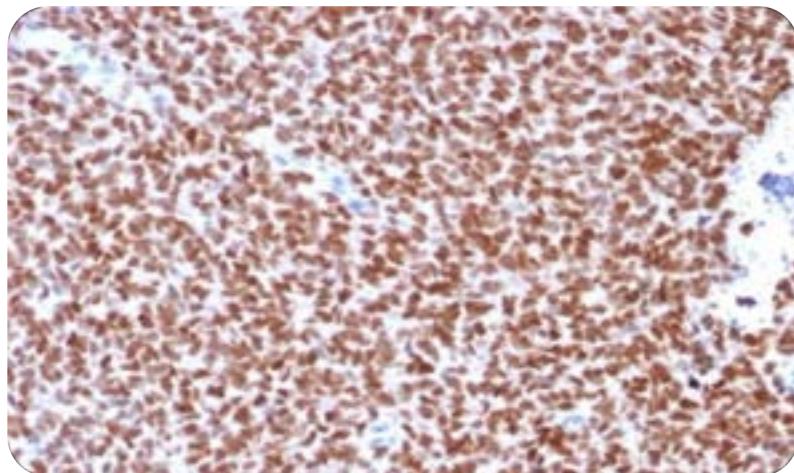
ESTUDIO INMUNOHISTOQUIMICO

- ❖ NKX 2.2
- ❖ FLI-1
- ❖ PAX 7
- ❖ CD99
- ❖ ENOLASA NE
- ❖ VIMENTINA
- ❖ CD57
- ❖ CAVEOLINA-1
- ❖ S100
- ❖ ERG *EWSR1-ERG* | *t(21;22)(q22;q12)* | $\approx 10\%$
- ❖ CK (difuso en SE Adamantinoma like)



ESTUDIO INMUNOHISTOQUÍMICO

NKX 2.2 (S:80-100%-E:89%)



Tinción nuclear

OTROS:

- NB olfatorio
- Sarcoma sinovial pobemente diferenciado
- Condrosarcoma mesenquimal
- Carcinoma de células pequeñas
- Melanoma

NKX2.2 is a Useful Immunohistochemical Marker for Ewing Sarcoma

Akihiko Yoshida, MD,*† Shigeki Sekine, MD, PhD,‡ Koji Tsuta, MD, PhD,*
Masashi Fukayama, MD, PhD,† Koh Furuta, MD, PhD,* and Hitoshi Tsuda, MD, PhD*

TABLE 1. NKX2.2 Comparative Immunohistochemistry in Small Round Cell Tumors

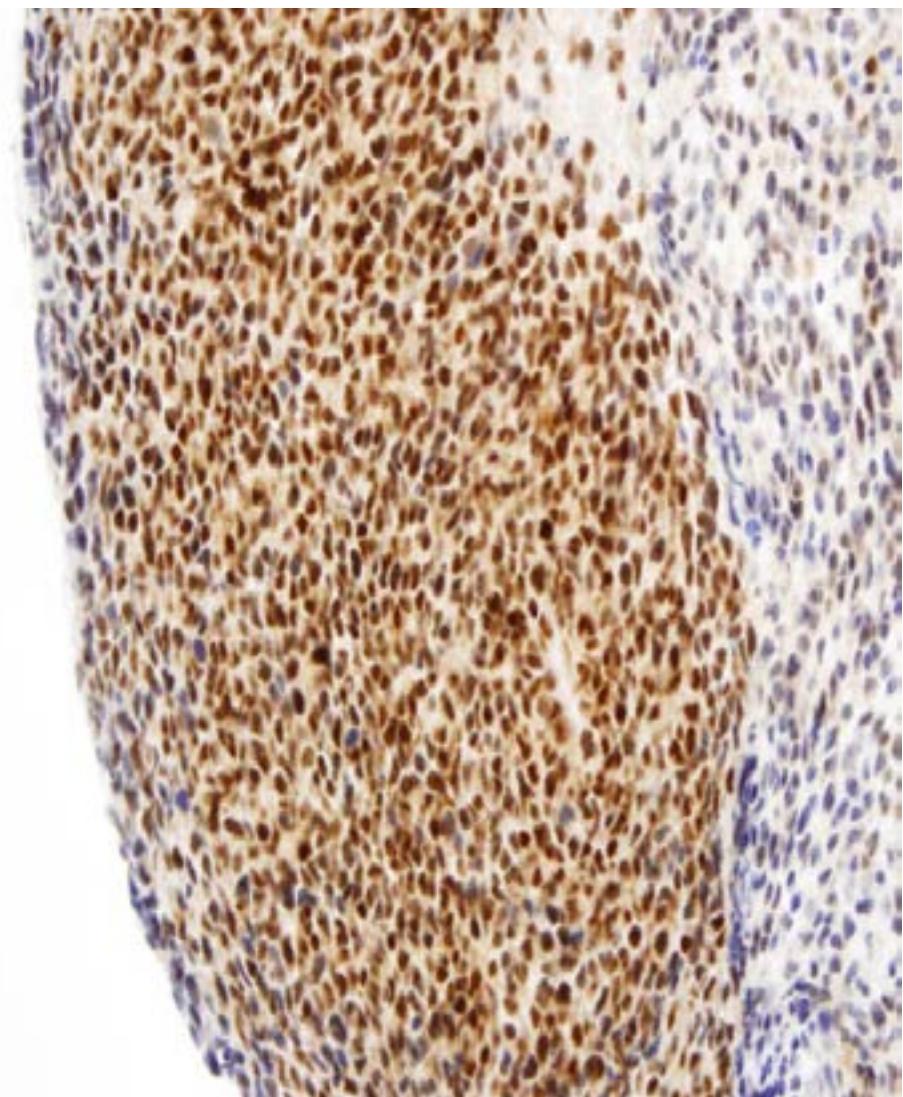
Tumor Type	Positivity	Extent
Ewing sarcoma	28/30 (93%)	F0, D28
Non-Ewing small round cell tumor	14/130 (11%)	F8, D6
Neuroblastoma	0/15 (0%)	—
Olfactory neuroblastoma	3/3 (100%)	F0, D3
Poorly differentiated synovial sarcoma	1/9 (11%)	F1, D0
Round cell liposarcoma	0/8 (0%)	—
Rhabdomyosarcoma	0/17 (0%)	—
Desmoplastic small round cell tumor	0/7 (0%)	—
Soft tissue myoepithelioma	0/3 (0%)	—
Extraskeletal myxoid chondrosarcoma	0/1 (0%)	—
Solitary fibrous tumor (round cell rich)	0/3 (0%)	—
Mesenchymal chondrosarcoma	3/9 (33%)	F2, D1
Small cell osteosarcoma	0/2 (0%)	—
Small cell carcinoma	5/20 (25%)	F4, D1
Merkel cell carcinoma	0/9 (0%)	—
Medulloblastoma	0/3 (0%)	—
Malignant melanoma	2/6 (33%)	F1, D1
Lymphoma	0/11 (0%)	—
Plasma cell tumor	0/4 (0%)	—

D indicates diffuse (> 50%); F, focal (5%-50%); M, moderate; S, strong; W, weak.

ESTUDIO INMUNOHISTOQUIMICO

FLI-1

- ❖ Alta Sensibilidad y baja especificidad.
- ❖ Positividad en 70-84% de SE.
- ❖ Positividad hasta 90% en SE con fusión EWSR1-FLI1
- ❖ Células endoteliales y linfocitos T normales.



OTROS:

- Linfoma linfoblástico
- TDCPR
- Sarcoma Sinovial.
- Carcinoma de cel. Merkel
- Tumores vasculares.
- Melanoma

ESTUDIO INMUNOHISTOQUÍMICO

PAX 7

- ❖ Alta Sensibilidad, similar a NKX 2.2.
- ❖ Positividad en 90% de SE.

OTROS:

- Rábdomiosarcoma
- Sarcoma sinovial.
- Sarcoma BCOR.
- OS cél. pequeñas



Tumor type	Positivity
Ewing sarcoma	27/30 (90%)
Non-Ewing small round cell tumor	24/141
Neuroblastoma	0/10 (0%)
Olfactory neuroblastoma	0/5 (0%)
Alveolar rhabdomyosarcoma	7/10 (70%)
Small cell carcinoma	0/10 (0%)
Lymphoma	0/10 (0%)
Mesenchymal chondrosarcoma	0/10 (0%)
Small-cell osteosarcoma	1/5 (20%)
Poorly-differentiated synovial sarcoma	7/10 (70%)
Desmoplastic small round cell tumor	1/10 (10%)
Round cell liposarcoma	0/10 (0%)
Merkel cell carcinoma	0/8 (0%)
Medulloblastoma	0/3 (0%)
Retinoblastoma	0/5 (0%)
Cellular extraskeletal myxoid chondrosarcoma	0/5 (0%)
Melanoma, small-cell type	0/7 (0%)
BCOR-CCNB3 sarcoma	8/10 (80%)
CIC-rearrangement sarcoma	0/10 (0%)
Miscellaneous*	0/3 (0%)

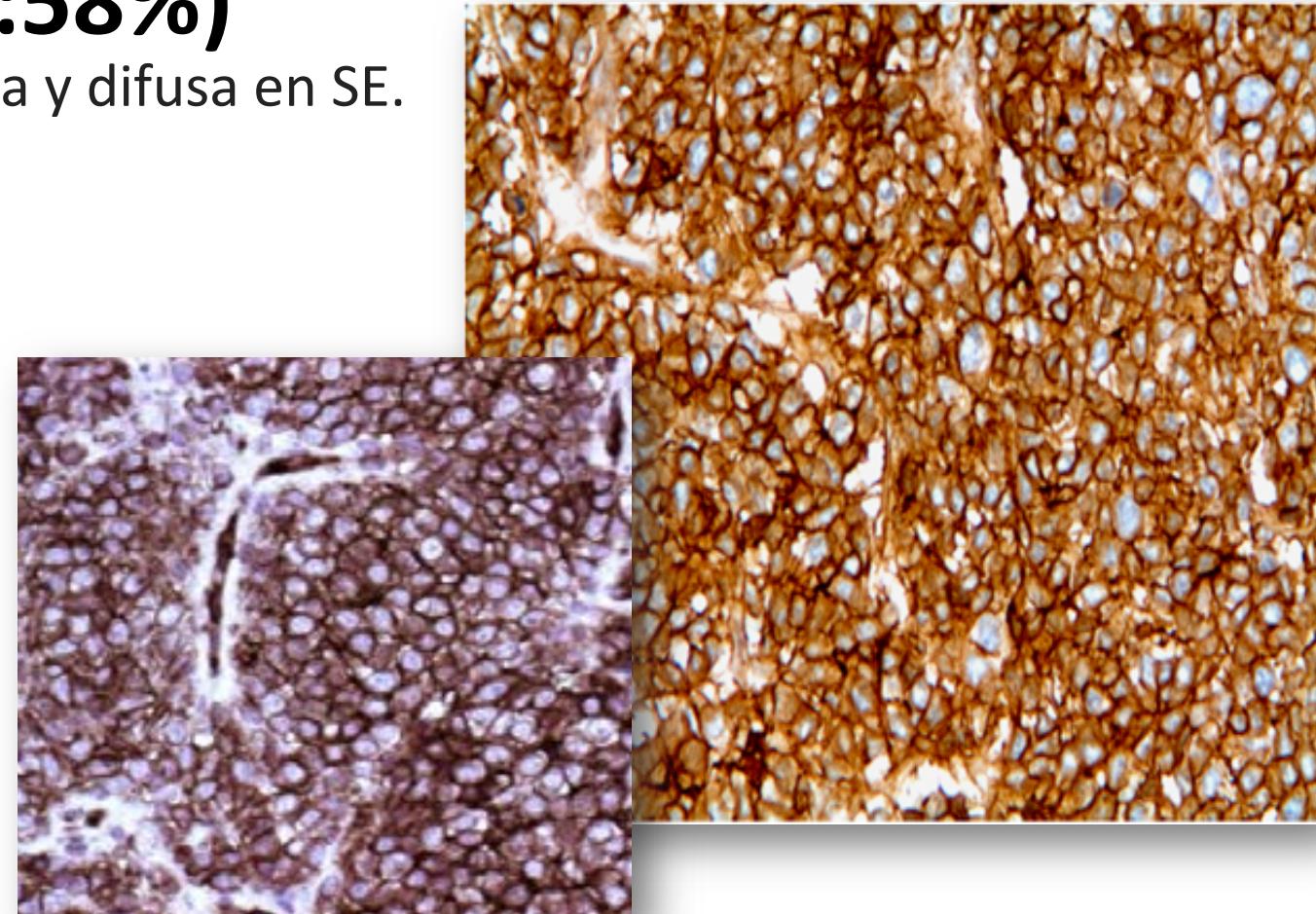
ESTUDIO INMUNOHISTOQUIMICO

CD99 (S: 88%-E:58%)

- ❖ Positividad membranosa intensa y difusa en SE.
- ❖ Hasta 95% de SE.

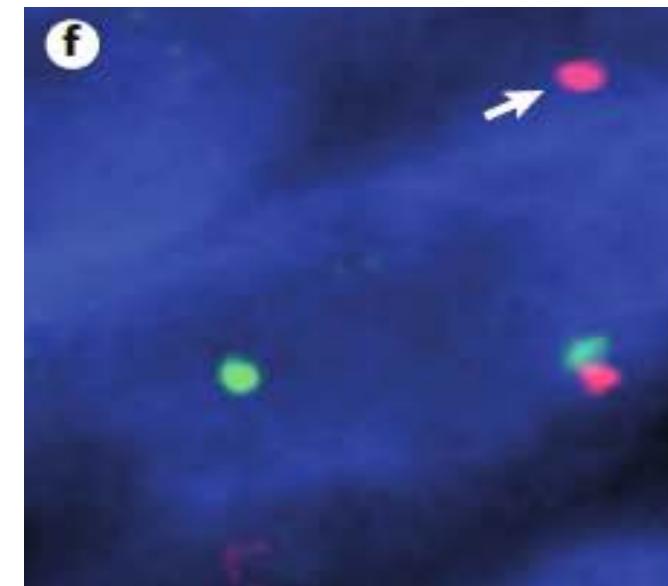
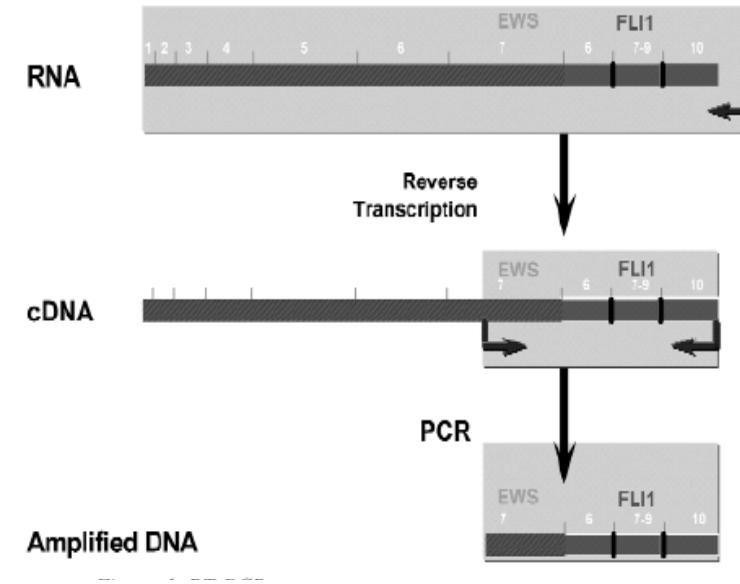
OTROS:

- Linfoma linfoblástico
- TDCPR
- Sarcoma Sinovial.
- Rabdomiosarcoma
- Condrosarcoma mesenquimal.
- Tumores neuroendocrinos
- OS de células pequeñas.
- Carcinoma de cel. Merkel
- Etc...
- **NEGATIVO EN NEUROBLASTOMA**



ESTUDIO GENÉTICO/MOLECULAR

Recomendable en todos los casos para complementar el diagnóstico, ambas técnicas con buen rendimiento.



