Cancer Research Center

مرکز تحقیقات سرطان

دانشگاه علوم پزشکی شهید بهشتی

# Sarcoma in Iran

## 5th International Cancer Congress

Leila Asef MD

Surgical oncologist fellowship

- **The nationwide distributions of soft tissue and bone sarcoma in Iran from 2009-2014: Data on incidence rates, histological subtypes, tumor primary sites and grades**

- Data → Iranian National Cancer Registry (INCR)
- 14630 pts → soft tissue and bone sarcomas ( 14630 cases out of initially 19868 )
- Morphological and topographical classifications were based on the ICD-O-3 and WHO guidelines
- classifications purposed by the International Agency for Research on Cancer (IARC)

- Combined crude incidence was calculated 3.2/100,000
- for STS →2.7/100,000
- for BS → 0.5/100,000
- increasing with the age
- 16.47% of cases had BS
- 83.53% of cases had STS
- with male predilection
- ASIR calculated 2.8 and 2.6 for STS in males and females

  ASIR calculated 0.51 and 0.37 for BS in males and females

- **Sarcoma, osteosarcoma, leiomyosarcoma, liposarcoma and spindle cell sarcoma were the most common morphologies.**

- **Connective tissue of lower limb, long bone of lower limb, skin and uterus were the most frequent primary tumor sites.**

- **The majority of tumors were of unknown/undifferentiated grade (grade 9), then grade 3, 1, 2, 4 and score 0 had the highest frequencies, respectively.**

- highest ASIR of sarcoma was detected in Khuzestan, Kohgiloyeh and Boyer-Ahmad, Isfahan, Tehran, Fars, Khorasan Razavi provinces. Analysis of the incidence trends showed a slight increase over the study period.

- tumors account for less than 1% of all adult cancers and constitute approximately 21% of all diagnosed pediatric solid tumors.

- Sarcomas can affect any age group with a higher incidence in young and adolescent population and their occurrence is not limited to a specific anatomic site.

- It is obvious that there is a difference in incidence of sarcomas among these countries. The reasons for this are quite complex and may depend on different environmental, lifestyle, socio-economic, genetic and cultural factors.

- **(ASIR) for both STS and BS (with 95% CI) were calculated by adjusting for the age distribution of the total Iranian and World Segi's population.**

- **incidence rates were presented by age at diagnosis.**

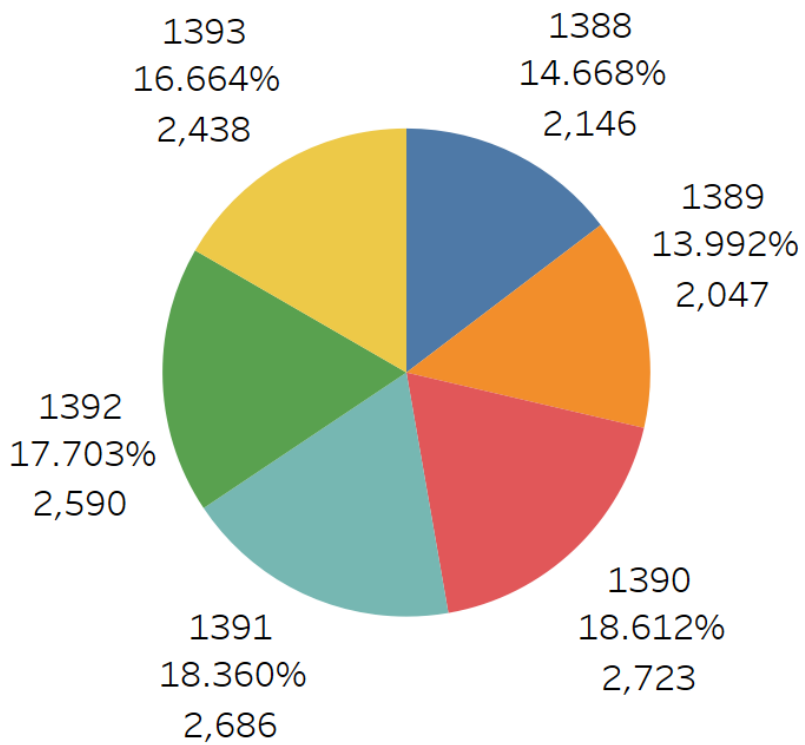
- **grouped into 3 age cohorts from 0 to 14, 15-64 and 65+ years. For the further analyzes the patients were grouped in 5 years age cohorts from 0 to 4, 4-9, 10-14 up to 80 years**

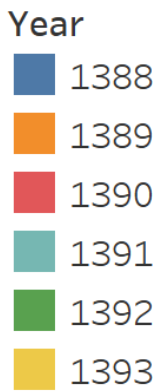
- 118 different morphologies
- 117 different tumor locations
- for 6 different tumor grades, including score 0, grade 1, 2, 3, 4, and 9
- with the regards of patients' sex and abovementioned age cohorts, and finally the respective incidence rates were obtained according to these variables.

