



ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Tumorji mehkih tkiv s fuzijami NTRK

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November 2019



• Tumorji mehkih tkiv

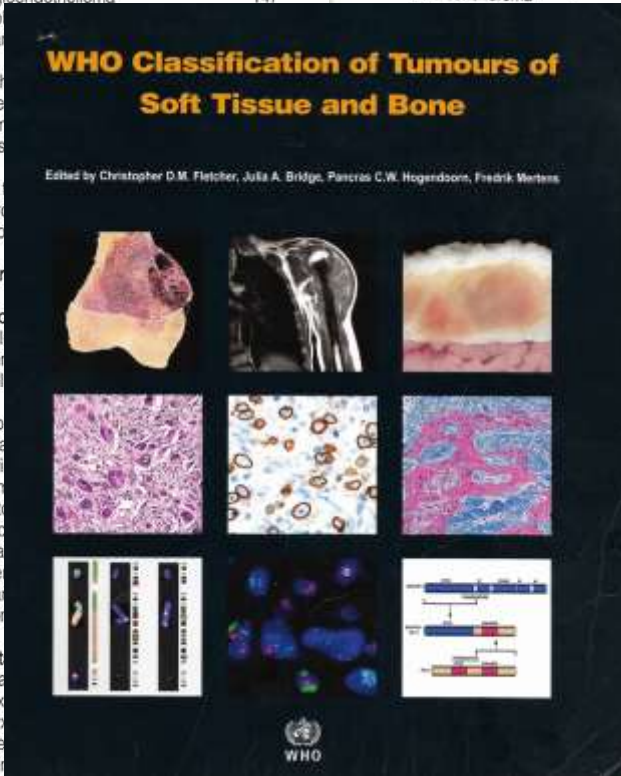
• **redki**

- maščobni,
- fibroblastni
- mišični
- žilni
- nejasne diferenciacije
- ...

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WHO (ang. World Health Organization) klasifikacija tumorjev mehkih tkiv in kosti - trenutno 4. izdaja, 2013.