SARCOMAS EMERGENTES EWING LIKE

La medicina de precisión y estudios con técnicas recientes ha permitido la identificación de algunos subgrupos nuevos dentro de lesiones clasificadas por OMS como "sarcomas indiferenciados / no clasificados".



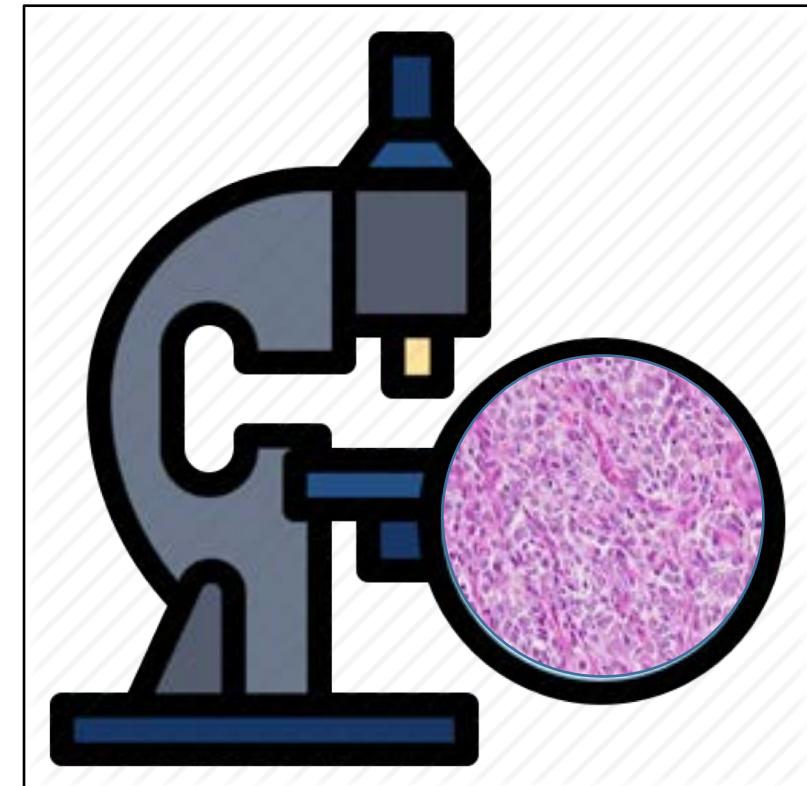
UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

- Undifferentiated spindle cell sarcoma
- Undifferentiated pleiomorphic sarcoma
- Undifferentiated round cell sarcoma
- Undifferentiated epithelioid sarcoma
- Undifferentiated sarcoma NOS



SARCOMAS EWING LIKE

- ❖ Subgrupo emergente de sarcomas de células redondas y azules, que comparten diversos grados de similitud morfológica, IHQ, molecular y clínica con el SE.
- ❖ Carecen de translocación característica del SE y fusión entre un gen de la familia TET (EWSR1 o FUS) con familia ETS (FLI1, ERG, ETV1, ETV4 o FEV).
- ❖ En la actualidad los casos diagnosticados han sido confirmados por estudios moleculares (FISH, PCR o NGS).



SARCOMAS EWING LIKE

TABLE 2 Ewing-like sarcoma fusions

Fusion	Reference	Diagnosis
EWSR1-NFATc2	Szuhai et al. (2009)	Ewing-like
EWSR1-POU5F1	Antonescu et al. (2010); Yamaguchi et al. (2005)	Ewing-like; myoepithelial tumors of soft tissue
EWSR1-SMARCA5	Sumegi et al. (2011)	Ewing-like
EWSR1-ZSG (ZNF278 or PATZ1)	Mastrangelo et al. (2000)	Ewing-like
EWSR1-SP3	Wang et al. (2007)	Ewing-like
CIC-DUX4	Italiano et al. (2012)	Ewing-like
CIC-FOXO4	Sugita et al. (2014)	Ewing-like
BCOR-CCNB3	Pierron et al. (2012)	Ewing-like
BCOR-MAML3	Specht et al. (2016)	Ewing-like
ZC3H7B-BCOR	Specht et al. (2016)	Ewing-like

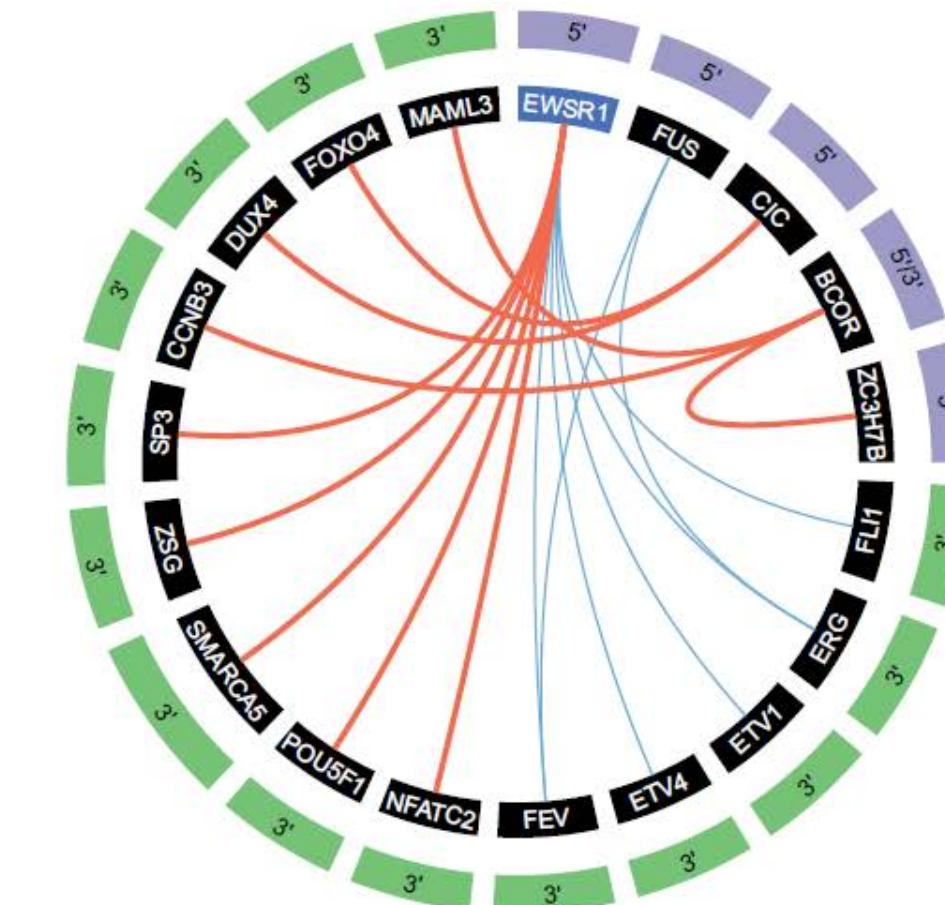


FIGURE 1 Overview of fusions in classical Ewing sarcoma and Ewing-like tumors. Classical Ewing sarcoma fusions are depicted by the blue lines and involve fusions between members of the TET family of RNA binding proteins (EWSR1 and FUS) and the ETS family of transcription factors, most commonly FLI1. The focus of this review will be on the Ewing-like fusions (red and bold). The 5' partners are highlighted in purple, whereas the 3' partners are highlighted in green [Color figure can be viewed at wileyonlinelibrary.com]

SARCOMAS EWING LIKE

REVIEW ARTICLE

WILEY

Ewing-like sarcoma: An emerging family of round cell sarcomas

Samuele Renzi¹ | Nathaniel D. Anderson² | Nicholas Light² | Abha Gupta^{1,3,4}

Published online 2016 Sep 21. doi: 10.1002/humu.23044

Targeted Next Generation Sequencing of CIC-DUX4 Soft Tissue Sarcomas Demonstrates Low Mutational Burden and Recurrent Chromosome 1p Loss

Clinicopathologic Diversity of Undifferentiated Sarcoma With BCOR-CCNB3 Fusion

Analysis of 11 Cases With a Reappraisal of the Utility of Immunohistochemistry for BCOR and CCNB3

Atsushi Matsuyama, MD* Etsuro Shiba, MD* Yoshitaka Umekiwa, MD† Kanae Notsuka, MD† Takahiro Kamiya, MD‡ Hiroyuki Yanai, MD‡ Chika Miyazaki, MD|| Reiko Watanabe, MD|| Ichiro Ito, MD‡ Tomoko Tamaki, MD** Shinichi Hayashi, MD†† and Masanori Hisanaga, MD*

ORIGINAL ARTICLE

BCOR-CCNB3 (Ewing-like) Sarcoma

A Clinicopathologic Analysis of 10 Cases, In Comparison With Conventional Ewing Sarcoma

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/304034621>

Ewing sarcoma and the new emerging Ewing-like sarcomas: (CIC and BCOR-rearranged-sarcomas). A systematic review

Histopathology, 2017 Mar;70(4):657-663. doi: 10.1111/his.13112. Epub 2016 Dec 16.

The utility of ETV1, ETV4 and ETV5 RNA in-situ hybridization in the diagnosis of CIC-DUX sarcomas.

Smith SC^{1,2}, Palanisamy N^{3,4}, Martin E¹, Almenara J¹, McHugh JE⁴, Choi EH⁴, Lucas DR⁴, Betz BL⁴, Thomas D⁴, Patel RM^{4,5}.

Received February 2016; accepted October 2016

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BCOR-CCNB3 fusions are frequent in undifferentiated sarcomas of male children

Tricia L. Peters^{1,2,9}, Althea Kupper^{1,2,9}, Samanthi Polikarpakosil^{1,2}, Frank Y. Lin^{1,4}, Stephen P. Sarabia^{1,2}, Yu Liang¹, Wei-Liang Wong¹, Alexander J. Lazarus¹, Harsila Vardhanapati¹, Hye-Chun¹, Dennis M. Murray¹, David A. Whistler^{1,2,3,4}, Matthew Okuno¹, Sherry J. Pilon^{1,2,3,4}, M. John H. Fetter¹, Dolores López-Terrada^{1,2,3,4}, D. Williams Parsons¹, and Angshuman Roy^{1,2,3,4}

Research Watch

BCOR-CCNB3 Fusions Occur in Ewing-Like Sarcomas

DOI: 10.1158/2159-8290 CD-RW2012-034 Published April 2012

BCOR-CCNB3 Fusion Positive Sarcomas
A Clinicopathologic and Molecular Analysis of 36 Cases With Comparison to Morphologic Spectrum and Clinical Behavior of Other Round Cell Sarcomas

Yu-Chien Kao, MD,^{†,‡} Adeleman A. Owashri, DDS,[§] Yim-Shao Sung, MSE,[¶] Lei Zhang, MD,[¶] Yumi Fujisawa, MSE,[¶] Jen-Chieh Lee, MD, PhD,^{||} Leonard Wexler, MD,[¶] Pedram Argani, MD,[¶] David Swanson, BSc,^{**} Brendan C. Dickson, MD,^{**} Christopher D. M. Fletcher, MD, FRCPATH,^{††} and Cristina R. Antoniou, MD,[¶]



**SARCOMAS CON
REORDENAMIENTO DEL REPRESOR
TRANSCRIPCIONAL CAPICUA
(CIC)**

SARCOMAS CON REORDENAMIENTO CIC

- ❖ Corresponden al subgrupo mas grande de Sarcomas de tipo Ewing like (70%).
- ❖ Actualmente la OMS los incluye dentro de los Sarcomas indiferenciados con fenotipo de células redondas.
- ❖ Primera descripción en 2006 por Kawamura-Saito.
- ❖ Curso agresivo con metástasis tempranas.
- ❖ No se conocen factores de riesgo asociados



GENÉTICA

t(4:19) (q35;q13) / t(10:19) (q26;q13)

GEN CIC

Crom 19

- Regula vías señalización TK
- Reprime expresión de genes

GEN DUX4

Crom 4 o 10



FUSIÓN CIC-DUX4

Factores de transcripción aberrantes

Promueven la oncogénesis desregulando cientos de genes

Sobreexpresión Factores transcripcionales ETV1, ETV4, ETV5 entre otros
(familia PEA3)

FUSIONES ALTERNATIVAS: Gen FOXO4, NUTM1

EPIDEMIOLOGÍA

- ❖ Amplio rango etario (6–81)
- ❖ Más frecuente en adultos jóvenes (x:30 años).
- ❖ Ligera predilección sexo masculino (2:1)



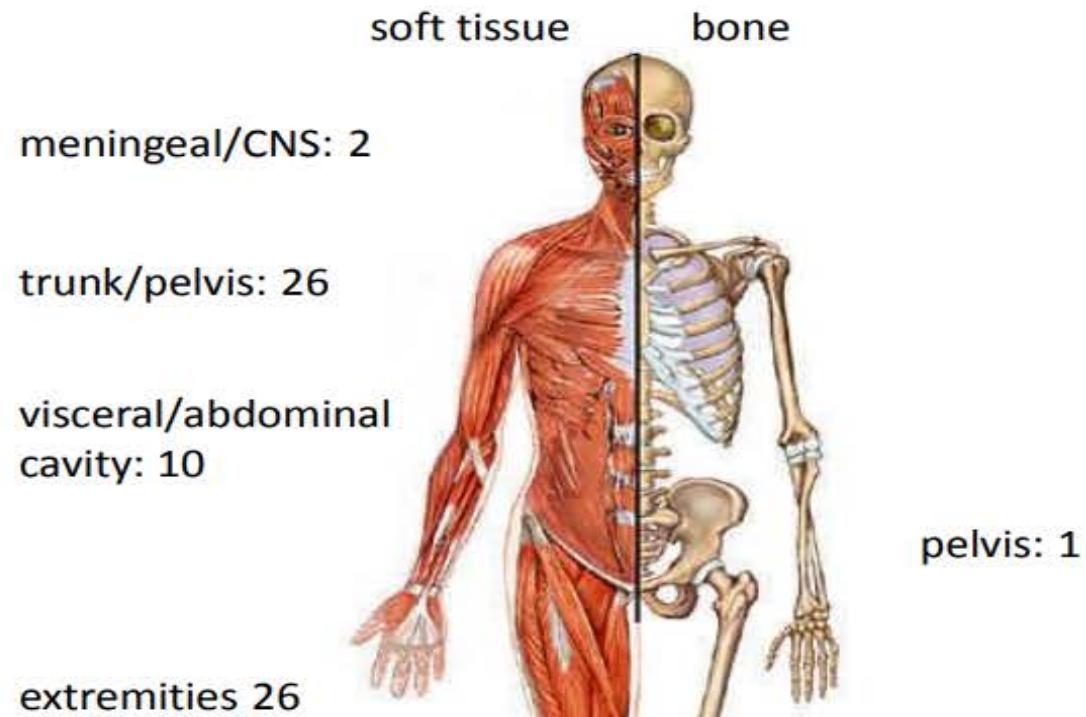
Table 2. *C/C-rearranged sarcoma meta-analysis.*

