ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Tumorji mehkih tkiv s fuzijami NTRK

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November 2019

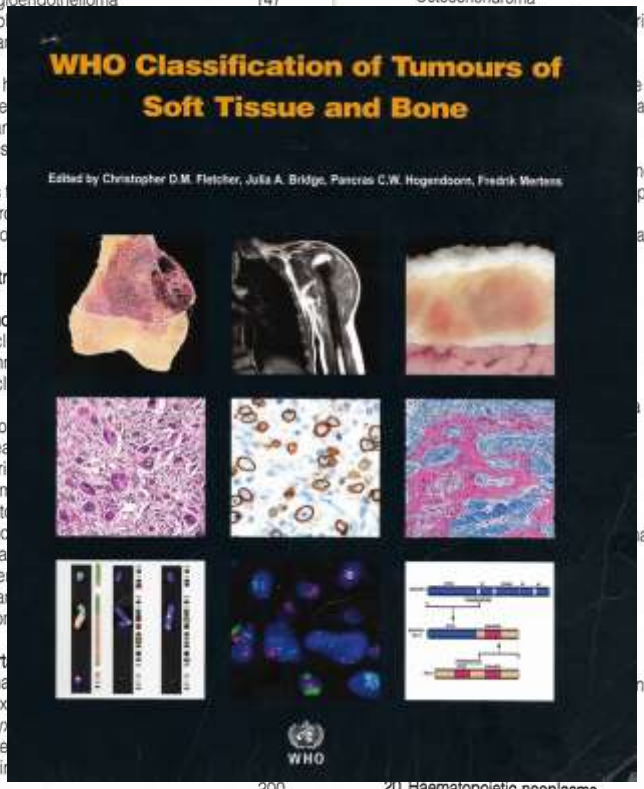
- Tumorji mehkih tkiv

- **redki**

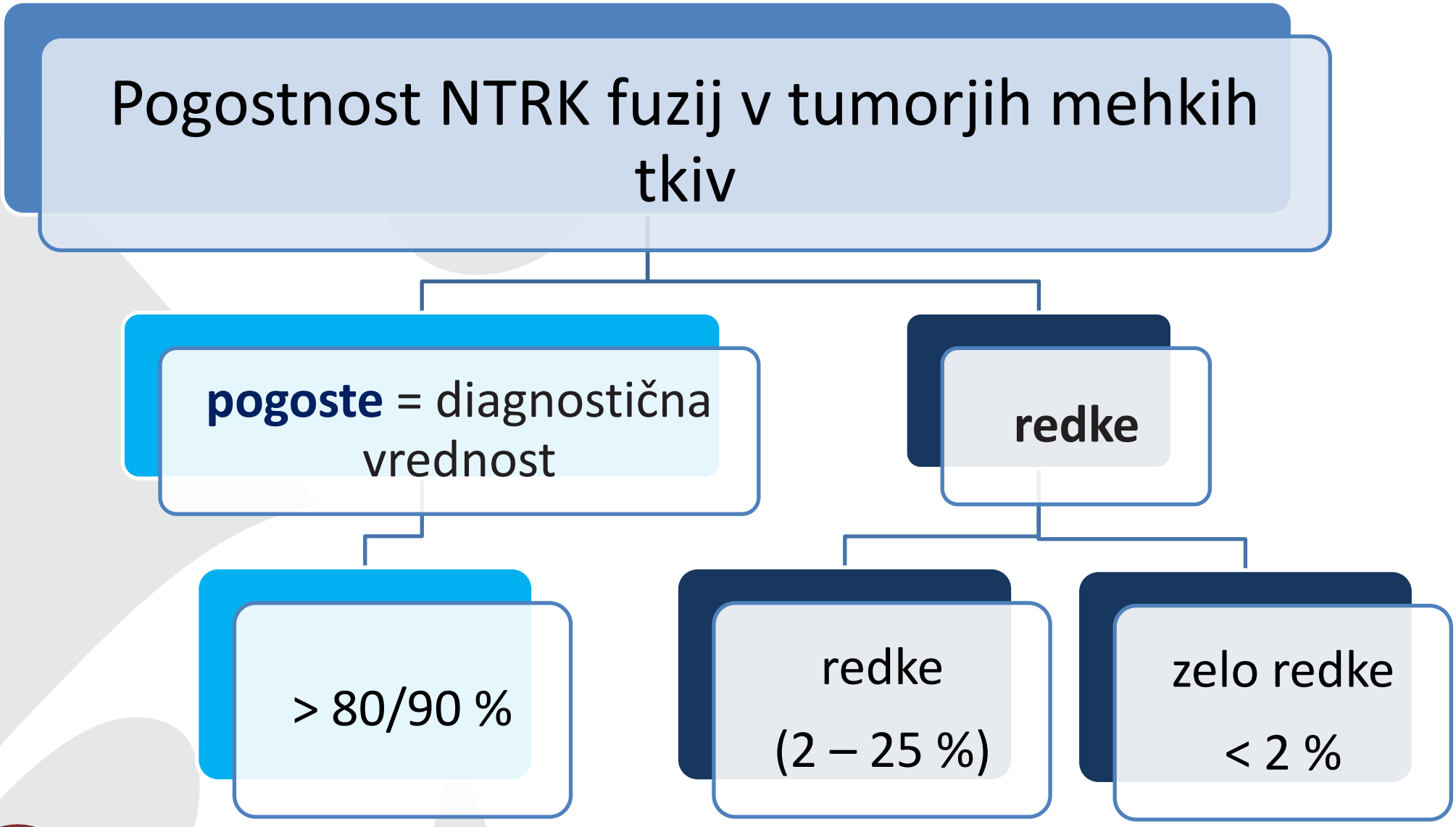
- maščobni,
- fibroblastni
- mišični
- žilni
- nejasne diferenciacije
- …