Pogostnost NTRK fuzij v tumorjih mehkih tkiv

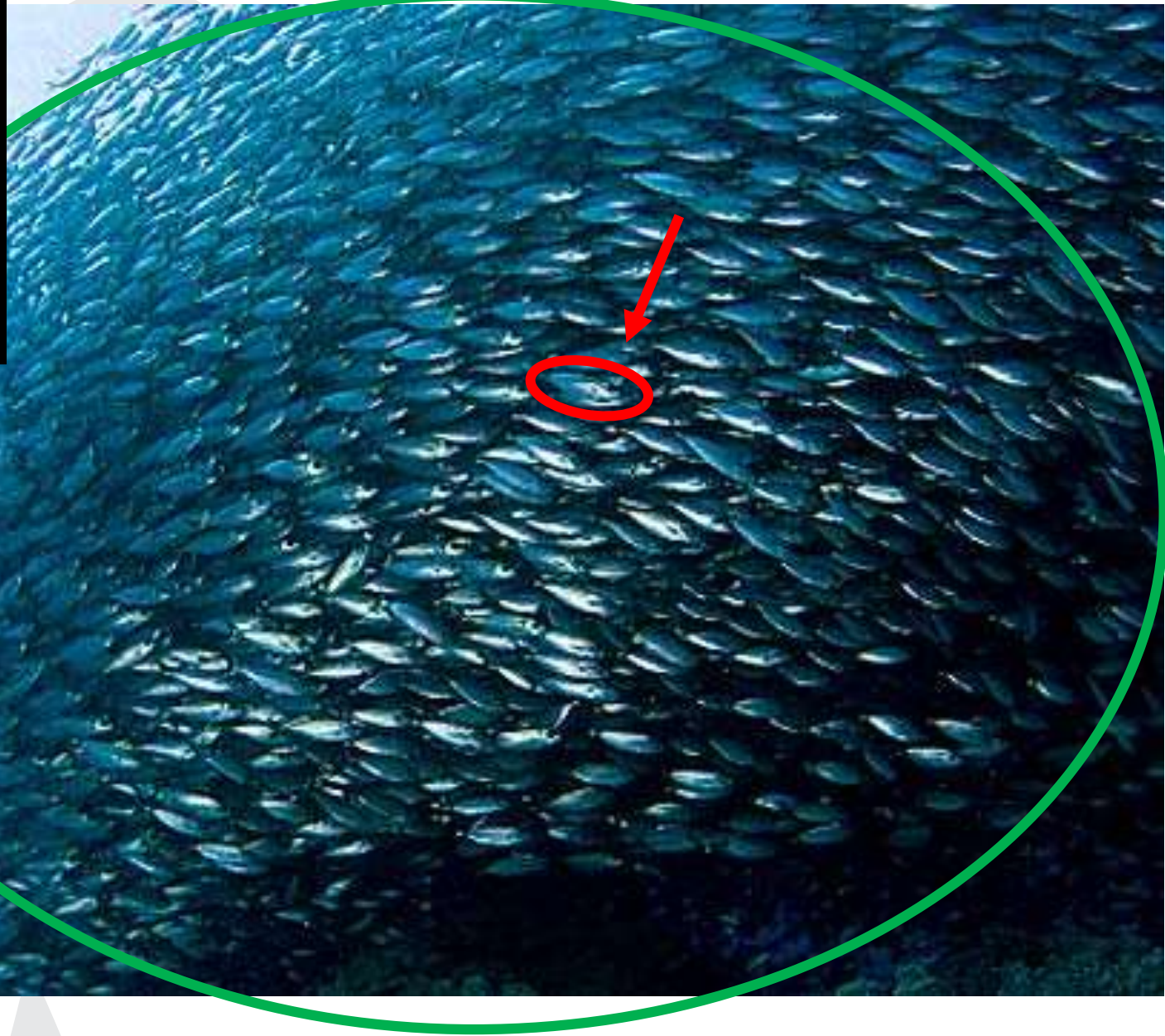
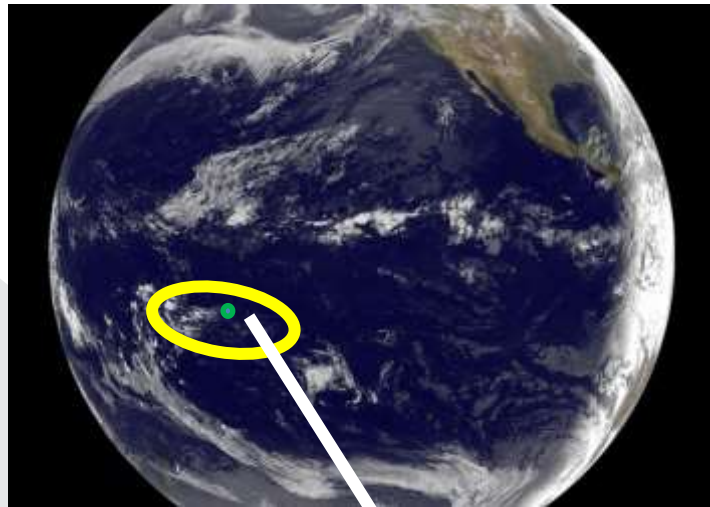
pogoste = diagnostična vrednost

> 80/90 %

redke

redke
(2 – 25 %)

zelo redke
< 2 %



Tumorji mehkih tkiv s fuzijami NTRK



Oj

Tumorji mehkih tkiv s ...

... **pogosto** prisotnimi NTRK fuzijami

> 80/90 %

infantilni fibrosarkom

ETV6-NTRK3, EML4-NTRK3,
RET fuzije, ...

Značilnosti :

- Kdaj?: prvo leto življenja
- Kje?: mehka tkiva okončin, trupa, supraklavikularno
- Intermediarni biološki potencial
- Celokupno preživetje ~ 90 %
- Možnost lokalnega recidiva ~ 50 %
- Možnost za pojav zasevkov ~ 10 %
- Terapija izbora: kirurgija (+ KT/RT)