# ASIR :

- 88 → 3.59 M: 3.62 F: 3.54
- 89 → 3.37 M: 3.47 F: 3.25
- 90 → 4.04 M: 4.27 F: 3.83
- 91 → 3.96 M: 4.18 F: 3.74
- 92 → 3.79 M: 3.92 F: 3.66
- 93 → 3.56 M : 3.67 F: 3.44

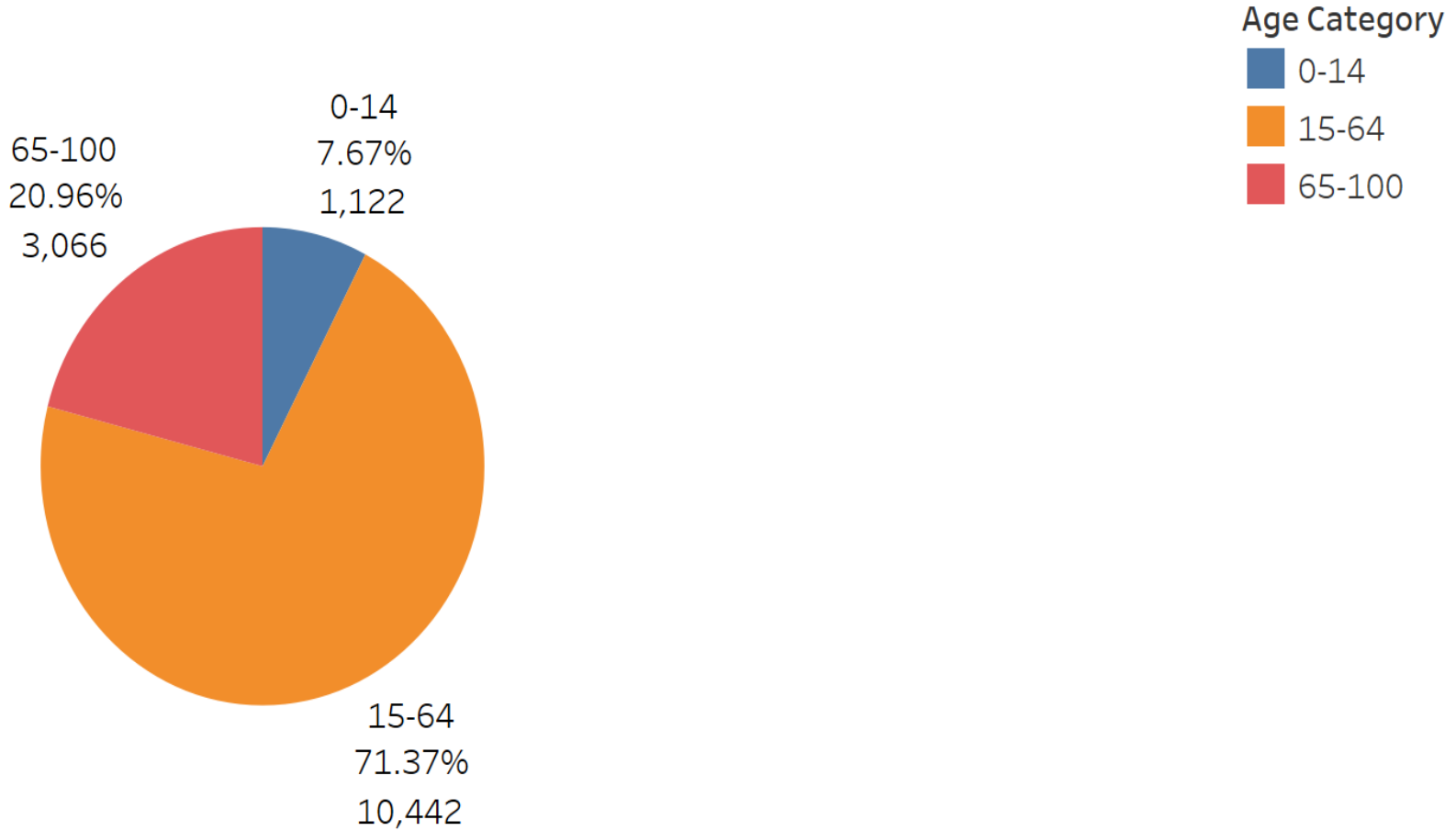
# Year


1393
16.664%
2,438
1388
14.668%
2,146
1389
13.992%
2,047
1392
17.703%
2,590
1390
18.612%
2,723
1391
18.360%
2,686