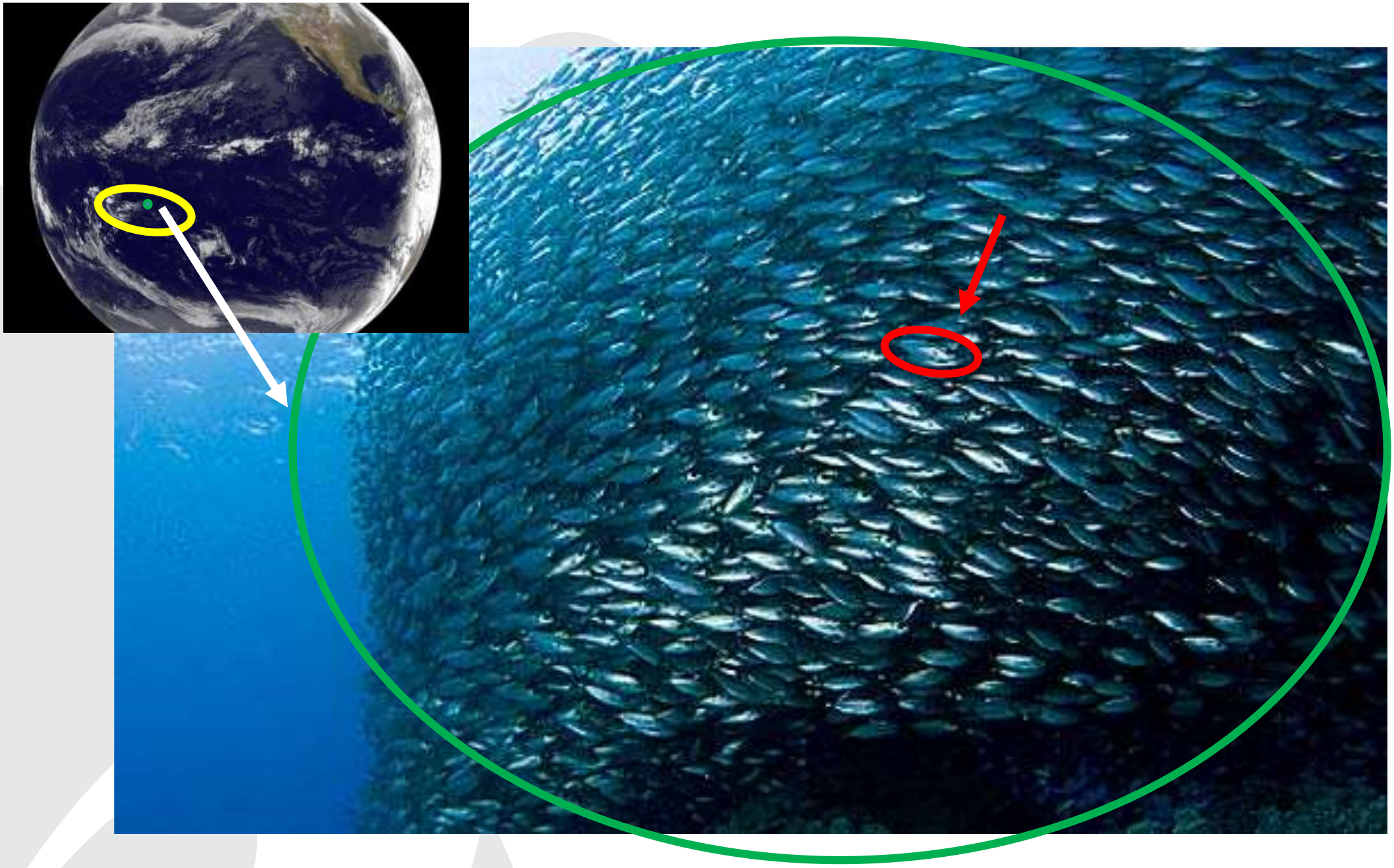
Contents

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



Pogostnost NTRK fuzij v tumorjih mehkih tkiv





Tumorji mehkih tkiv s fuzijami NTRK

?

Tumorji mehkih tkiv s ...

... **pogosto** prisotnimi NTRK fuzijami

> *80*/90 %

infantilni fibrosarkom

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