Cases with <i>C/C</i> or <i>DUX</i> rearrangement (Total of cases: 85)	N / (%)
2-Age group (age range)	
<10 years	4 (4.7%)
10-20 years	22 (25.8%)
21-40 years	42 (49.4%)
>40 years	17 (20%)

LOCALIZACIÓN

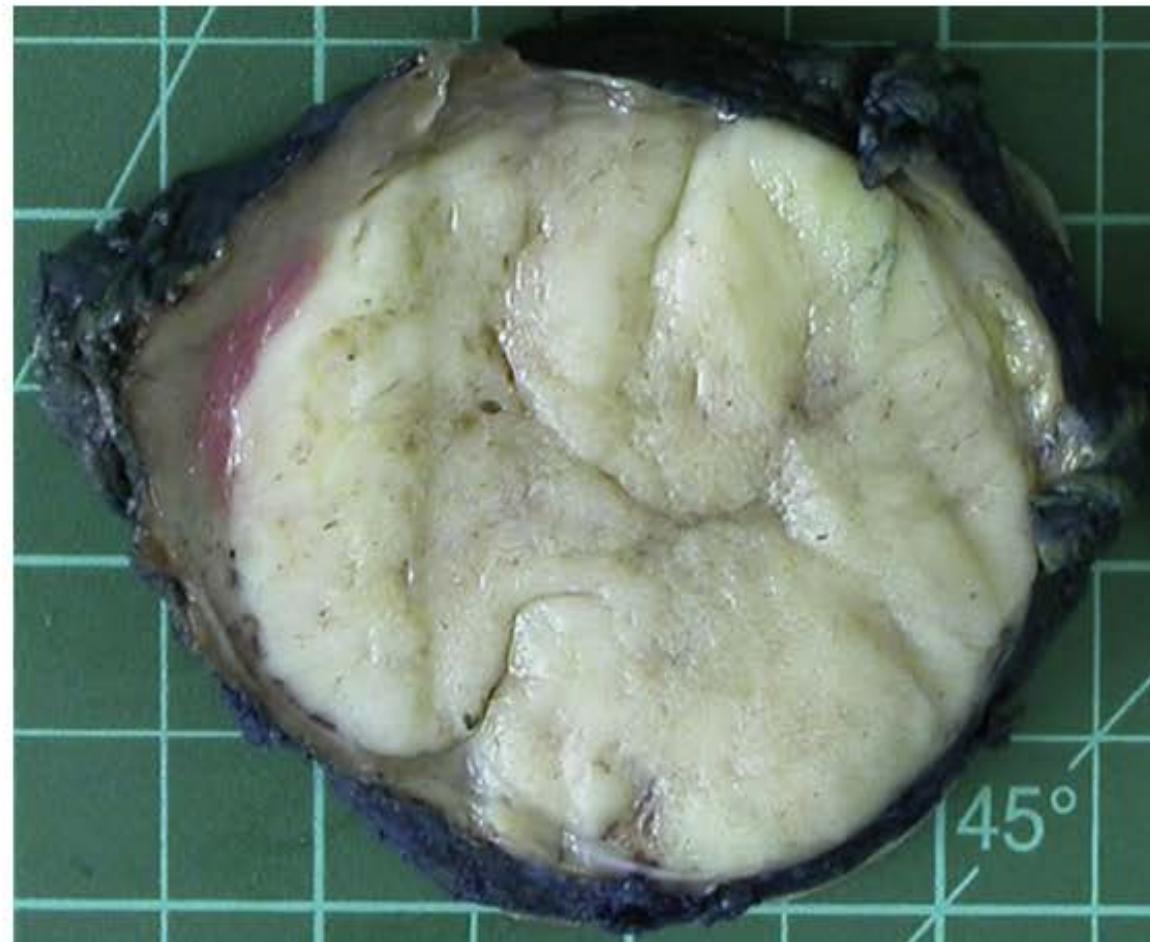
- ❖ Tejidos blandos (90%), órganos viscerales y hueso (<5%)
- ❖ Extremidades, tronco y pelvis.

CIC-rearranged sarcoma: localisation



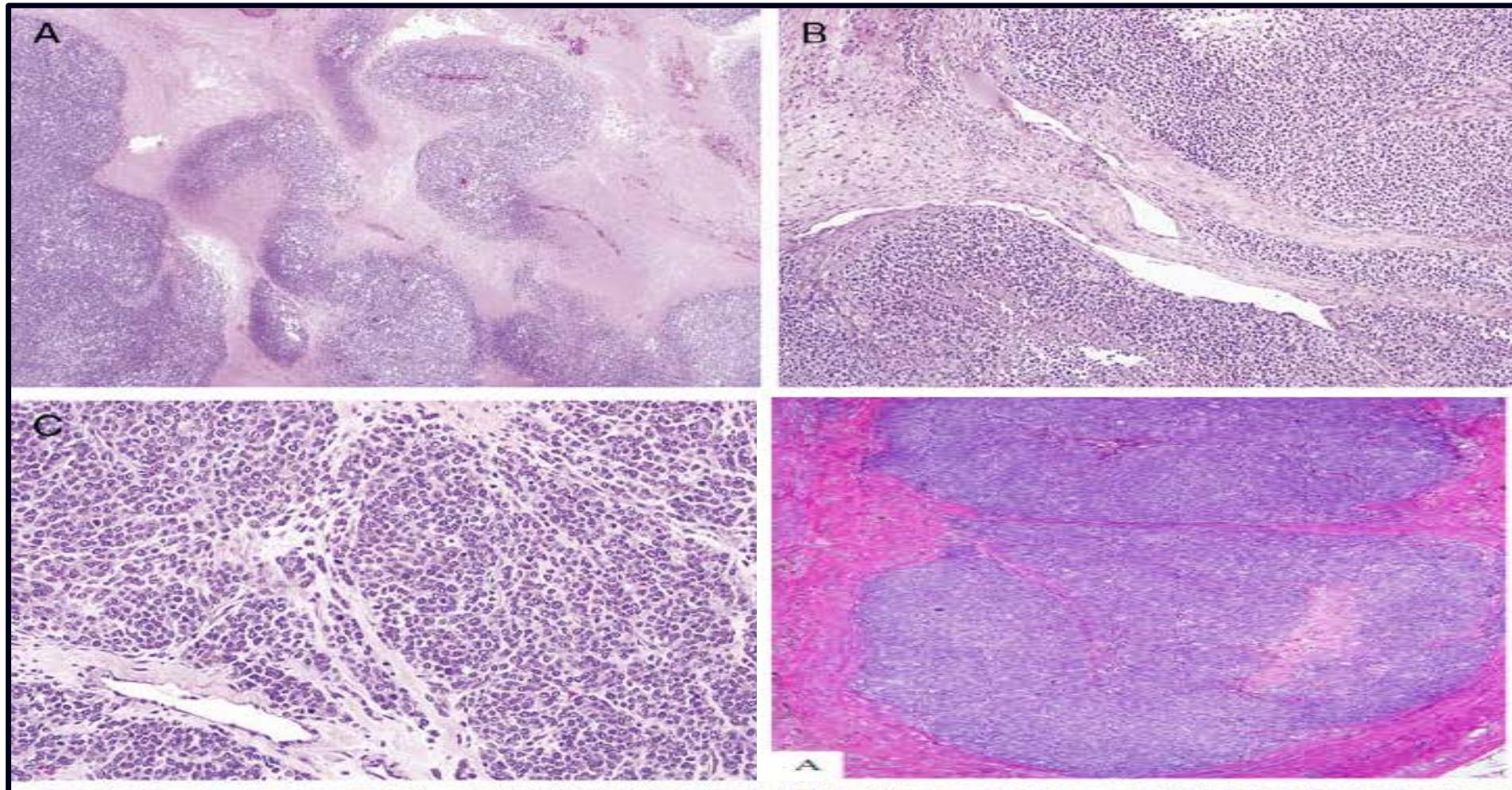
Italiano et al. *Genes, Chromosomes and Cancer* 2012 (n=15)
Yoshida et al. *Am J Surg Pathol* 2016 (n=20)
Gambarotti et al. *Histopathology* 2016 (n=7)
Choi et al. *Am J Surg Pathol* 2016 (n=4)
Graham et al. *Hum Pathol* 2012 (n=3)
Kawamura-Saito et al. *Hum Mol Genet* 2006 (n=2)
Specht et al. *Genes, Chromosomes and Cancer* 2012 (n=8)

MACROSCOPÍA



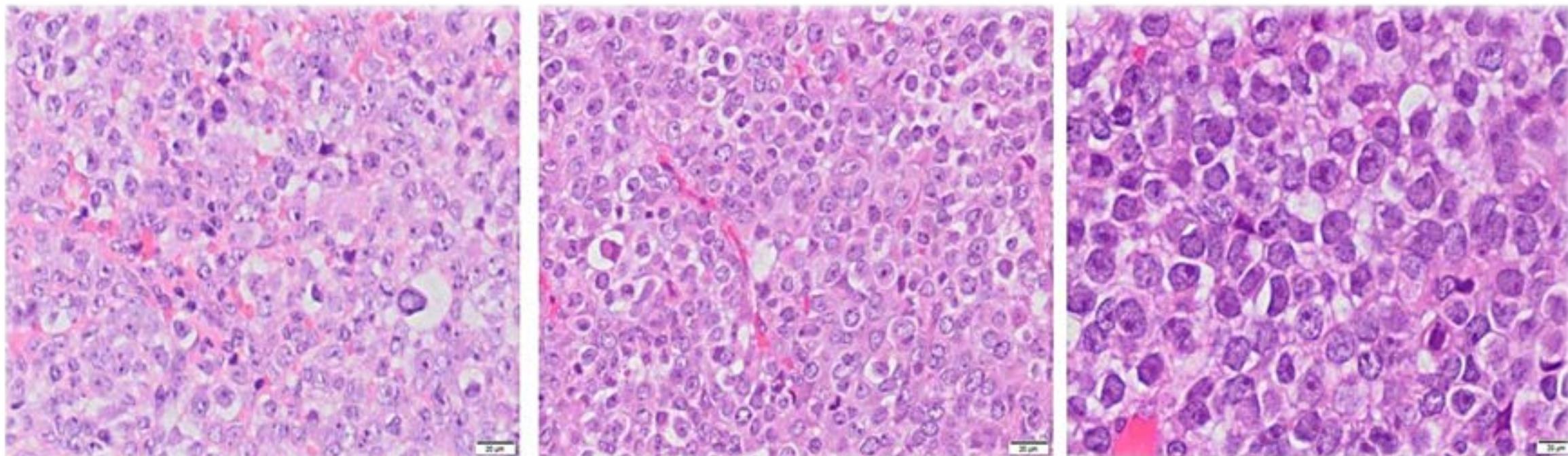
HISTOLOGÍA

□ Patrón lobulado



HISTOLOGÍA

- Células redondas a ovales de tamaño pequeño o mediano.
- Mayoría monótonas, con escaso pleomorfismo.
- Núcleos hiperchromáticos o con cromatina vesiculosa.
- Nucléolo variable.