Year
1388
1389
1390
1391
1392
1393

- **Total ASIR: 3.485**
- **Total SSIR: 3.228**

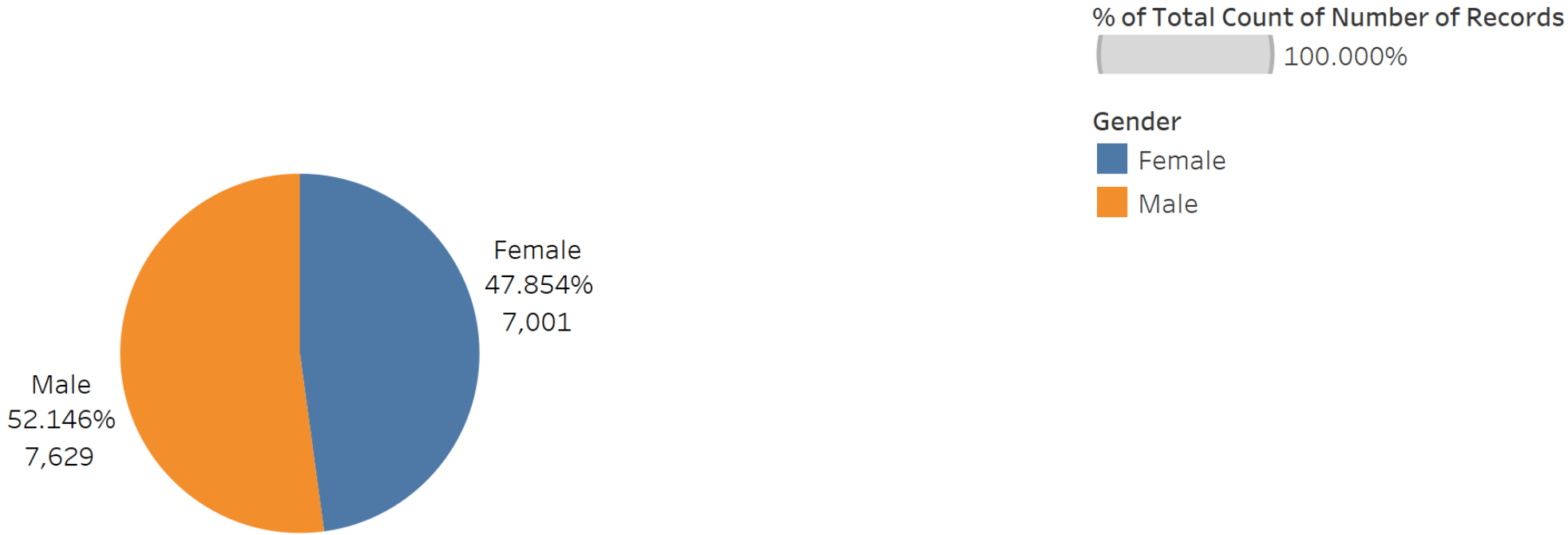
# Age Category



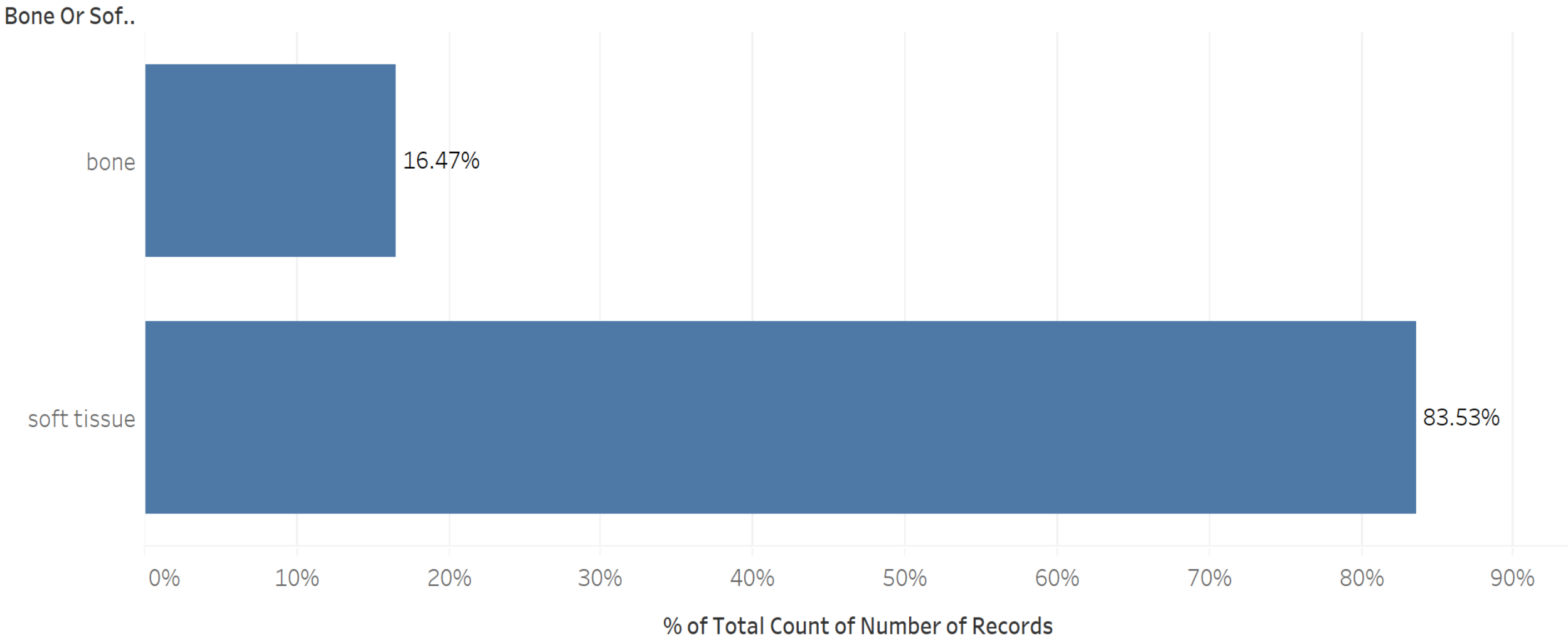
# Based on national Data:

- Median age at the time of sarcoma diagnosis ( both STS & BS ) was:
- 47 Y/O
- Median age for Bone Sarcoma was:
- 25 Y/O
- Median age for Soft Tissue Sarcoma was:
- 50 Y/O