Značilnosti :

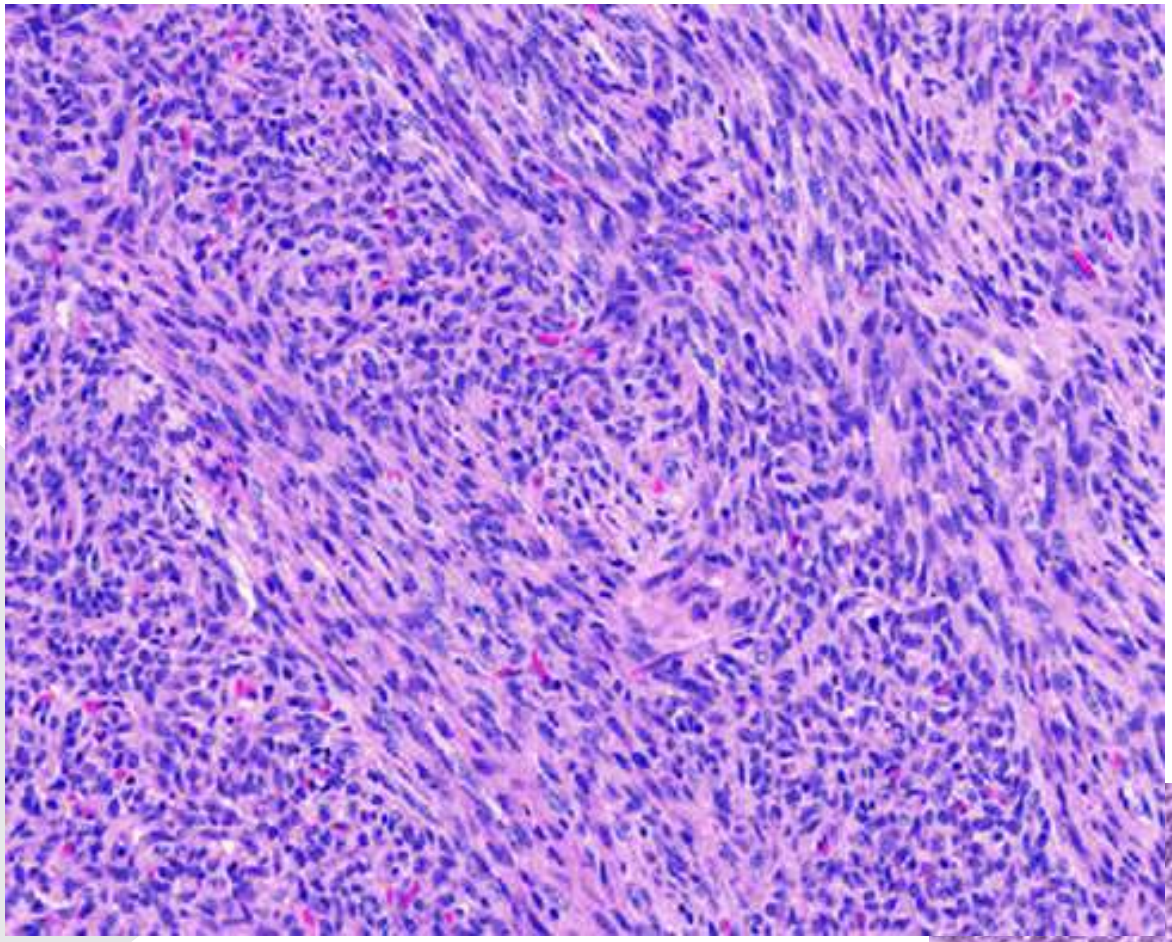
- **Kdaj?: prvo leto življenja**
- **Kje?: mehka tkiva okončin, trupa, supraklavikularno**
- **Intermediarni biološki potencial**
- **Celokupno preživetje ~ 90 %**
- **Možnost lokalnega recidiva ~ 50 %**
- **Možnost za pojav zasevkov ~ 10 %**
- **Terapija izbora: kirurgija (+ KT/RT)**