HISTOLOGÍA

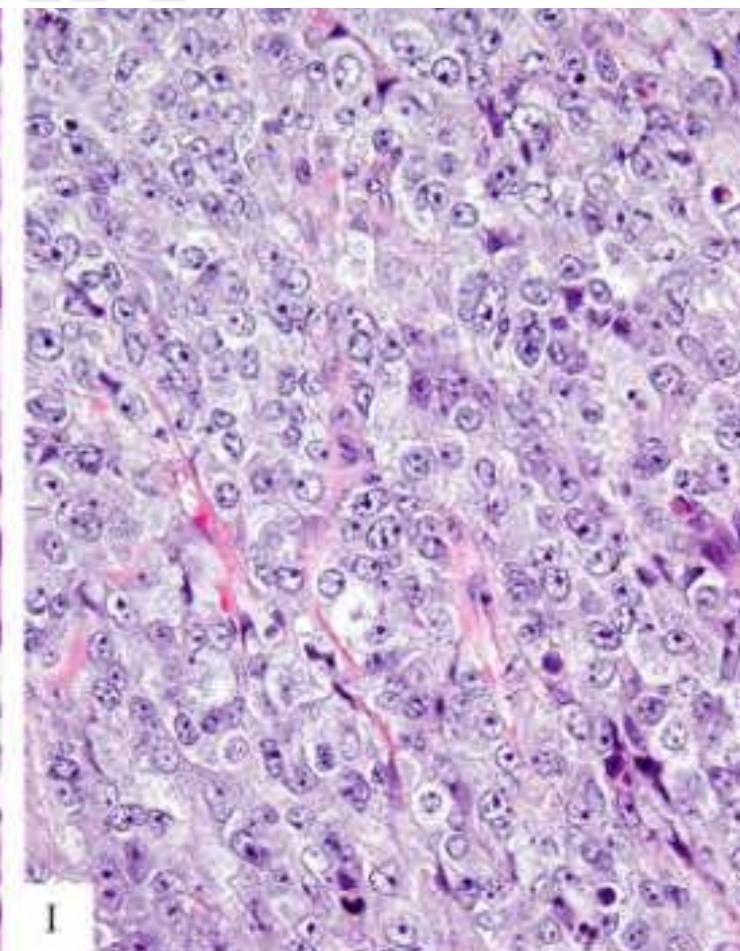
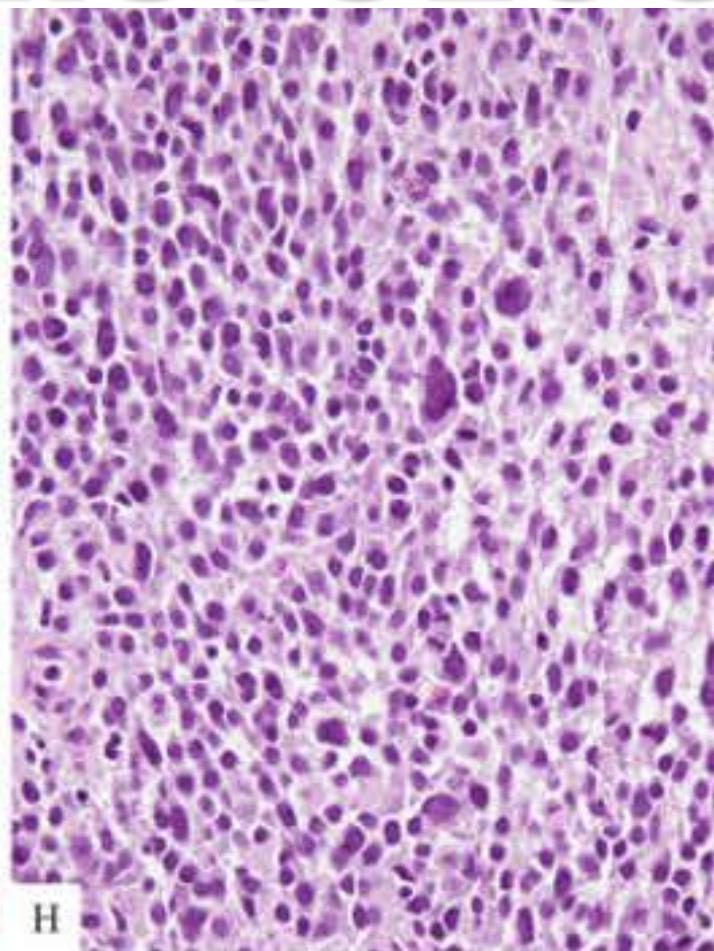
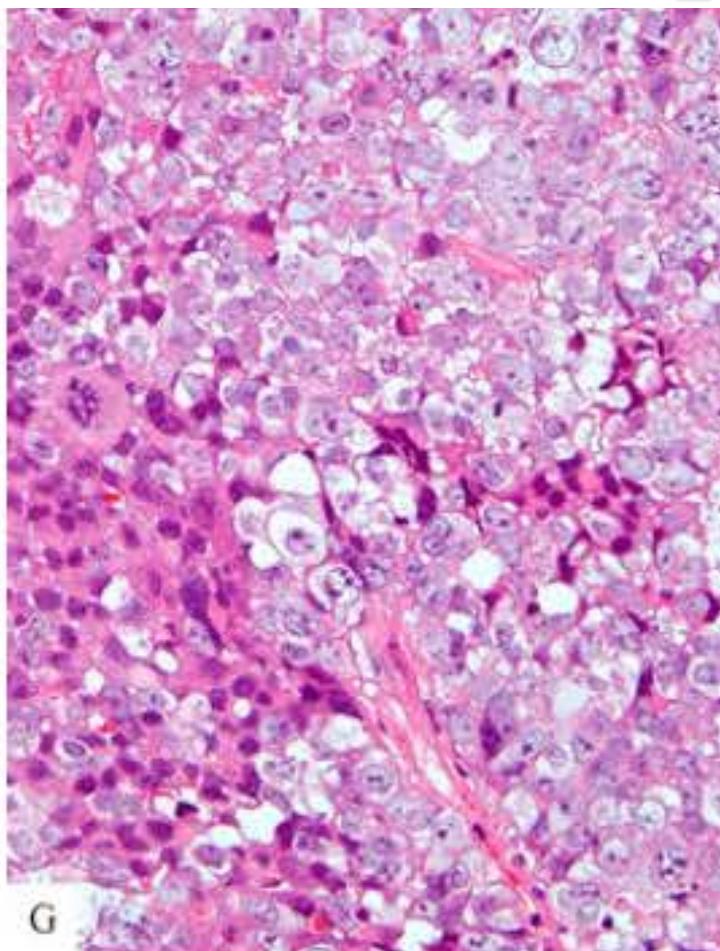
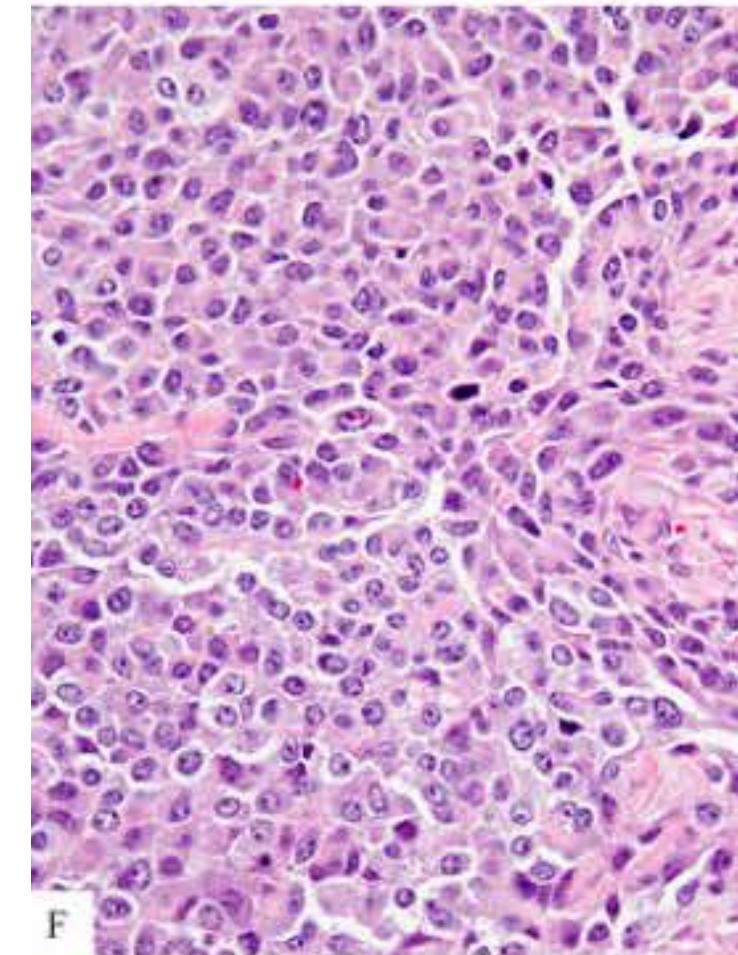


Figure 1. Morphologic spectrum of *CIC*-rearranged sarcomas

HISTOLOGÍA

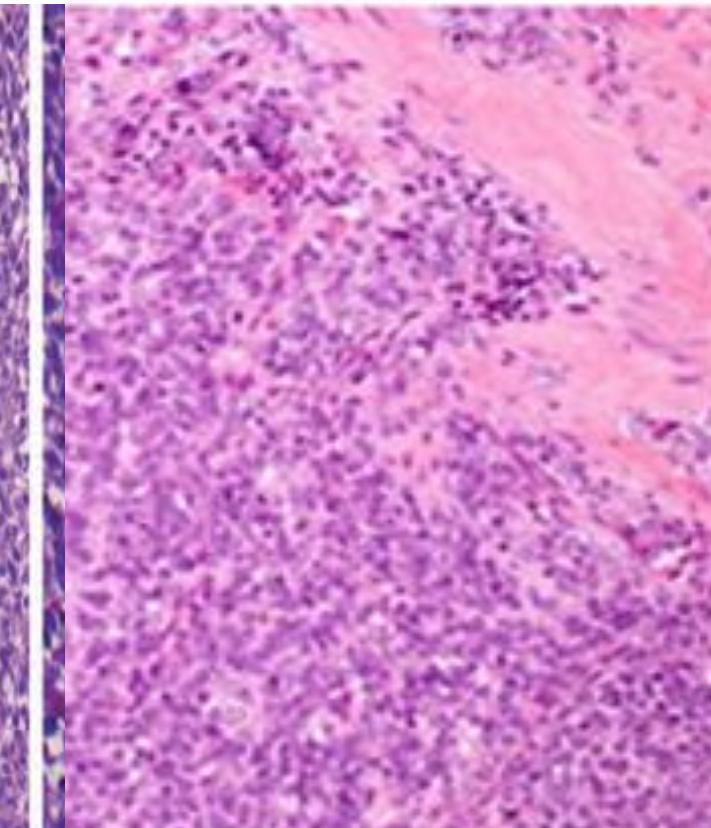
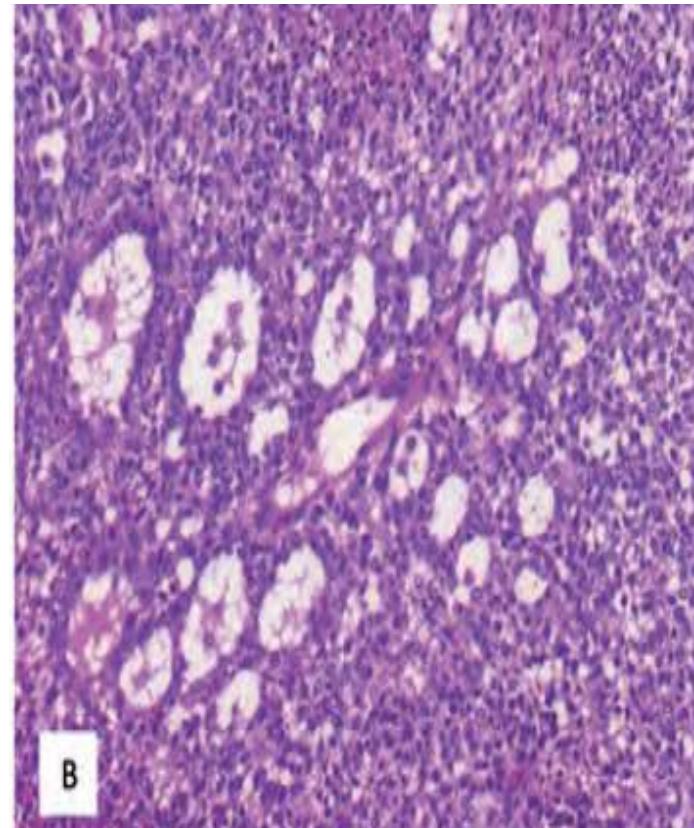
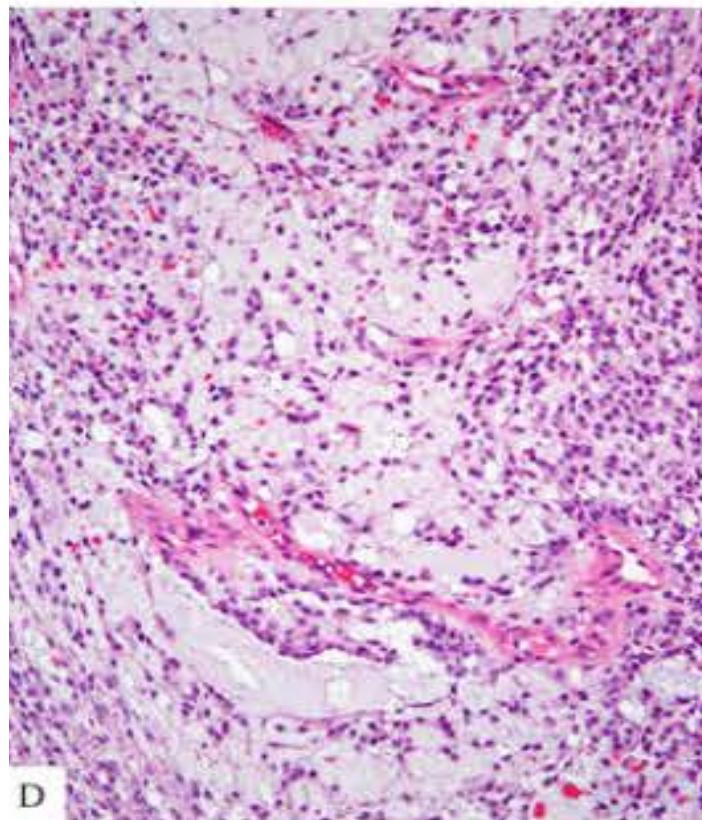
- Células fusadas, plasmocitoides, rhabdoides o epitelioides, pero generalmente no como patrón predominante
- > variabilidad de las células, > citoplasma y > recuento mitótico de SE.
- No presenta rosetas.



Células epitelioides a plasmocitoides

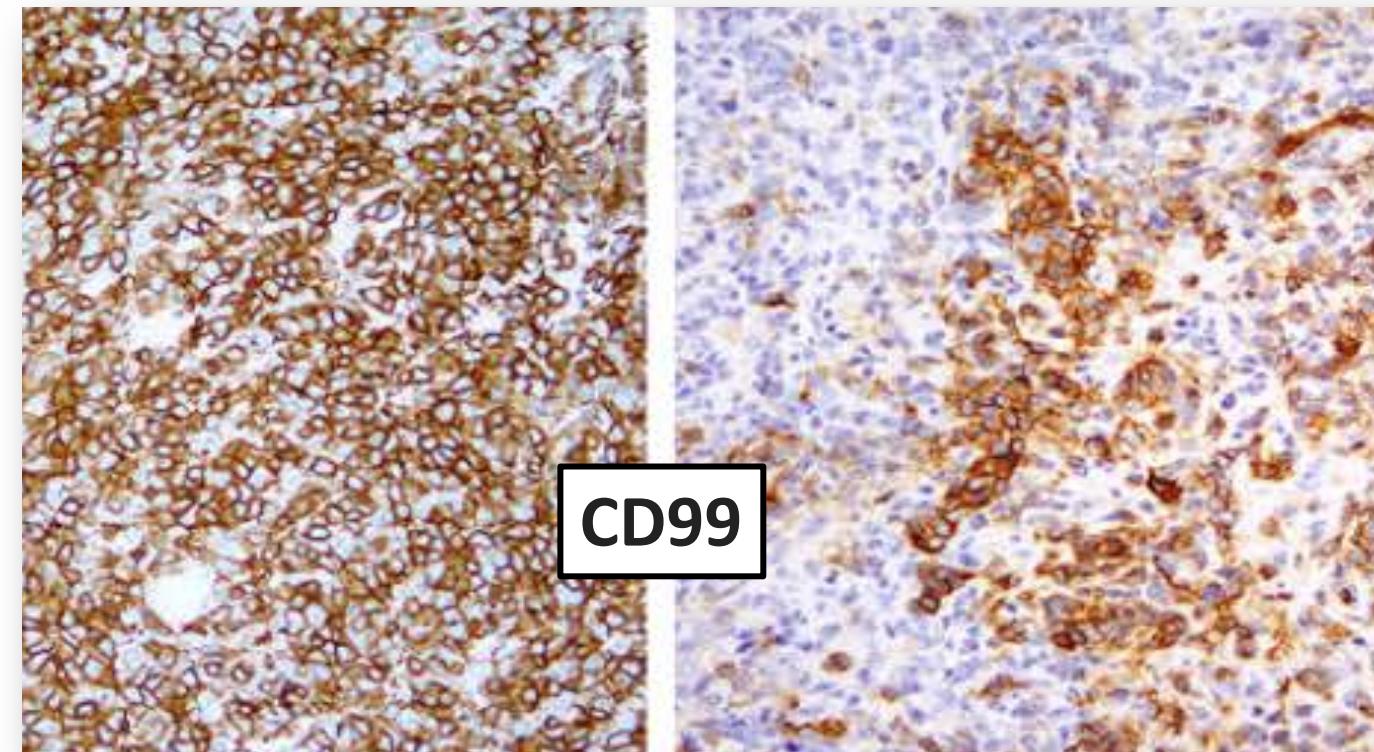
HISTOLOGÍA

- Estroma variable, desmoplásico, esclerótico, edematoso, mixoide.
- A veces apariencia microquística, reticular o pseudoacinar.