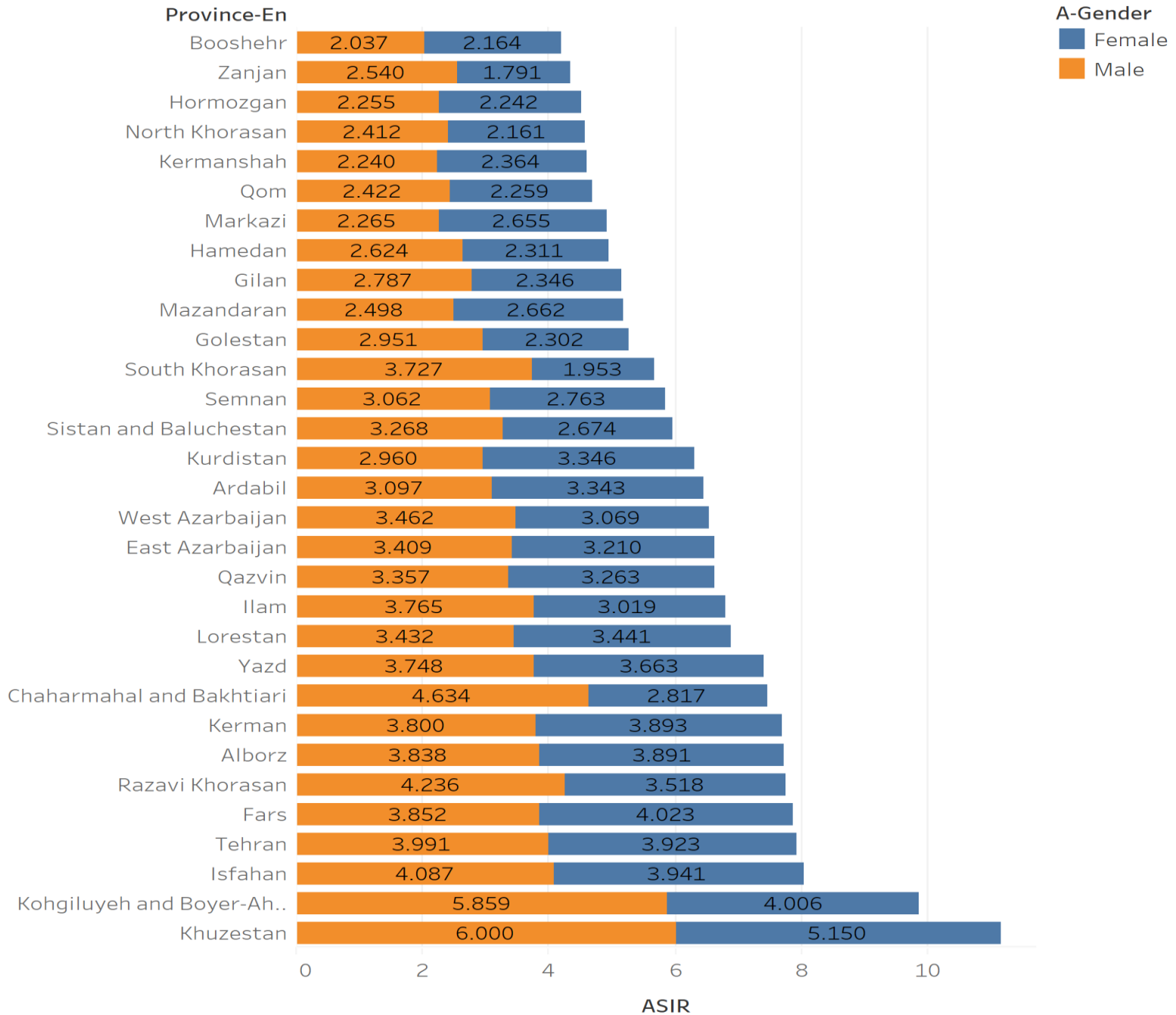
# Gender


% of Total Count of Number of Records
100.000%
Gender
Female
Male
Female
47.854%
7,001
Male
52.146%
7,629