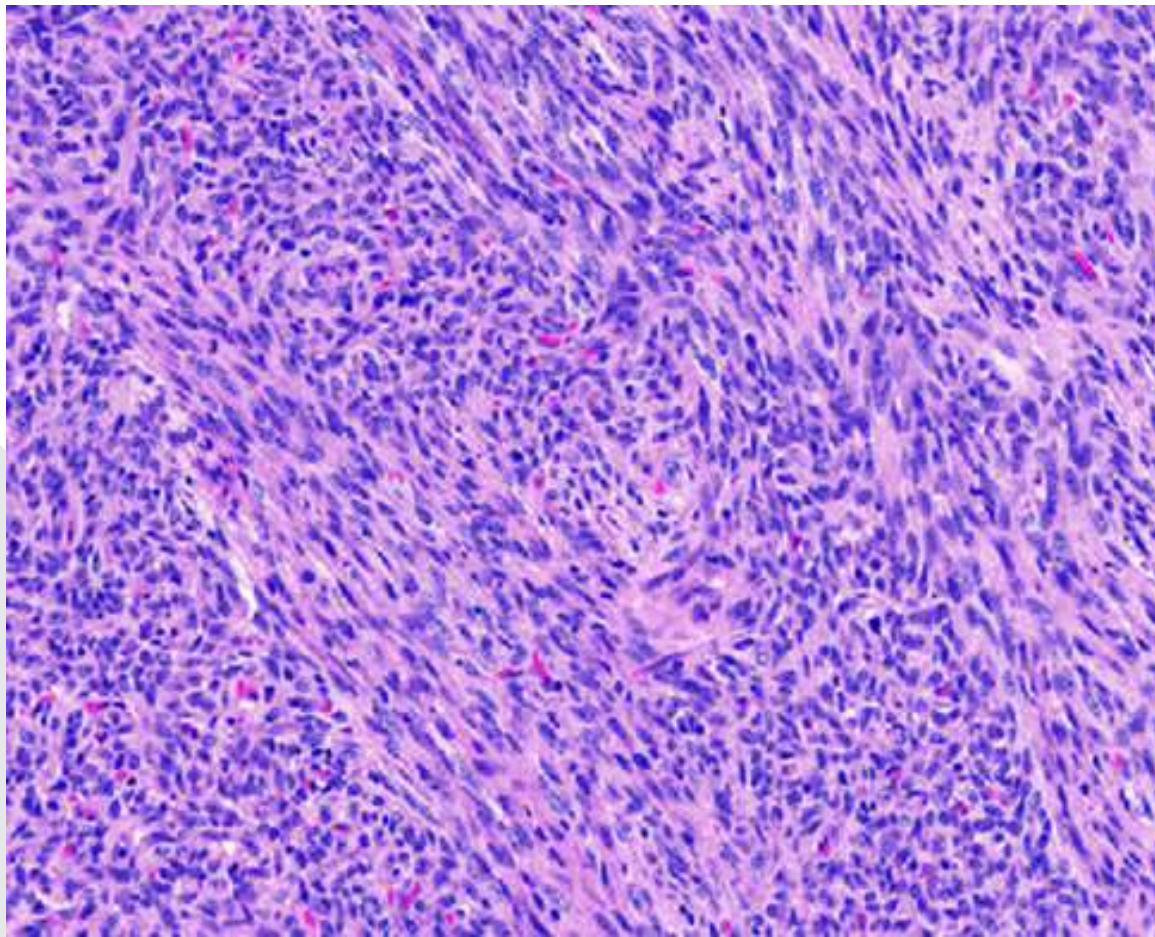
celularni kongenitalni mezoblastni nefrom

ETV6-NTRK3, EML4-NTRK3, ...

Značilnosti :