ESTUDIO INMUNOHISTOQUIMICO

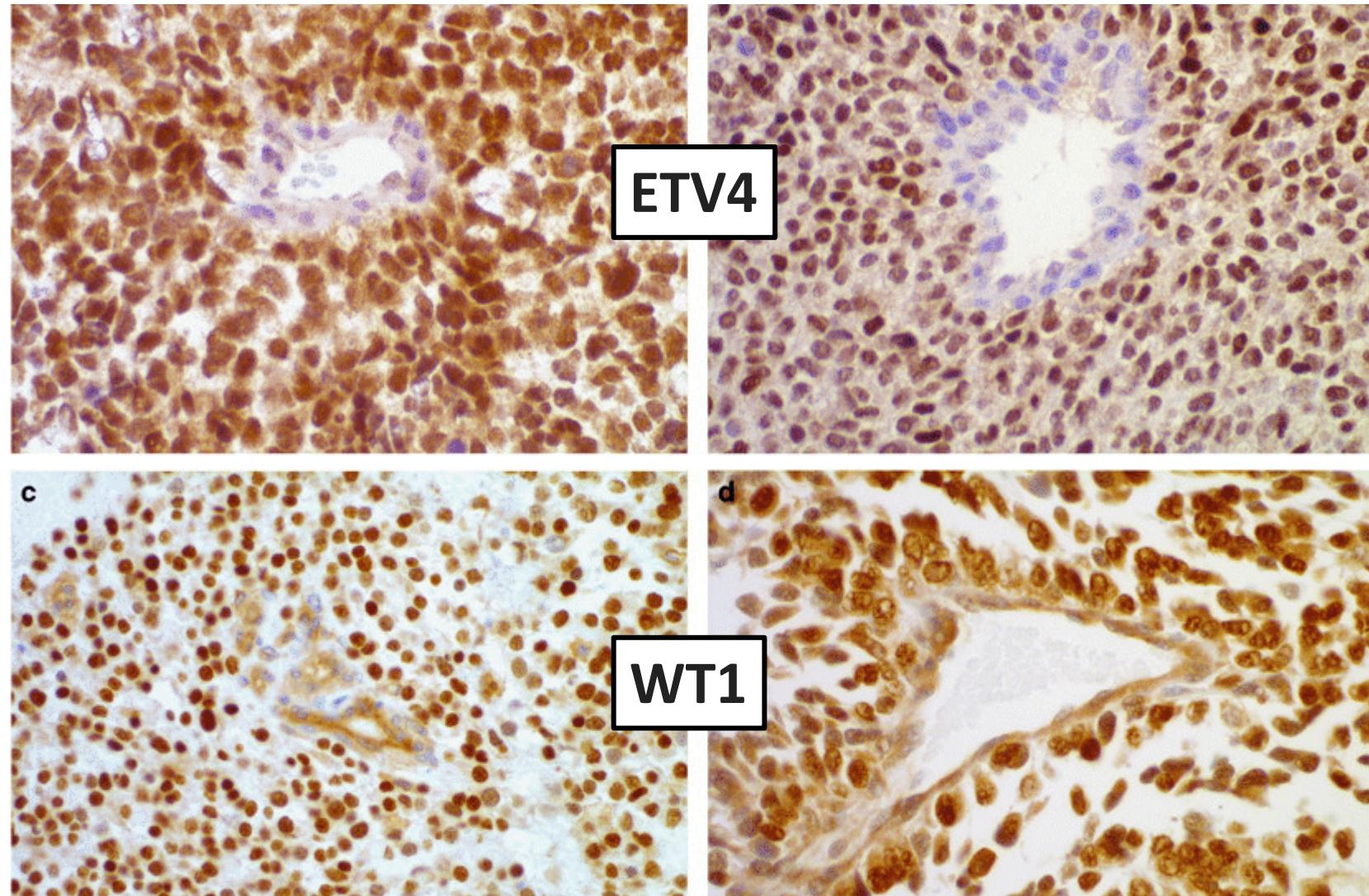
- ❖ CD99 mb (+/-, difuso o focal)
- ❖ WT-1 (++) nuclear)
- ❖ ETV-4 (++) nuclear,>90%)
- ❖ FLI1 -/+
- ❖ ERG -/+
- ❖ CK/EMA +/-
- ❖ DESMINA +/-



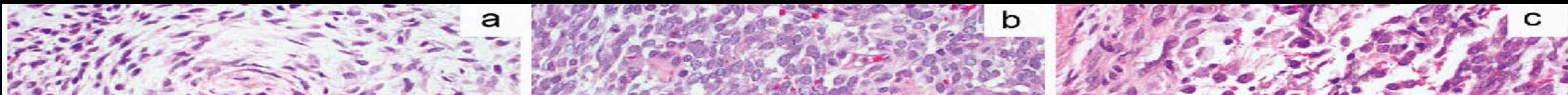
NEGATIVOS:

PAX7, NKX 2.2, MIOG, BCOR, CCNB3, TLE-1

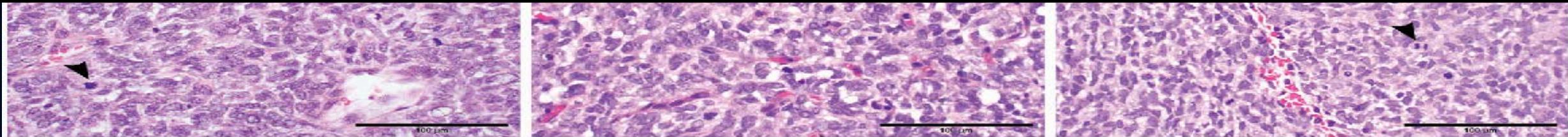
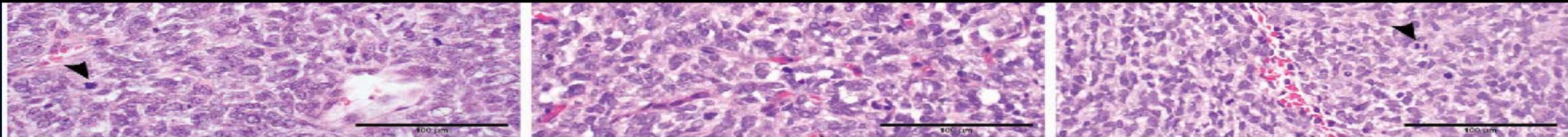
ESTUDIO INMUNOHISTOQUIMICO



SARCOMAS EWING LIKE

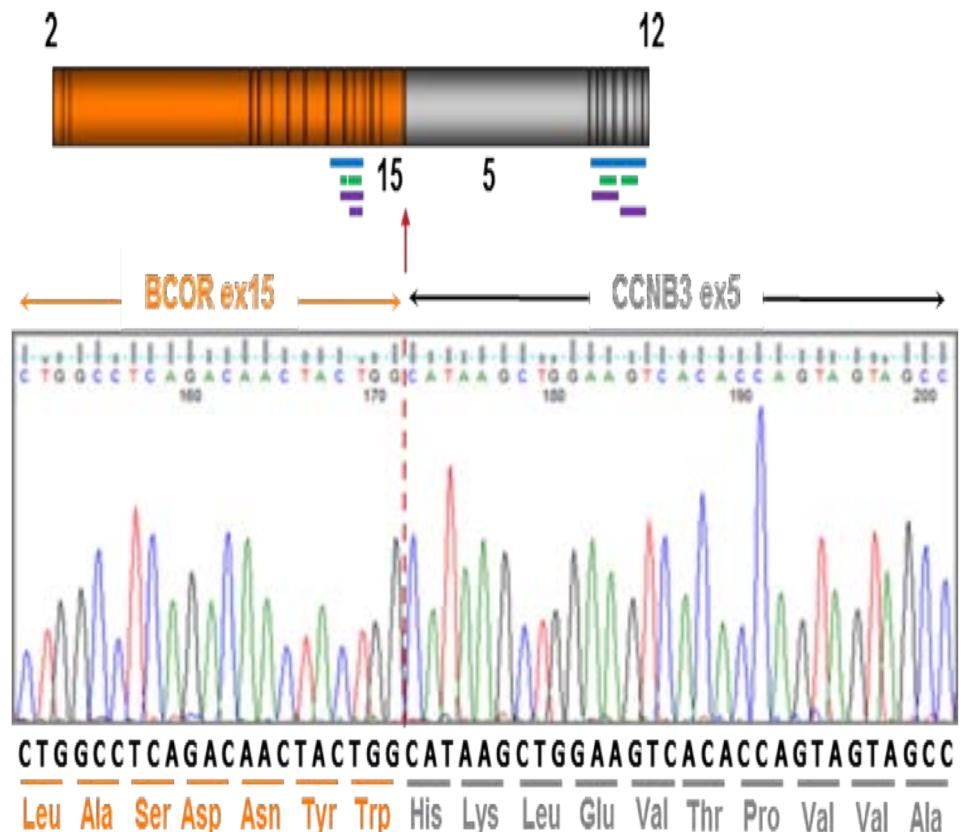


SARCOMAS CON REORDENAMIENTO BCOR



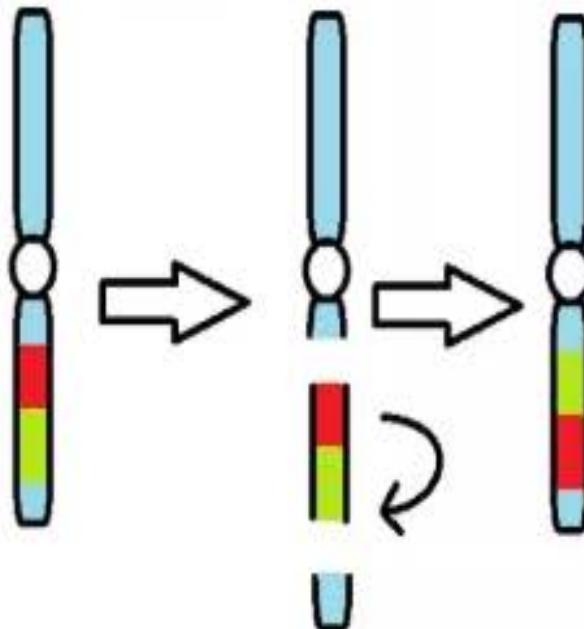
SARCOMAS CON REORDENAMIENTO BCOR

- ❖ 2do tumor mas frecuente de los Sarcomas de tipo Ewing like (4-14 %).
- ❖ Descrito por 1ra vez en 2012.
- ❖ Clínica y morfología similar a SE.
- ❖ No se conocen factores de riesgo asociados



GENÉTICA

Paracentric Inversion



**Inversión paracéntrica crom X
inv(X)(p11.4p11.22)**

GEN BCOR

Represor transcripcional
del gen Bcl6



GEN CCNB3

Codifica Ciclina B3
específica

FUSIÓN BCOR-CCNBE (88% casos)

Sobreexpresión CCNB3

Promueve un aumento de proporción de células en fase S del ciclo

Otras fusiones: BCOR-MAML3, BCOR-ZC3H7B

EPIDEMIOLOGÍA

- ❖ Principalmente adolescentes
- ❖ Sexo masculino aprox 85%.

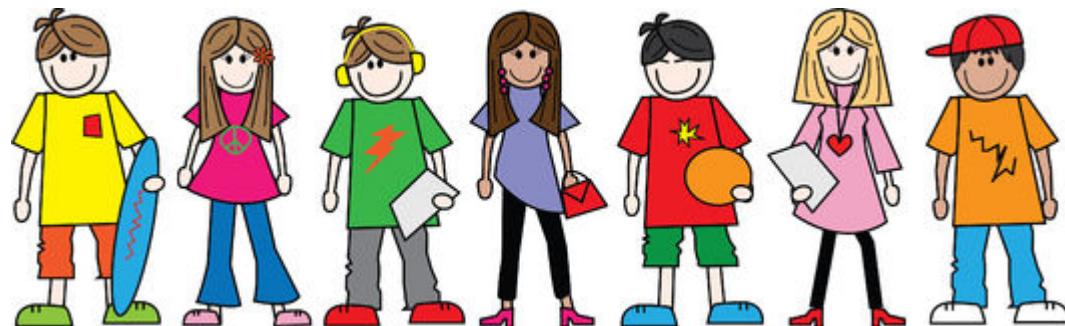


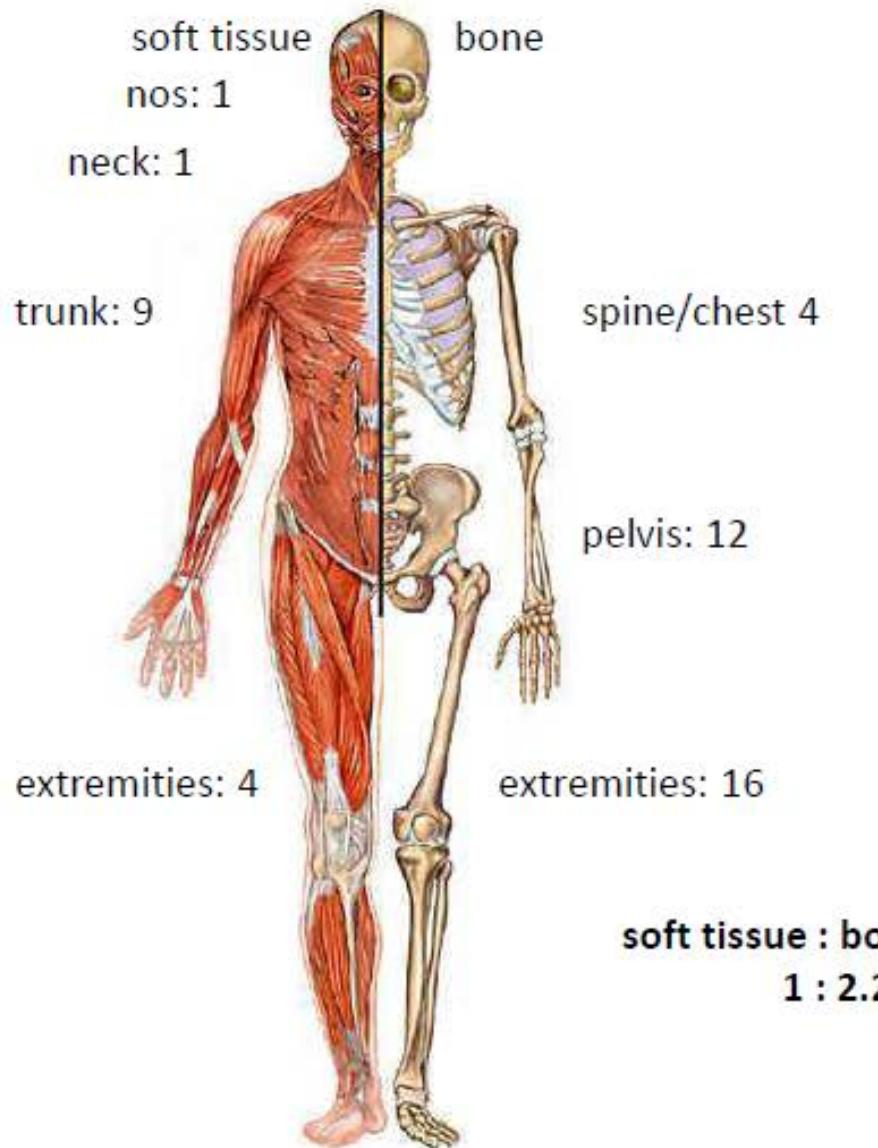
Table 4. *BCOR*-rearranged sarcomas meta-analysis.