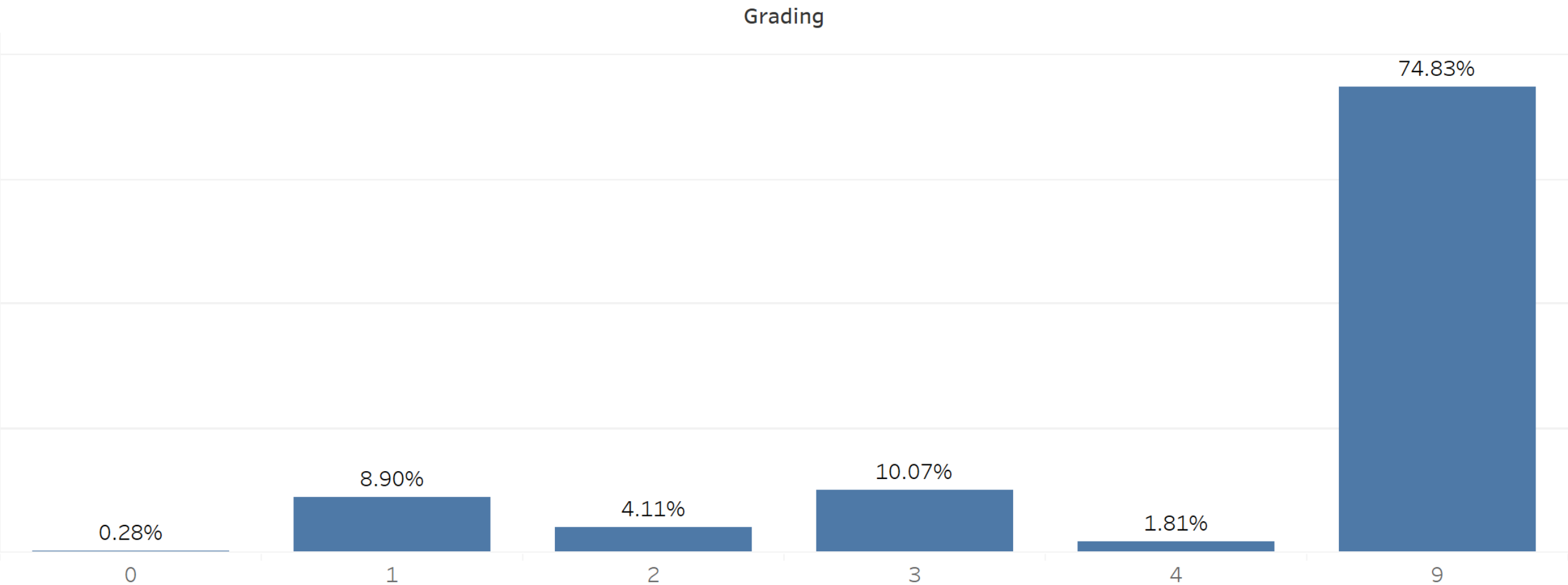
# Bone & Soft Tissue



# ASIR


Province-En
A-Gender
Female
Male
Booshehr 2.037 2.164
Zanjan 2.540 1.791
Hormozgan 2.255 2.242
North Khorasan 2.412 2.161
Kermanshah 2.240 2.364
Qom 2.422 2.259
Markazi 2.265 2.655
Hamedan 2.624 2.311
Gilan 2.787 2.346
Mazandaran 2.498 2.662
Golestan 2.951 2.302
South Khorasan 3.727 1.953
Semnan 3.062 2.763
Sistan and Baluchestan 3.268 2.674
Kurdistan 2.960 3.346
Ardabil 3.097 3.343
West Azarbaijan 3.462 3.069
East Azarbaijan 3.409 3.210
Qazvin 3.357 3.263
Ilam 3.765 3.019
Lorestan 3.432 3.441
Yazd 3.748 3.663
Chaharmahal and Bakhtiari 4.634 2.817
Kerman 3.800 3.893
Alborz 3.838 3.891
Razavi Khorasan 4.236 3.518
Fars 3.852 4.023
Tehran 3.991 3.923
Isfahan 4.087 3.941
Kohgiluyeh and Boyer-Ah.. 5.859 4.006
Khuzestan 6.000 5.150
0
2
4
6
8
10
ASIR