celularni kongenitalni mezoblastni nefrom

ETV6-**NTRK3**, EML4-**NTRK3**, ...

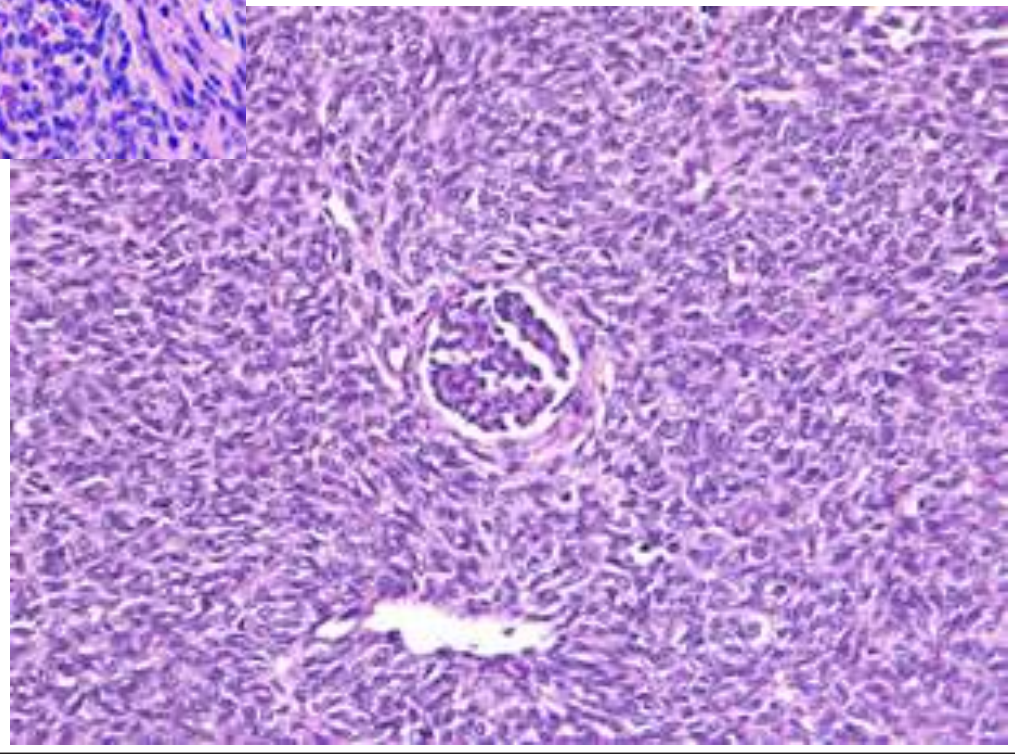
Značilnosti :