Cases with <i>BCOR</i> rearrangement (Total of cases: 68)	N/%
1-Sex	
Male	52 (81.2%)
Female	12 (18.8%)
2-Age group (age range)	
<10 years	10 (17.5%)
10-17 years	32 (56.1%)
>17 years	15 (26.4%)

LOCALIZACIÓN

3-Primary tumor localization(predominant)	
soft tissue	24 (36.9%)
bone	40 (61.5%)
visceral	1 (1.6%)
4-Primary tumor localization (region)	
Head/neck	1 (2.3%)
Trunk and abdominal region	5 (11.4%)
Pelvis and extremities:	36 (81.8%)
Axial skeleton:	2 (4.5%)

Pierron *et al.* Nature genetics 2014 (n=24)
 Puls *et al.* Am J Surg Pathol 2014 (n=10)
 Peters *et al.* Mod Pathol 2015 (n=6)
 Shibayama *et al.* Pathol Int 2015 (n=3)
 Li *et al.* Histopathology 2016 (n=4)



MACROSCOPÍA

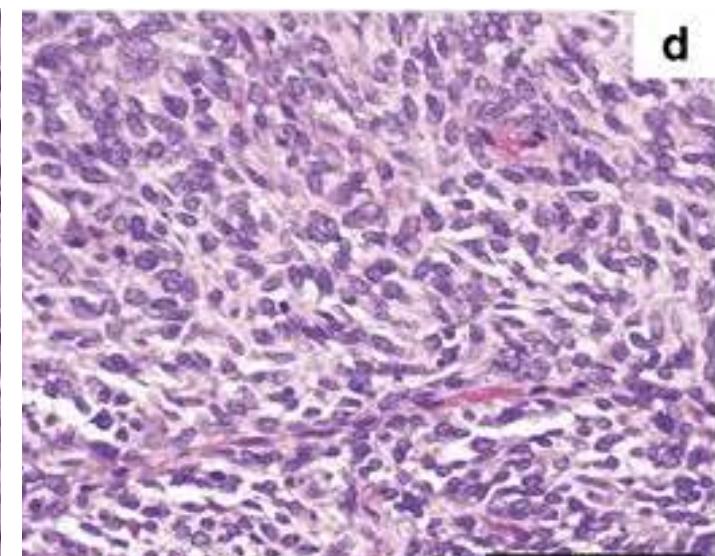
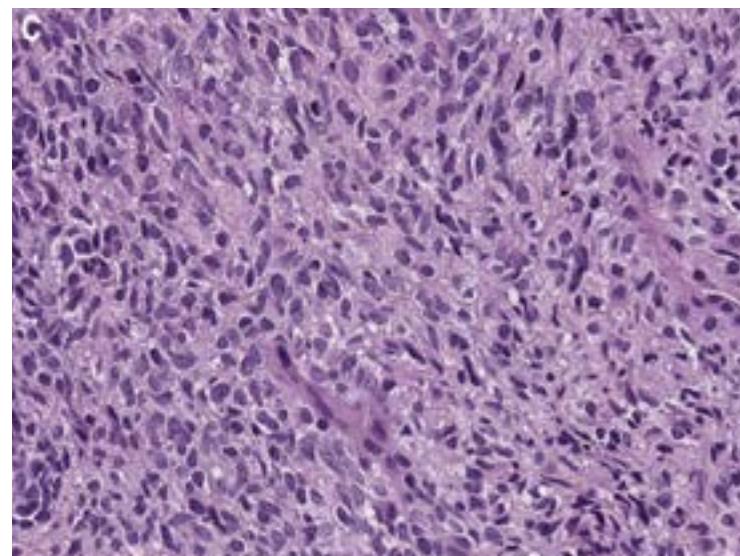
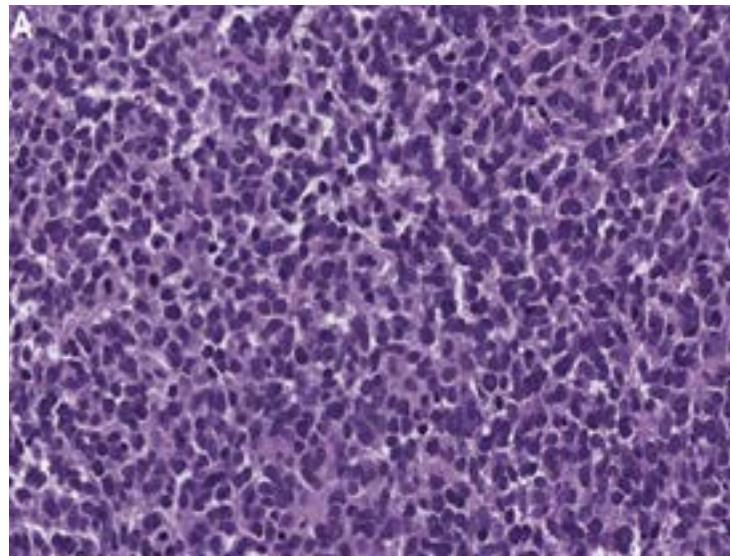


Post qt.

A

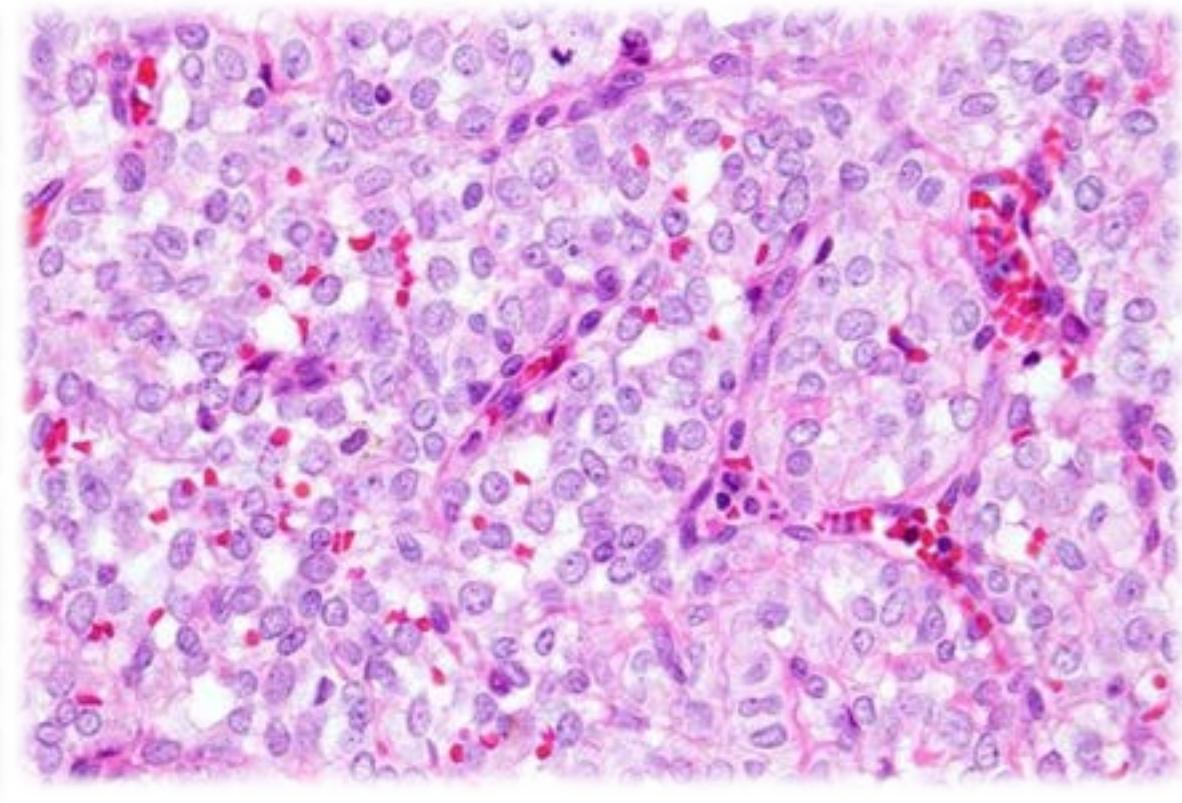
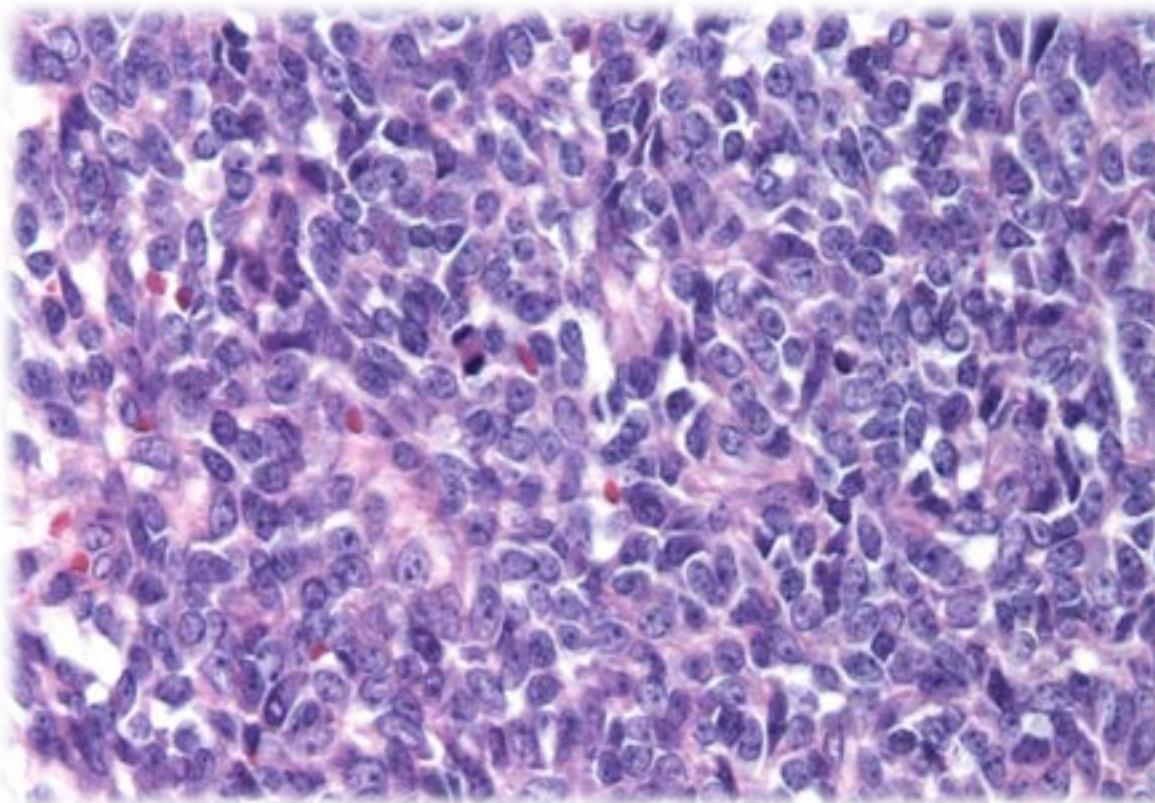
HISTOLOGÍA

- Células de tamaño pequeño a mediano.
- Redondas, ovoides o fusadas.
- Sábanas y fascículos cortos.



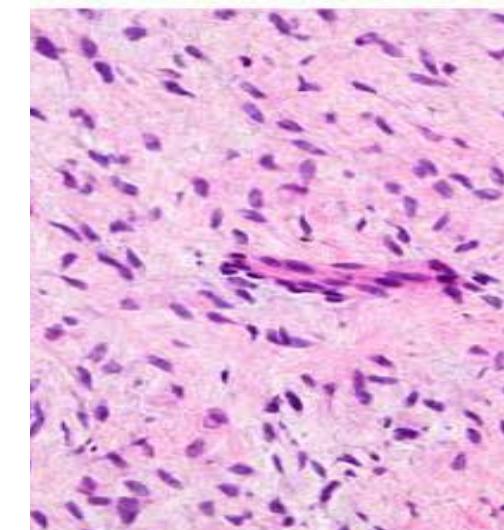
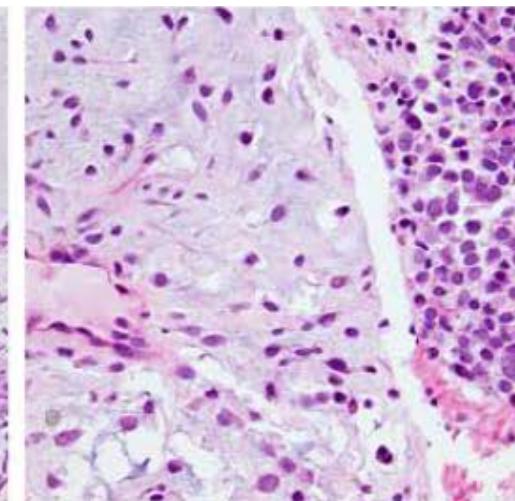
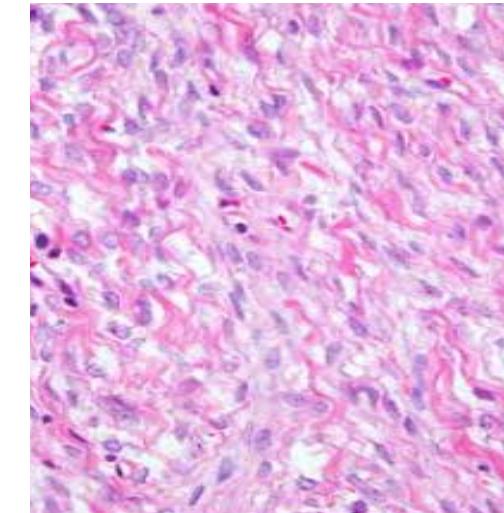
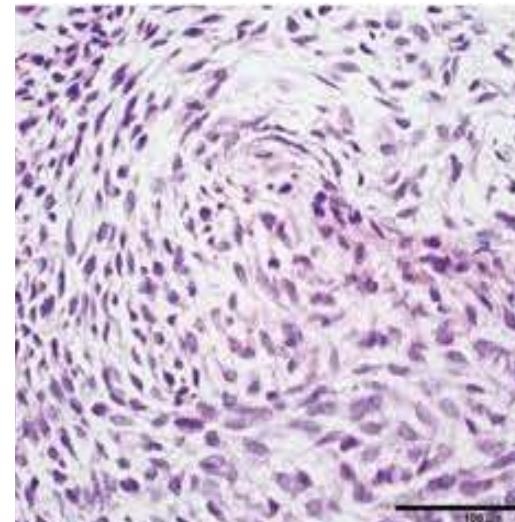
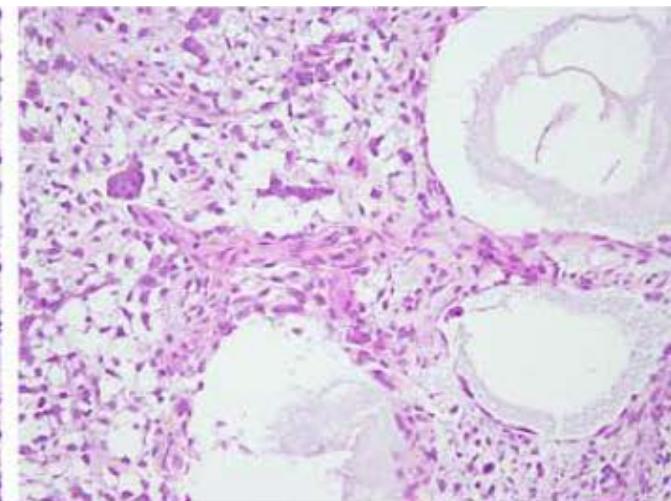
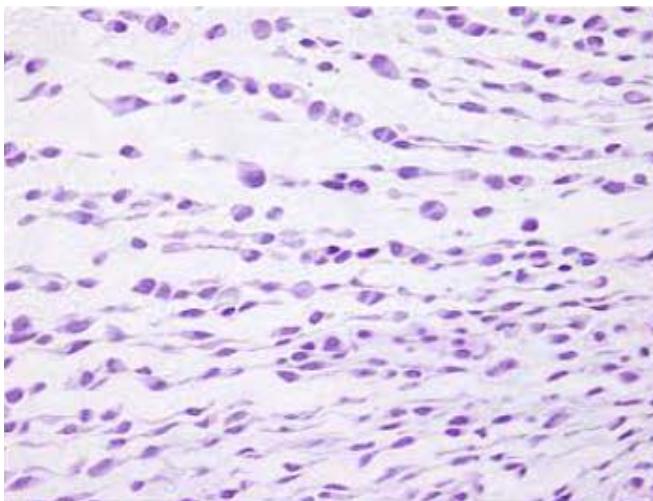
HISTOLOGÍA