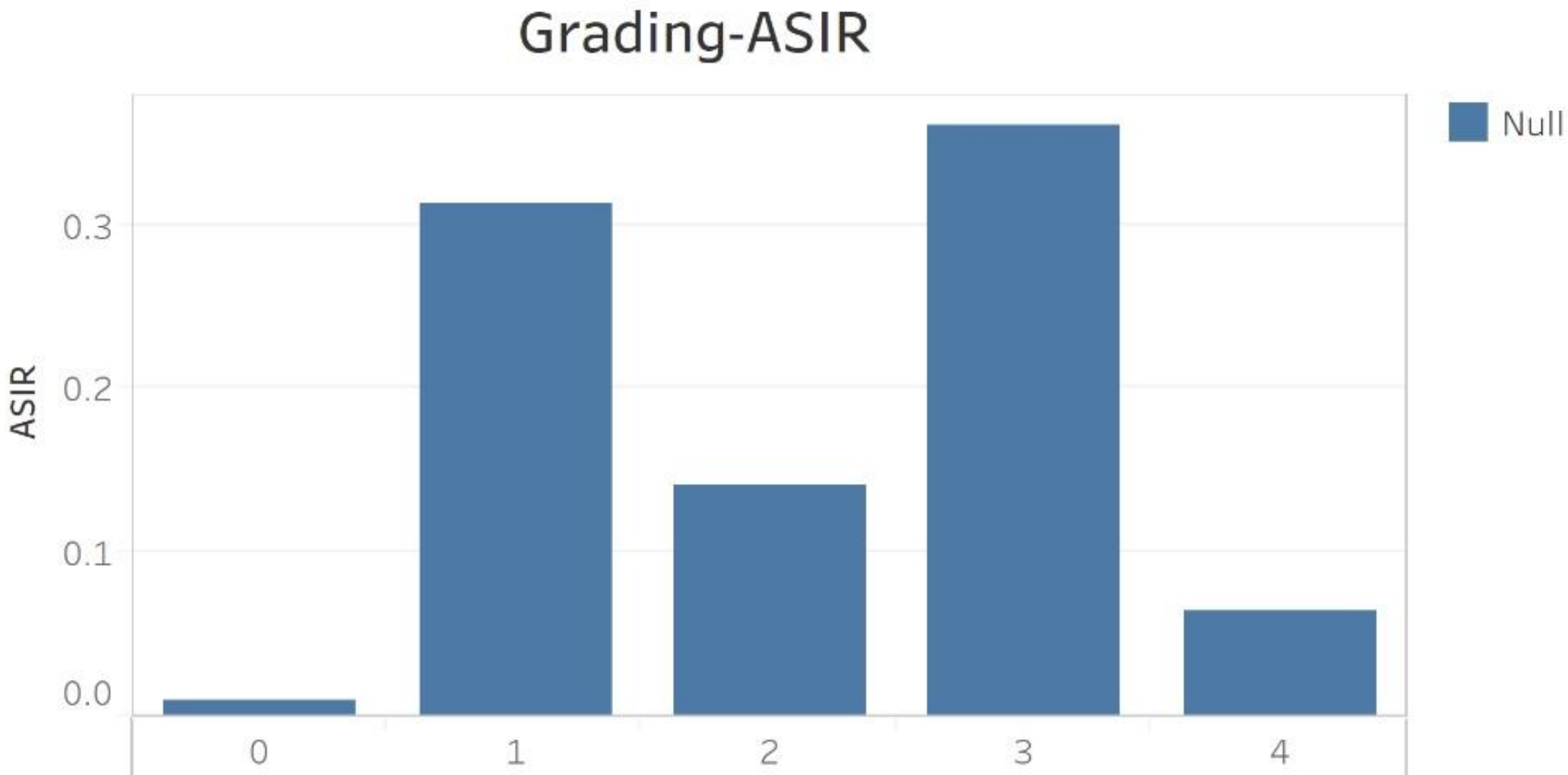
# Grading