- **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

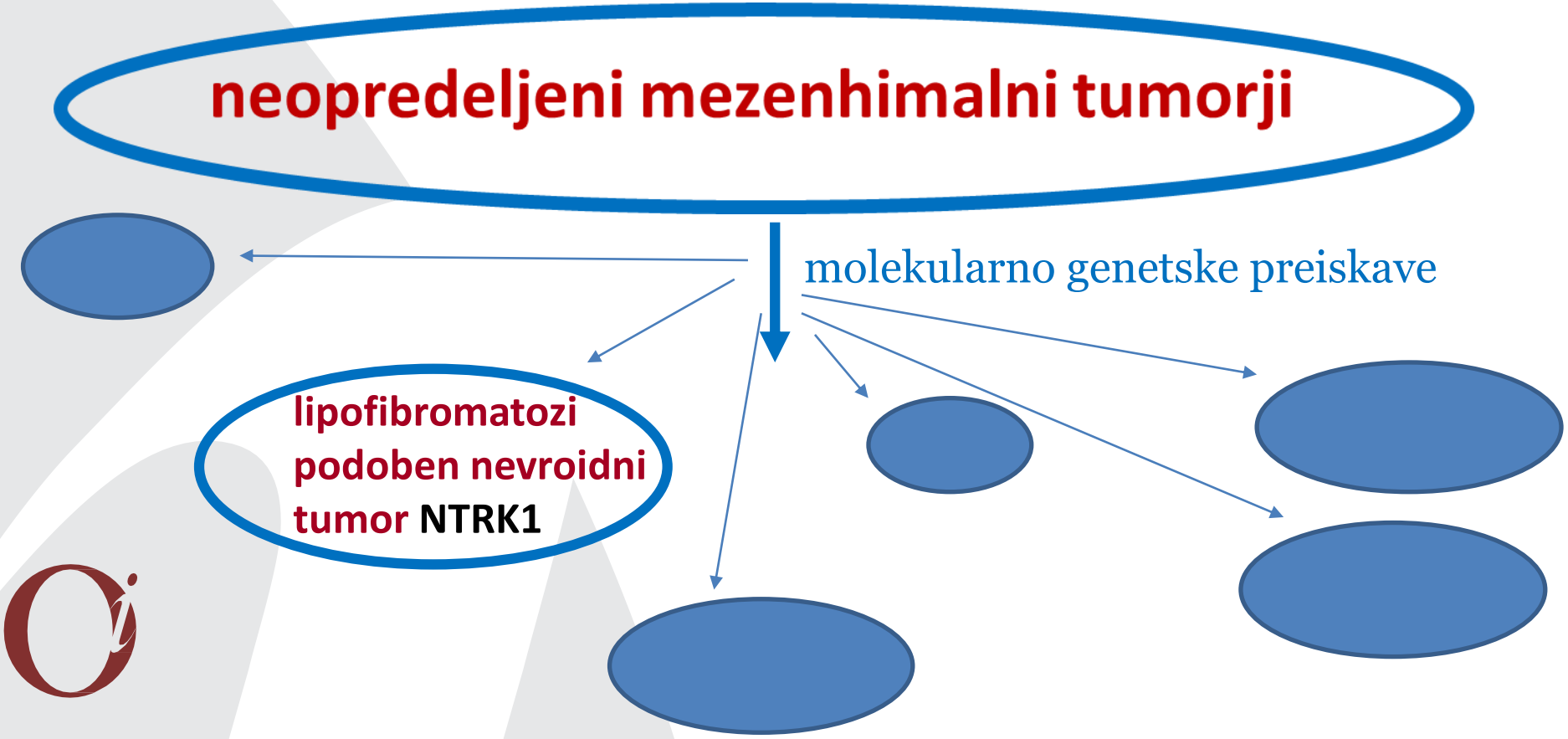
Genes Chromosomes Cancer. 2019 Feb;58(2):100-110. doi: 10.1002/gcc.22681. Epub 2018 Oct 11.