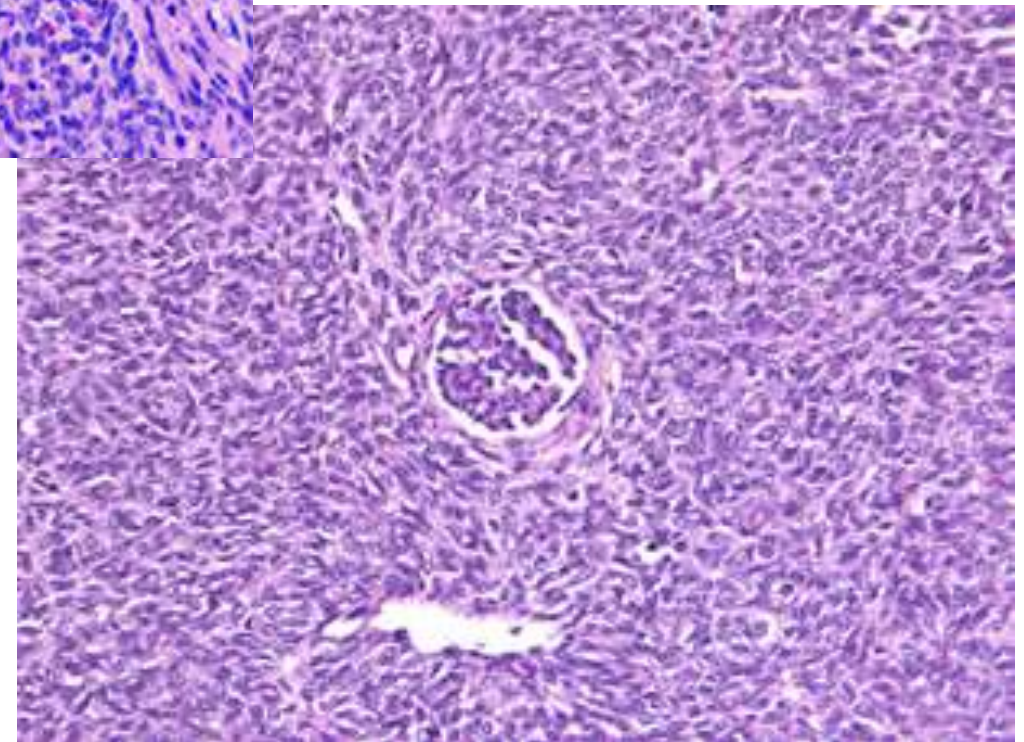
- Kdaj?: prvo leto življenja
- Kje?: ledvica
- Intermediarni biološki potencial
- Celokupno preživetje ~ 90 %
- Možnost lokalnega recidiva ~ 5-10 %
- Možnost za pojav zasevkov ~ 5-10 %
- Terapija izbora: kirurgija (+ KT)





Diferencialna diagnoza IF:

- fibrozni hamartoma otroštva
- primitivni miksoidni mezenhimalni tumor otroštva
- infantilna miofibromatoza
- lipofibromatoza
- lipofibroatozi podoben živčoidni tumor
- vretenastocelični rabdomisarkom
- fibrosakomatozna varianta DFSP
- fibromiksoidni sarkom nizkega gradusa
- maligni MPNST
- sinovijski sarkom
- ...



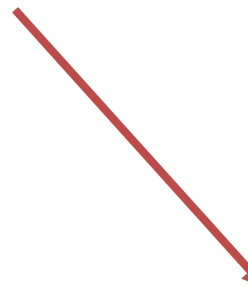
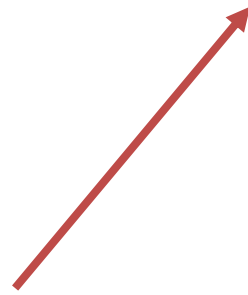
Molekularno genetske preiskave