- Núcleos de cromatina fina vesiculosa.
- Nucléolo ausente o pequeño.
- Escaso citoplasma

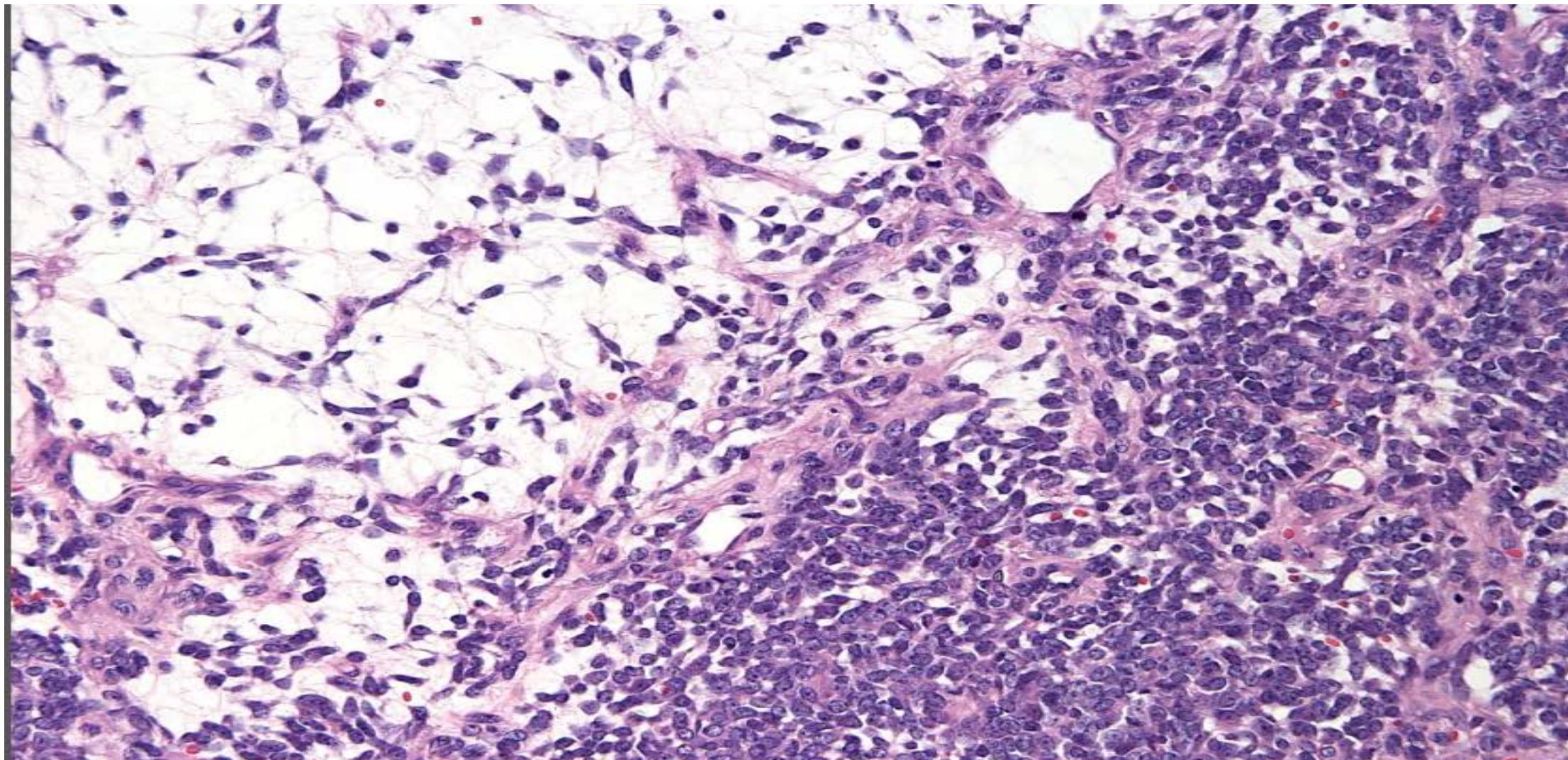


HISTOLOGÍA

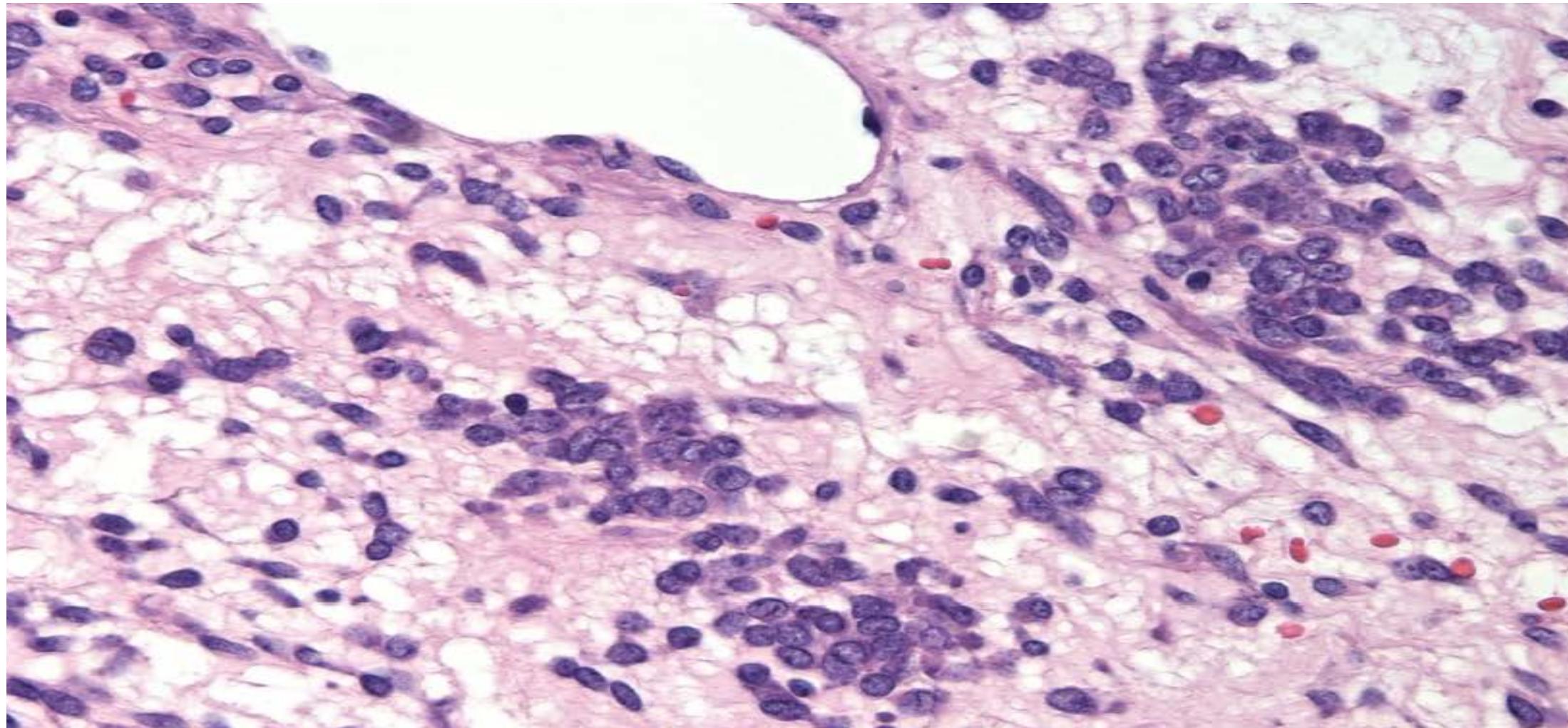
- Estroma mixoide (50%) entremezclado con células tumorales o formando un patrón microquístico.
- Estroma colágeno (20-30%)



HISTOLOGÍA

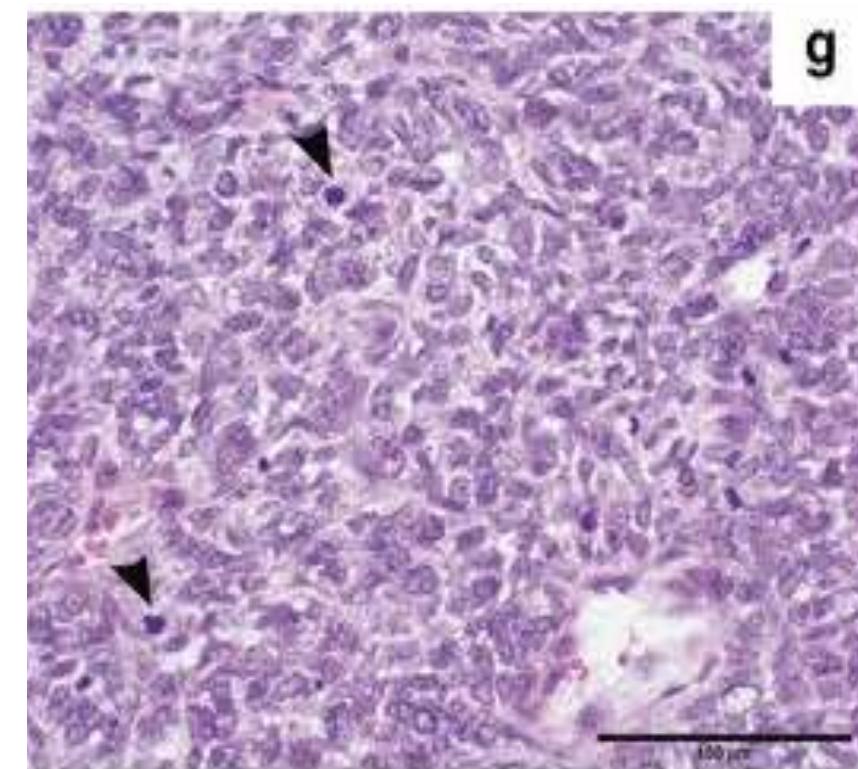
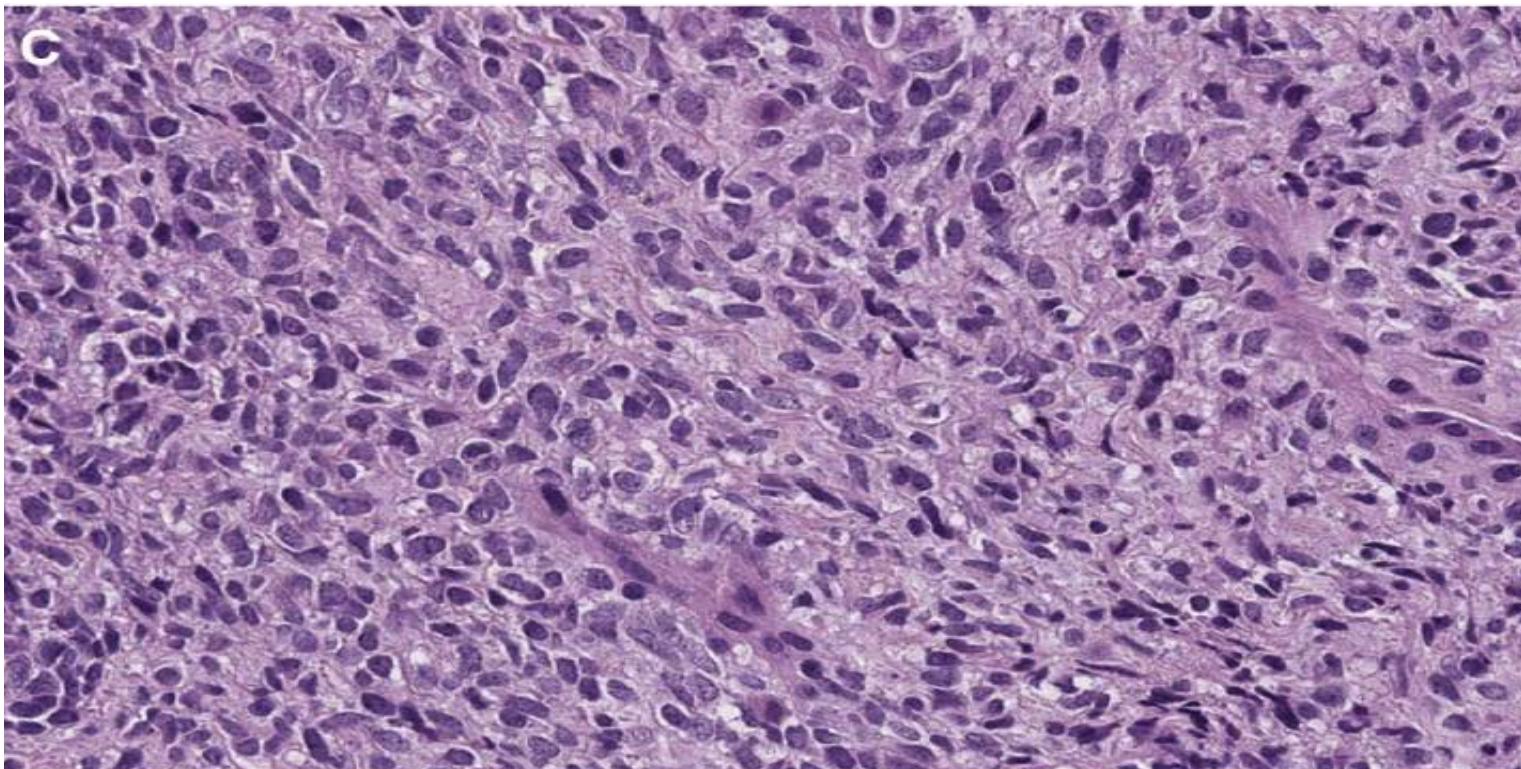