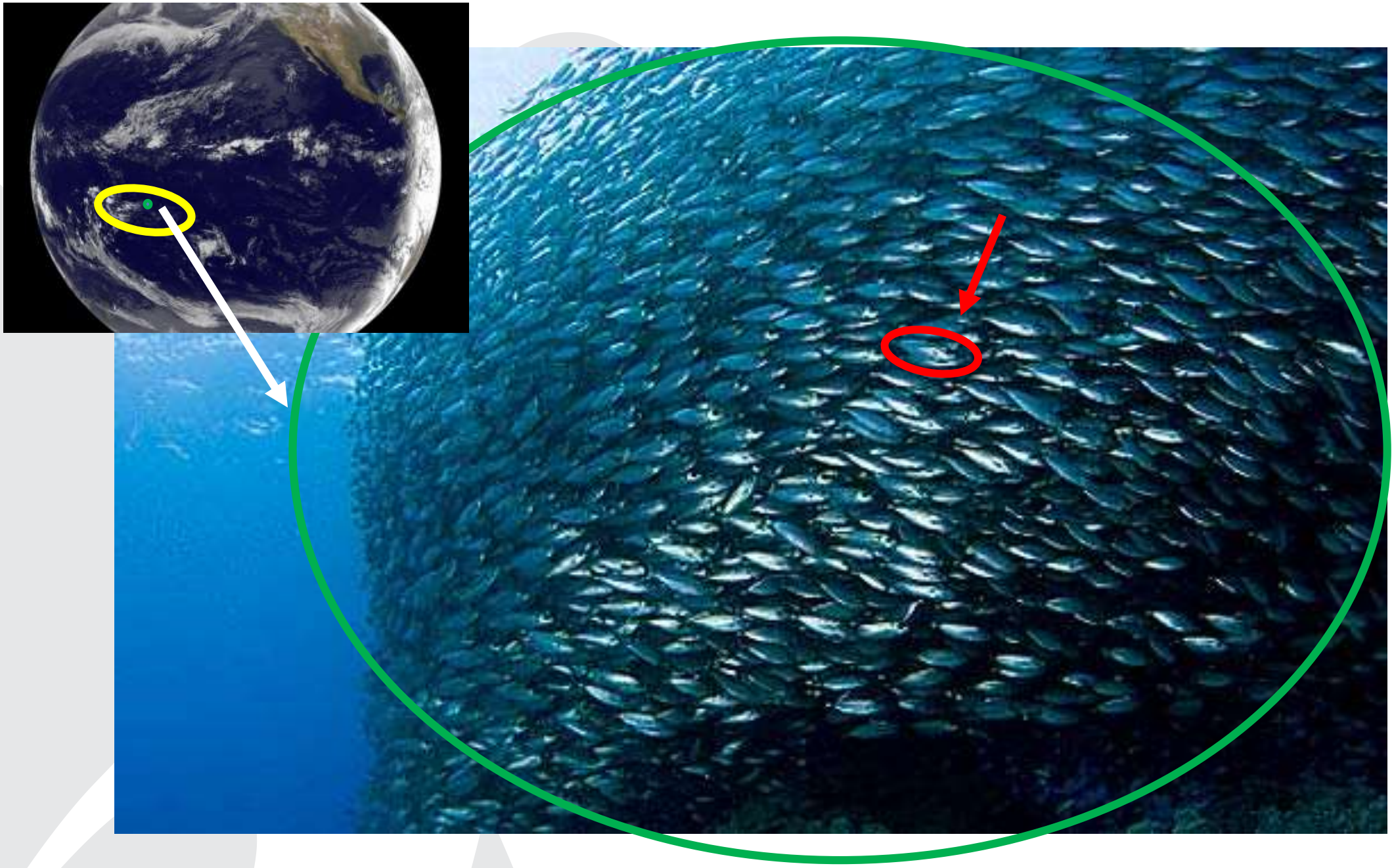
New advances in the molecular classification of pediatric mesenchymal tumors.

Suurmeijer AJH[1], Kao YC[2], Antonescu CR[3].

Izivi

- pediatrični tumorji
- histološko podobni
- nespecifičen imunohistokemični profil