morfologija



klinični podatki



IHK



FISH



molekularno
genetske preiskave



Izivi

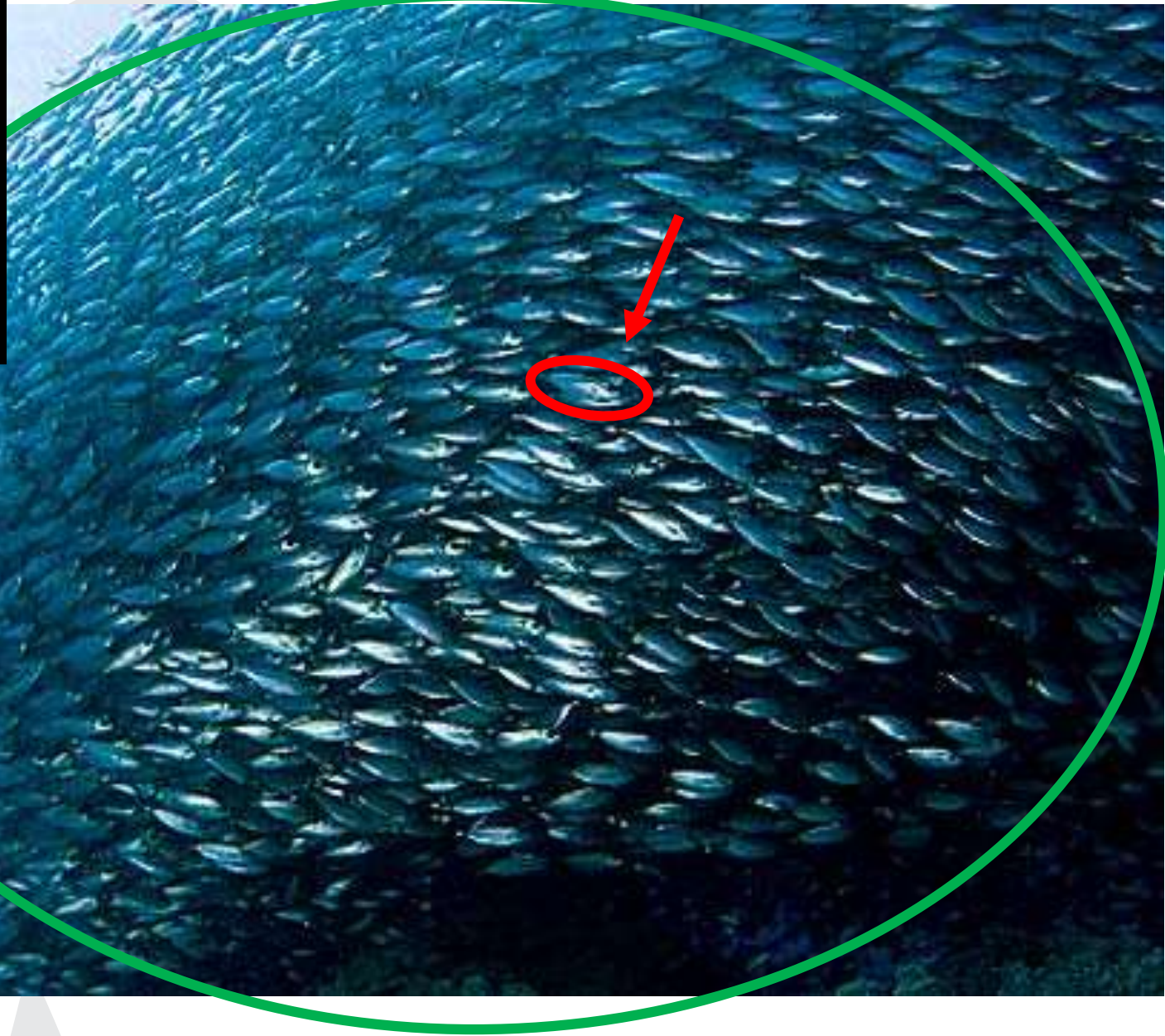
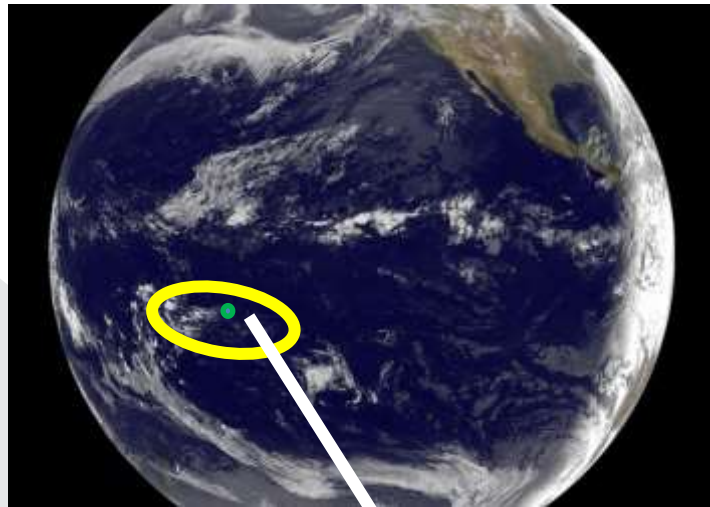
- pediatrični tumorji
- histološko podobni
- nespecifičen imunohistokemični profil

neopredeljeni mezenhimalni tumorji

molekularno genetske preiskave

lipofibromatozi
podoben nevroidni
tumor NTRK1





Tumorji mehkih tkiv z ...