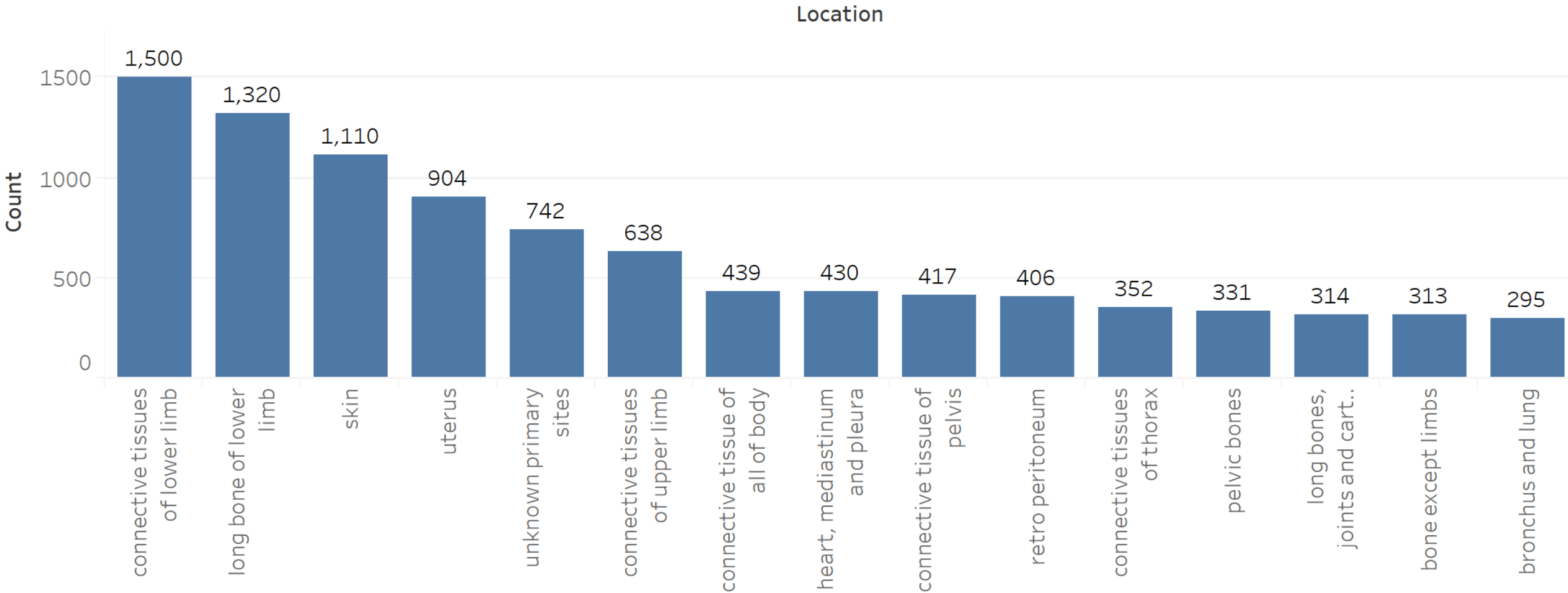
# 117 Morphology registered with Grade 9