Tumorji mehkih tkiv z …

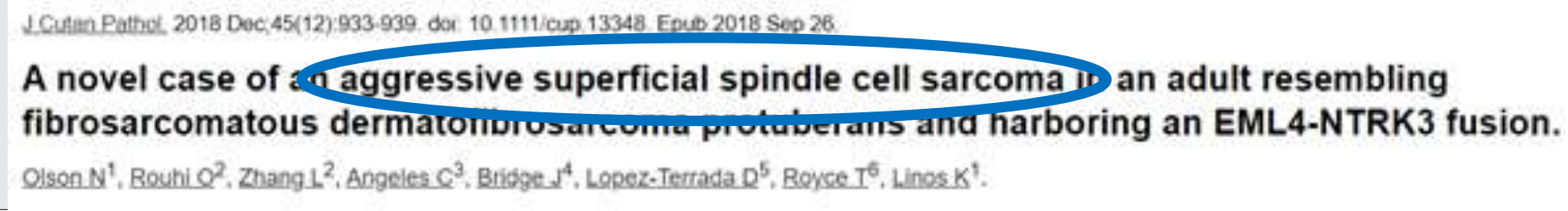
… **redko** prisotnimi NTRK fuzijami

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

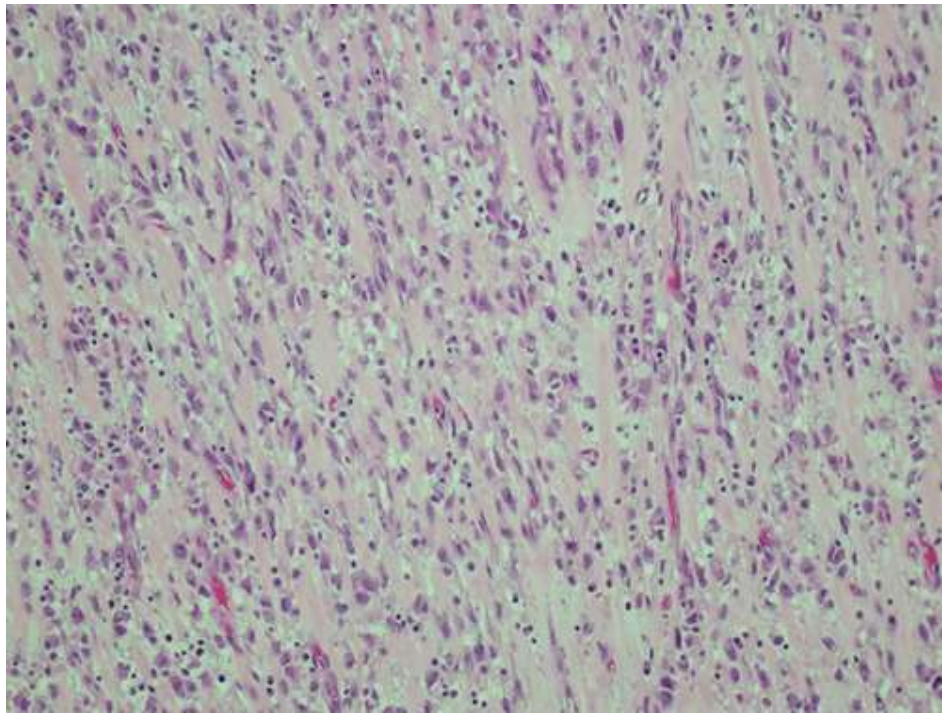
A novel case of an aggressive superficial spindle cell sarcoma in an adult resembling fibrosarcomatous dermatofibrosarcoma protuberans and harboring an EML4-NTRK3 fusion.

Olson N[1], Rouhi O[2], Zhang L[2], Angeles C[3], Bridge J[4], Lopez-Terrada D[5], Royce T[6], Linos K[1].

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**

Histopathology. 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 H[1], Yoshida A[2], Taguchi K[3], Kohashi K[1], Hatanaka Y[1], Yamashita A[4], Mori D[5], Oda Y[1].

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 = “četverno negativni”
  - **FGFR1**
  - **NTRK3**
  - **…**

Značilnosti :

- Eden bolj pogostih mehkotkivnih tumorjev
- Odrasli, otroci

Journal of Translational Medicine

RESEARCH Open Access

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

Eileen Shi, Juliann Chmielecki, Chih-Min Tang, Kai Wang, Michael C. Heinrich, Guhyun Kang, Christopher L. Corless, David Hong, Katherine E. Fero, James D. Murphy, Paul T. Fanta, Siraj M. Ali, Martina De Siena, Adam M. Burgoyne, Sujana Movva, Lisa Madlensky, Gregory M. Heerstand, Jonathan C. Trent, Razelle Kurzrock, Deborah Morosini, Jeffrey S. Ross, Olivier Harismendy and Jason K. Sicklick

uterini sarkom s histološkimi karakteristikami fibrosarcoma (4 primeri)

Značilnosti :