HISTOLOGÍA



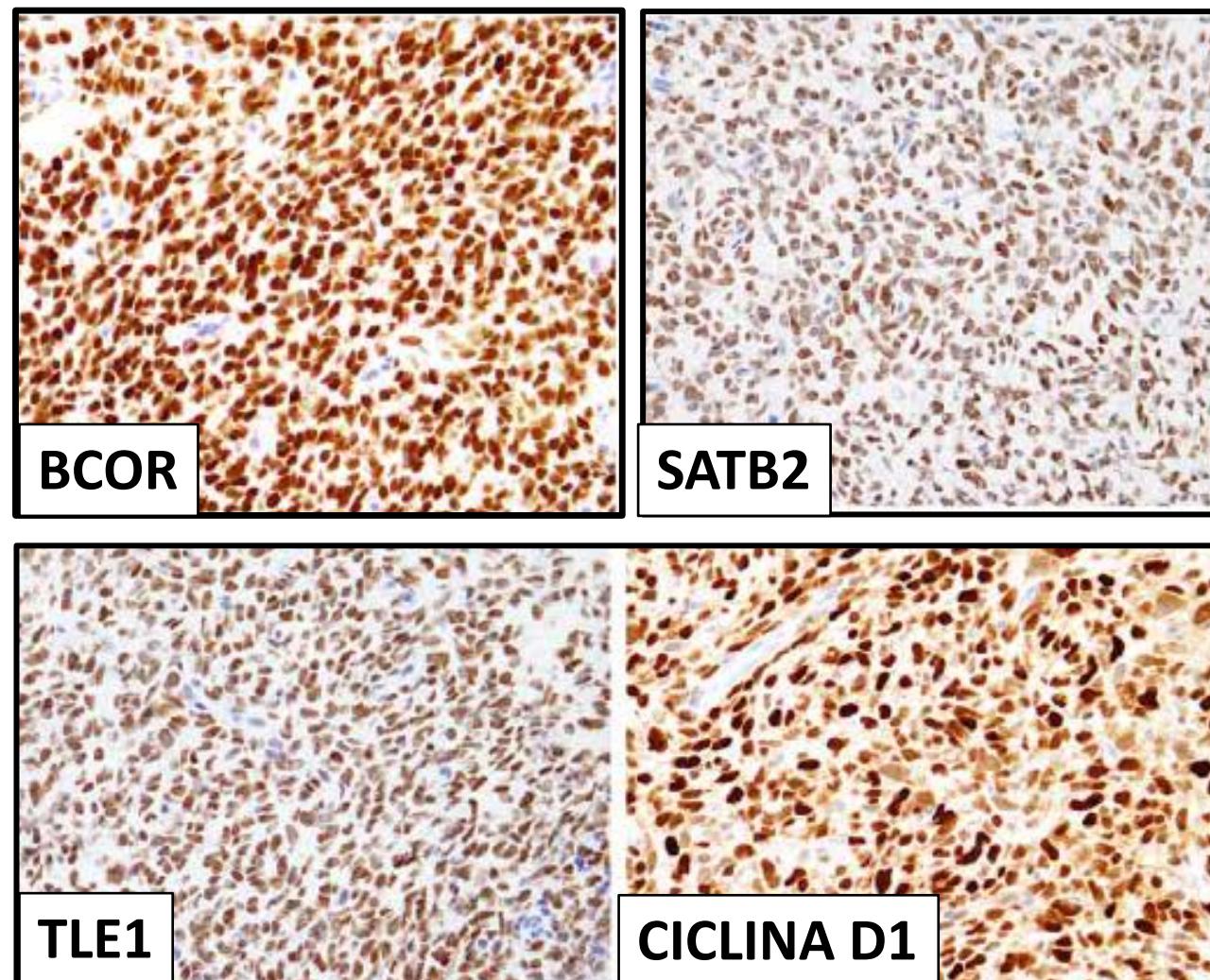
HISTOLOGÍA

- Rica red vascular, a veces de aspecto hemangiopericitoides.
- Necrosis focal o geográfica.
- Mitosis variables (5-45 X CAM)

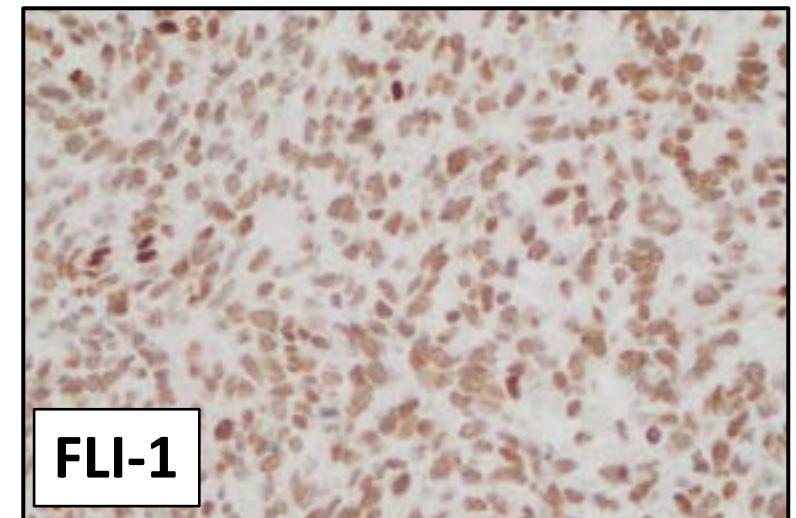
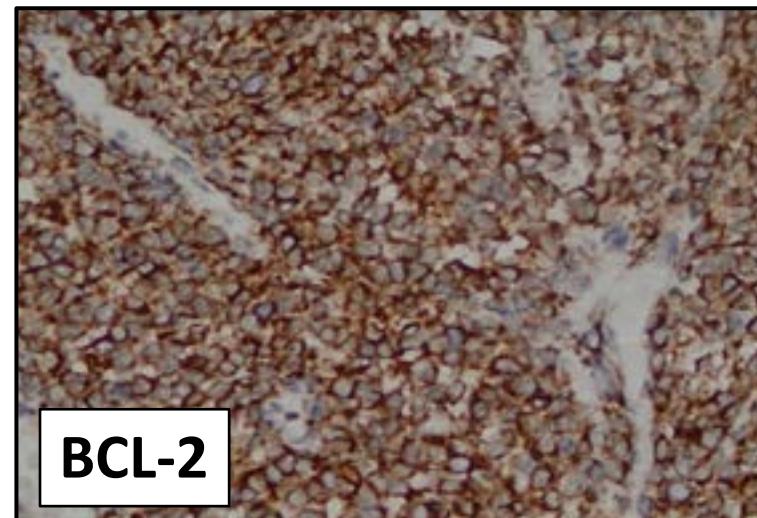
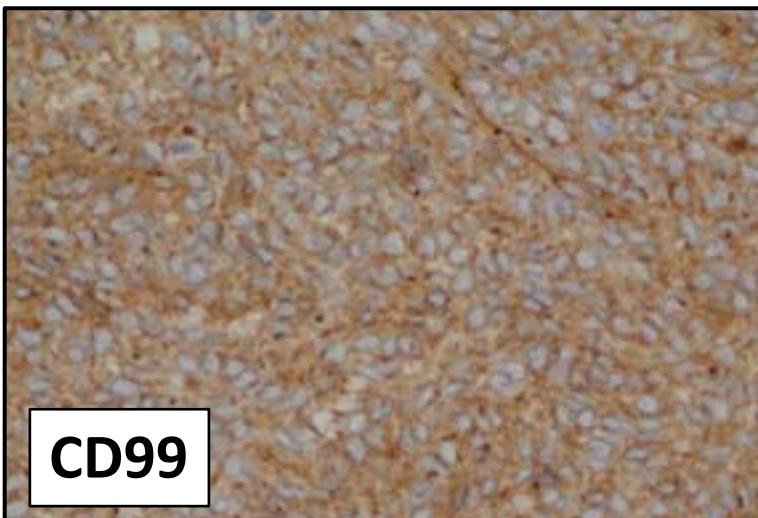
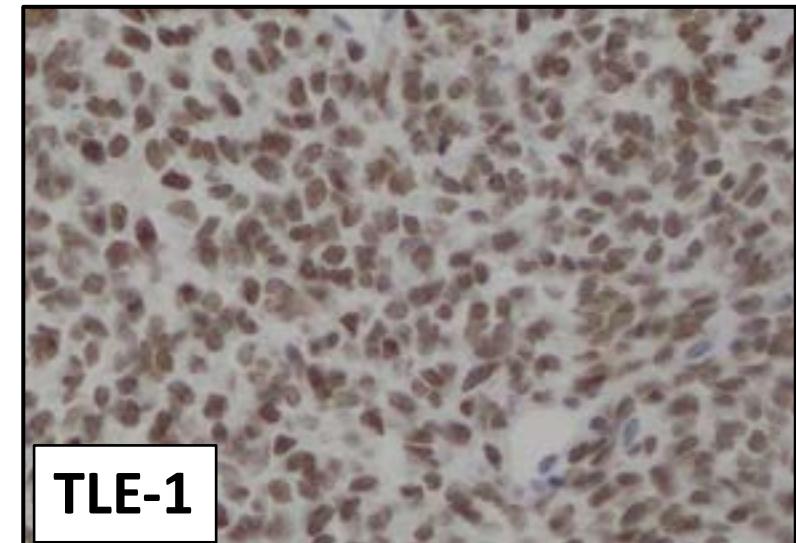
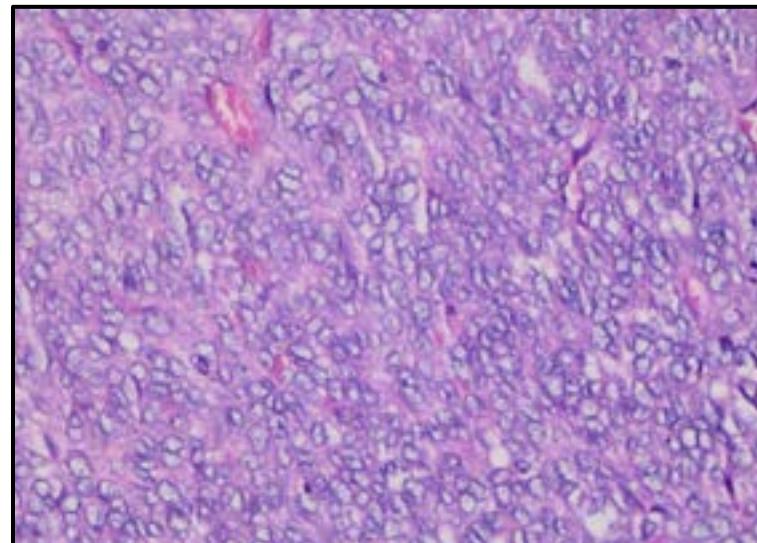
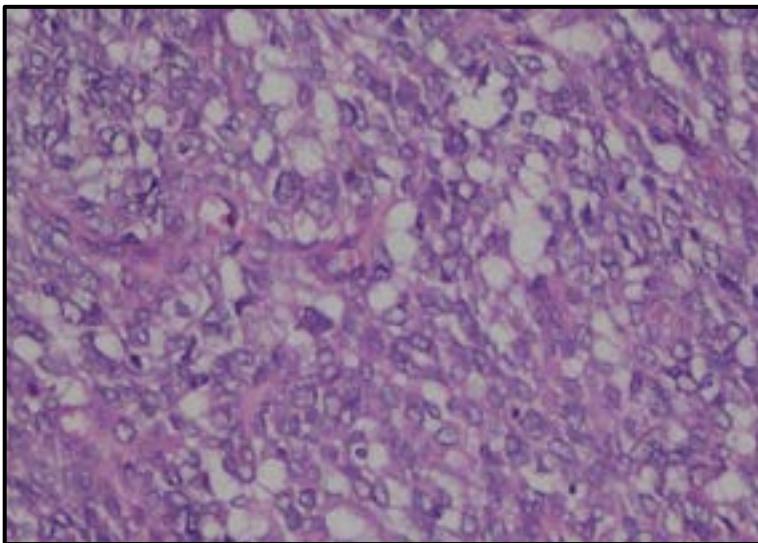


ESTUDIO INMUNOHISTOQUIMICO

- CD99 (82%)
- CCNB3 + (nuclear 94%)
- BCOR + (nuclear)
- SATB2 + (83%)
- Ciclina D1 (90%)
- TLE1 (80%)
- Bcl-2 (100%)



Masculino, 15 años, tumor partes blandas pared costal posterior.



CD99

BCL-2

FLI-1

MANEJO, EVOLUCIÓN Y PRONÓSTICO

SARCOMA DE EWING

SARCOMA CIC

SARCOMA BCOR

MANEJO	Bien establecido. (QT y CONTROL LOCAL)	Variables, en general esquema de SE. (30% con buena rpta a QT)	Variables, en general esquema SE (75% con rpta a QT)
MTT Diag. o seguimiento	20-30 % al diagnóstico.	70 %	30 %
Localización MTT	<ul style="list-style-type: none"> ❖ Pulmón (mas fte). ❖ Hueso ❖ Médula ósea ❖ Mixtas. 	<ul style="list-style-type: none"> ❖ Pulmón 63% ❖ Extrapulmonar 15% ❖ Mixtas 21% 	<ul style="list-style-type: none"> ❖ Extrapulmonar 50% ❖ Pulmón 37% ❖ Mixtas 13%
Sobrevida	76% (5 años)	40 %, Cerca del 60% fallece < 12 meses.	65% (20 casos no reportados) Otras series 72/75% Ninguno fallecido < 12 meses
Mal pronóstico	MTT, localización (pelvis) y tamaño (>8 cm)	Aún pocos casos MTT y localización	Aún pocos casos Esqueleto axial y tejidos blandos

(meta-análisis 85 casos)

(meta-análisis 68 casos)

RESUMEN

SARCOMA DE EWING

SARCOMA CIC

SARCOMA BCOR

EDAD	SEGUNDA DÉCADA.	TERCERA DÉCADA.	SEGUNDA DÉCADA.
SEXO	H:58% / M:42%	H:53% / M:47%	H:80-85% / M:15-20%
SITIO	<ul style="list-style-type: none"> ▪ HUESO 80%. ▪ TEJIDOS BLANDOS 15-20% ▪ OTROS 	<ul style="list-style-type: none"> ▪ TEJIDOS BLANDOS 90% ▪ HUESO 1% ▪ OTROS 9% 	<ul style="list-style-type: none"> ▪ HUESO 62% ▪ TEJIDOS BLANDOS 37% ▪ OTROS 1%
GENETICA	TRASLOCACIÓN CROMOSÓMICA <ul style="list-style-type: none"> ▪ EWSR1-FLI1 t(11;22) 85% ▪ EWSR1-ERG t(21;22) 10% ▪ EWSR1-ETV1 t(7;22) <1% ▪ EWSR1-ETV4 t(17;22) <1% ▪ EWSR1-FEV t(2;22) <1% ▪ FUS-FEV t(2;16) <1% ▪ FUS-ERG t(16;21) <1% ▪ OTROS (EWSR1-ETV5, TAF15) 	TRASLOCACIÓN CROMOSÓMICA <ul style="list-style-type: none"> ▪ CIC-DUX4 t(4;19) 53% ▪ CIC-DUX4 t(10;19) 13 % ▪ CIC-FOX01 2.3% ▪ CIC-partner desconocido 30% ▪ Rearreglo DUX4 2.3% 	INVERSIÓN PARACÉNTRICA CROMOSOMA X <ul style="list-style-type: none"> ▪ BCOR-CCNB3 88% ▪ BCOR-MAML3 1,5% ▪ BCOR-ZC3H7B 1,5% ▪ BCOR-partner desconocido 6%

RESUMEN ESTUDIO IHQ

	SARCOMA DE EWING	SARCOMA CIC	SARCOMA BCOR
CD99 (membrana)	++	+/-	+/-
NKX 2.2 (nuclear)	++	-	+/-
WT1 (nuclear)	-	++	-
TLE1 (nuclear)	-	-	++
ETV4 (nuclear)	-	++	-
BCOR (nuclear)	-	-	++
CCNB3 (nuclear)	-	-	++
PAX7 (nuclear)	++	-	+/-
FLI1 (nuclear)	++	+/-	+/-
CK/EMA	+/-	+/-	-
S100	-	-	-
DESMINA	-	+/-	-
OTROS	ERG, ENOLASA, CD57, SINAPTOFISINA		SATB2, CICLINA D1, BCL2

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SARCOMA DE EWING Y SARCOMAS EMERGENTES EWING -LIKE



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