... **redko** prisotnimi NTRK fuzijami

2 – 10 %

- **inflamatorni miofibroblastni tumor**
- ...

< 2 %

- **GIST**
- **uterini sarkom** s histološkimi karakteristikami fibrosarcoma
- ...



J.Cutan.Pathol. 2018 Dec;45(12):933-939. doi: 10.1111/cup.13348. Epub 2018 Sep 26.

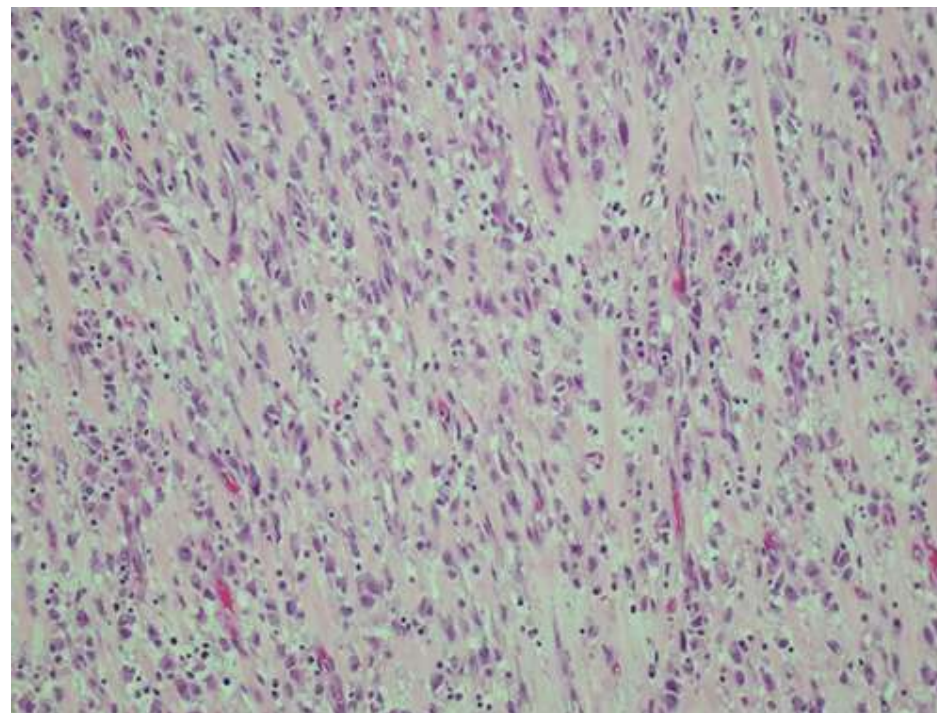
A novel case of an aggressive superficial spindle cell sarcoma in an adult resembling fibrosarcomatous dermatofibrosarcoma protuberans and harboring an EML4-NTRK3 fusion.

Olson.N¹, Rouhi.Q², Zhang.L², Angeles.C³, Bridge.J⁴, Lopez-Terrada.D⁵, Royce.T⁶, Linos.K¹.

inflamatorni miofibroblastni tumor

Značilnosti :

- Otroci, mladi odrasli
- Mezenterij, omentum, retroperitonej, medenica, pljuča, mediastinum, ...
- Intermediarni biološki potencial
- Celokupno preživetje ~ 90 %
- Možnost lokalnega recidiva ~ 50 %
- Možnost za pojav zasevkov < 5 %
- Terapija izbora: kirurgija



ALK fuzije 50-60 %, ROS1 10 %, redko RET, **ETV6-NTRK3**

Hisopathology, 2016 Jul;69(1):72-83. doi: 10.1111/his.12910. Epub 2016 Jan 19.

ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours.

Yamamoto.H¹, Yoshida.A², Taguchi.K³, Kohashi.K¹, Hatanaka.Y¹, Yamashita.A⁴, Mori.D⁵, Oda.Y¹.