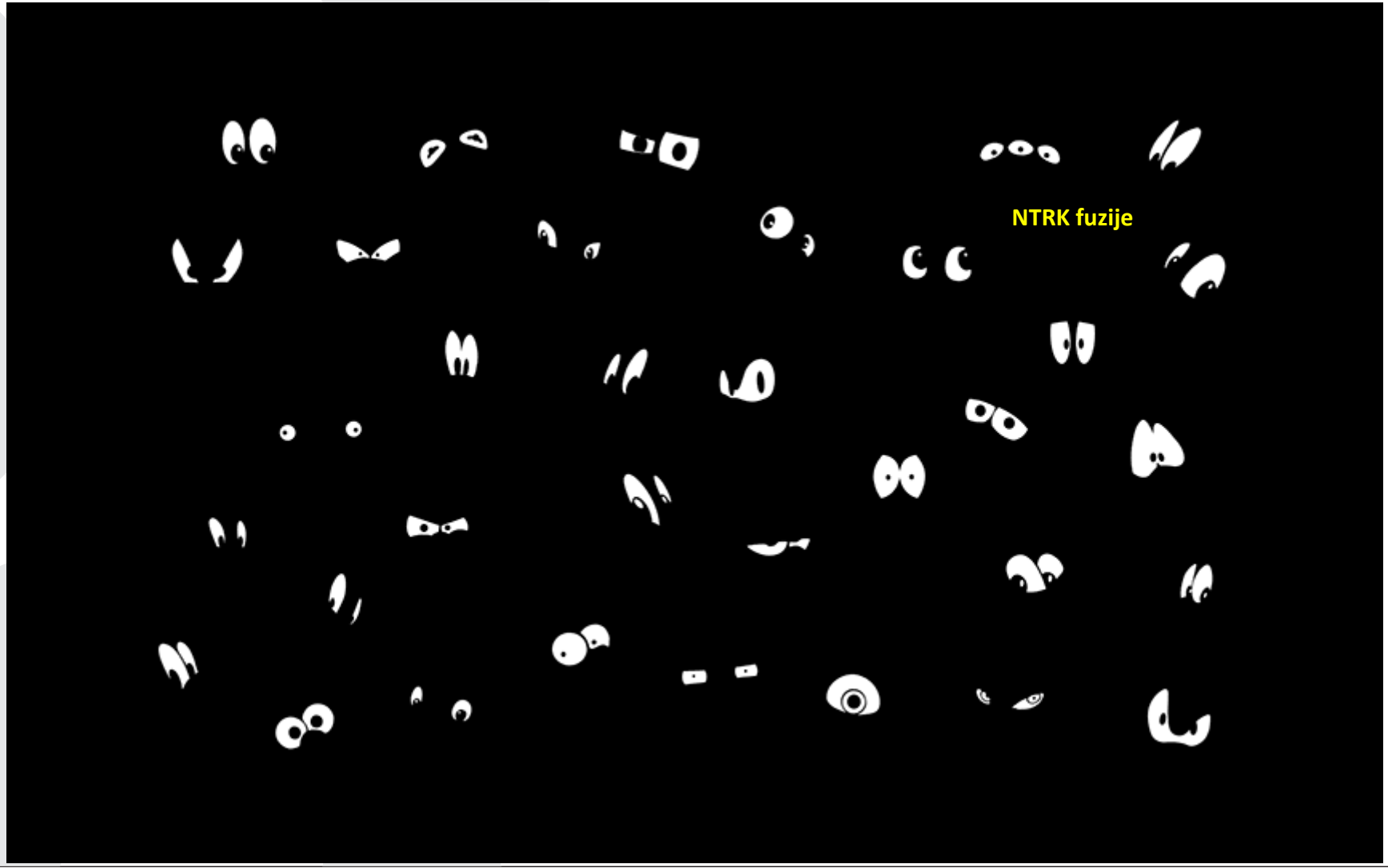
- Fuzije NTRK1 in NTRK3 z različnimi partnerji
- Mlajše ženske
- Agresiven potek

Genes, Chromosomes and Cancer / Volume 58, Issue 11

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).

- Hung YP, Fletcher CDM, Hornick JL. **Evaluation of pan-TRK immunohistochemistry in infantile fibrosarcoma, lipofibromatosis-like neural tumour and histological mimics.** Histopathology. 2018 Oct;73(4):634-644.

- 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.

- Miettinen M, Felisiak-Golabek A, Luiña Contreras A, Glod J, Kaplan RN, Killian JK, Lasota J. **New fusion sarcomas: histopathology and clinical significance of selected entities.** Hum Pathol. 2019 Apr;86:57-65.

- 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.

- Märkl B, Hirschbühl K, Dhillon C. **NTRK-Fusions - A new kid on the block.** Pathol Res Pract. 2019 Oct;215(10):152572.

- 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.