GIST = gastrointestinalni stromalni tumor

Mutacije v poteh:

- 70-80 % KIT
- 5-10 % PDGFRA
- 1-3 % RAS (BRAF, KRAS, NF1)
- 3 % SDH
- 5-15 % “divji tip”/neznano = “četrveno negativni”

- 
- **FGFR1**
 - **NTRK3**
 - ...

Značilnosti :

- Eden bolj pogostih mehko tkivnih tumorjev
- Odrasli, otroci



Shi et al. *J Transl Med* (2018) 10:339
DOI 10.1186/s12967-018-1075-6

Journal of
Translational Medicine

RESEARCH

Open Access



FGFR1 and NTRK3 actionable alterations in “Wild-Type” gastrointestinal stromal tumors

Eileen Shi¹, Juliann Chmielecki², Chih-Min Tang^{1,3}, Kai Wang², Michael C. Heinrich^{4,5}, Guhyun Kang^{1,6}, Christopher L. Corless⁵, David Hong⁷, Katherine E. Fero^{1,8}, James D. Murphy^{1,9}, Paul T. Fanta^{1,9}, Skaj M. Ali², Martina De Siena^{1,8}, Adani M. Burgoyne^{1,10}, Sujana Movva^{1,10}, Lisa Madlensky^{1,11}, Gregory M. Heestand^{1,12}, Jonathan C. Trent^{1,13}, Razeelle Kurtzrock^{1,14}, Deborah Morosini², Jeffrey S. Ross², Olivier Harismendy^{1,15} and Jason K. Sicklick^{1,16}

uterini sarkom s histološkimi karakteristikami fibrosarcoma (4 primeri)

Značilnosti :

- Fuzije NTRK1 in NTRK3 z različnimi partnerji
- Mlajše ženske
- Agresiven potek



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Am J Surg Pathol. 2018 Jun;42(6):791-798. doi: 10.1097/PAS.0000000000001055.

NTRK Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma.

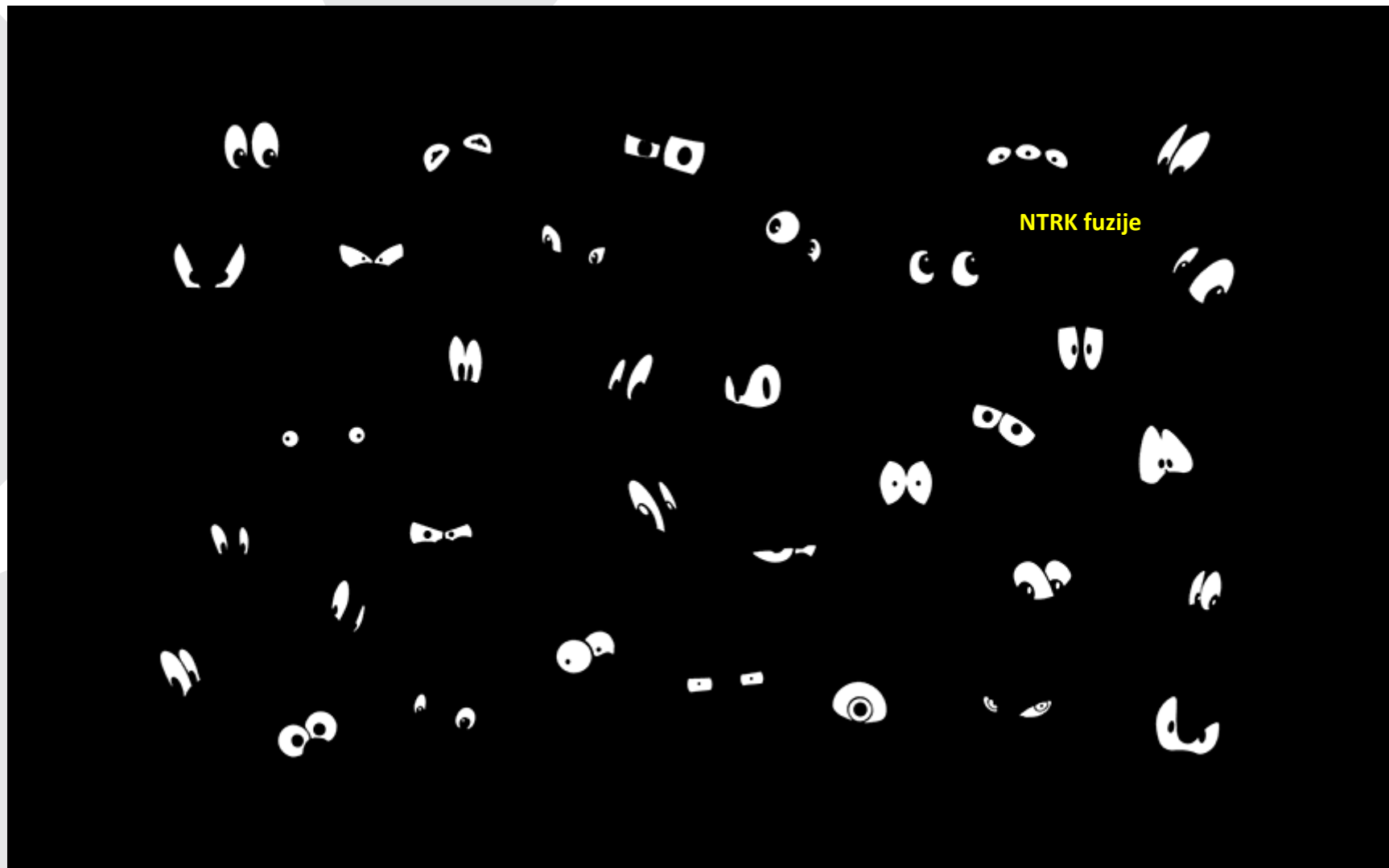
Chiang S¹, Cotzias P¹, Hyman DM², Drilon A³, Tap WD⁴, Zhang L¹, Hechtman JE¹, Frosina D¹, Jungbluth AA¹, Murali R¹, Park KJ¹, Soslow RA¹, Oliva E^{5,6}, Iafrate AJ^{5,6}, Benayed R¹, Ladanyi M¹, Antonescu CR¹.



RESEARCH ARTICLE

The histologic spectrum of soft tissue spindle cell tumors with *NTRK3* gene rearrangements

Albert J. Suurmeijer, Brendan C. Dickson, David Swanson, Lei Zhang, Yun-Shao Sung, Hsuan-Ying Huang, Christopher D. Fletcher, Cristina R. Antonescu✉



Reference

- [Vokuhl C](#), [Nourkami-Tutdibi N](#), [Furtwängler R](#), [Gessler M](#), [Graf N](#), [Leuschner I](#). **ETV6-NTRK3 in congenital mesoblastic nephroma: A report of the SIOP/GPOH nephroblastoma study.** [Pediatr Blood Cancer](#). 2018 Apr;65(4).
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- [Antonescu CR](#), [Dickson BC](#), [Swanson D](#), [Zhang L](#), [Sung YS](#), [Kao YC](#), [Chang WC](#), [Ran L](#), [Pappo A](#), [Bahrami A](#), [Chi P](#), [Fletcher CD](#). **Spindle Cell Tumors With RET Gene Fusions Exhibit a Morphologic Spectrum Akin to Tumors With NTRK Gene Fusions.** [Am J Surg Pathol](#). 2019 Oct;43(10):1384-1391.
- [Suurmeijer AJH](#)¹, [Kao YC](#)², [Antonescu CR](#)³. **New advances in the molecular classification of pediatric mesenchymal tumors.** [Genes Chromosomes Cancer](#). 2019 Feb;58(2):100-110.
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- Shi E, Chmielecki J, Tang CM, Wang K, Heinrich MC, Kang G, et al. **FGFR1 and NTRK3 actionable alterations in "Wild-Type" gastrointestinal stromal tumors.** [J Transl Med](#). 2016 Dec 14;14(1):339.
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- [Genes Chromosomes Cancer](#). 2019 Nov;58(11):739-746. **The histologic spectrum of soft tissue spindle cell tumors with NTRK3 gene rearrangements.** [Suurmeijer AJ](#), [Dickson BC](#), [Swanson D](#), [Zhang L](#), [Sung YS](#), [Huang HY](#), [Fletcher CD](#), [Antonescu CR](#).