- Sarcoma 822
- Osteosarcoma 807
- Ewing sarcoma 702
- Leiomyosarcoma 643
- Dermatofibroma sarcoma 551
- Spindle sarcoma 534
- MFH 492
- Kaposi sarcoma 421
- GIST 377
- PNET 283
- Liposarcoma 166
- Phyllodes tumor malignant 105

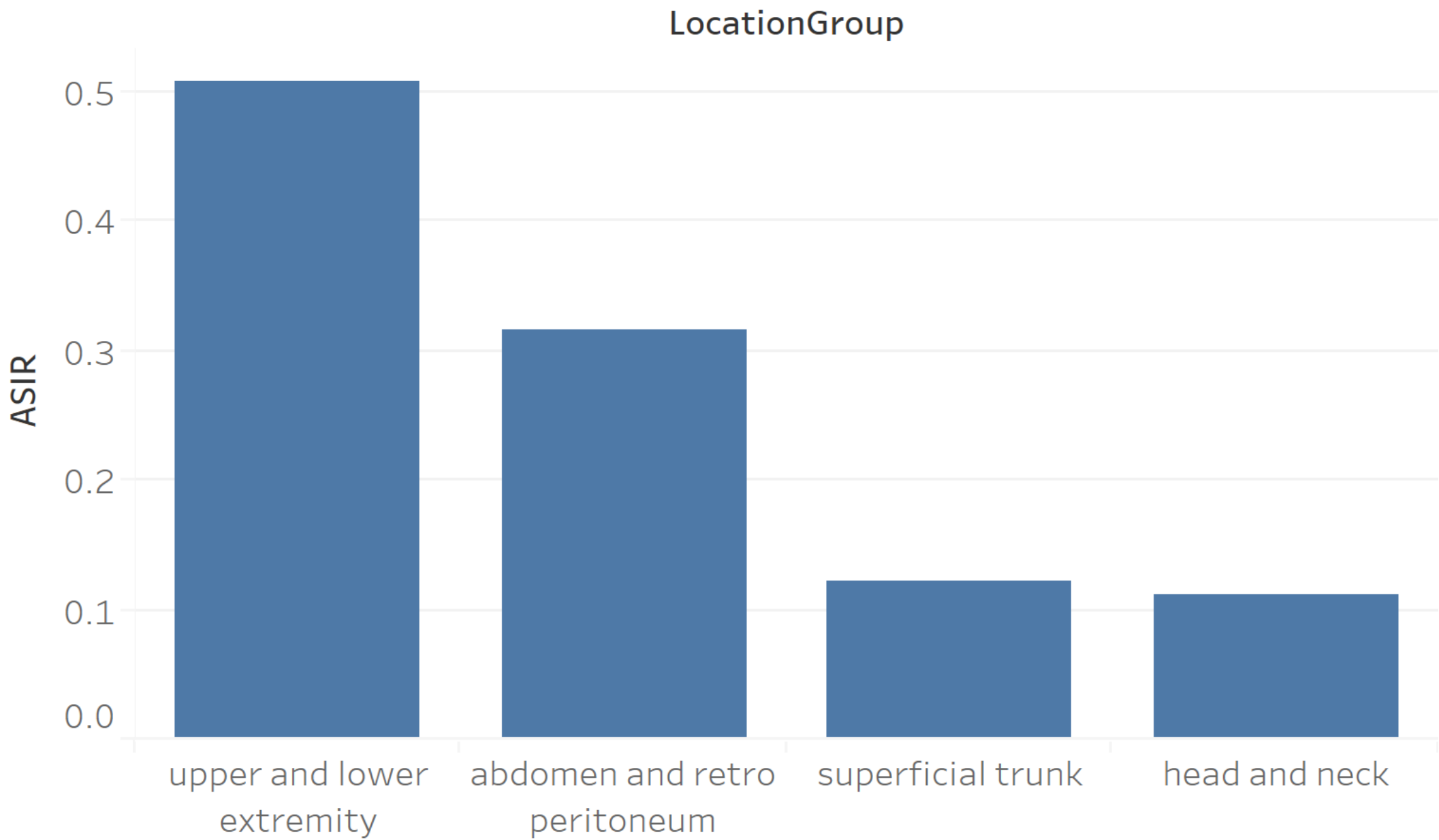
- Grading codes:
- 1) Grade 1 well differentiated
- 2) Grade 2 moderately differentiated
- 3) Grade 3 poorly differentiated
- 4) Grade 4 undifferentiated anaplastic
- 9) Grade or differentiated not determined
- 0) Score 0 No tumor necrosis

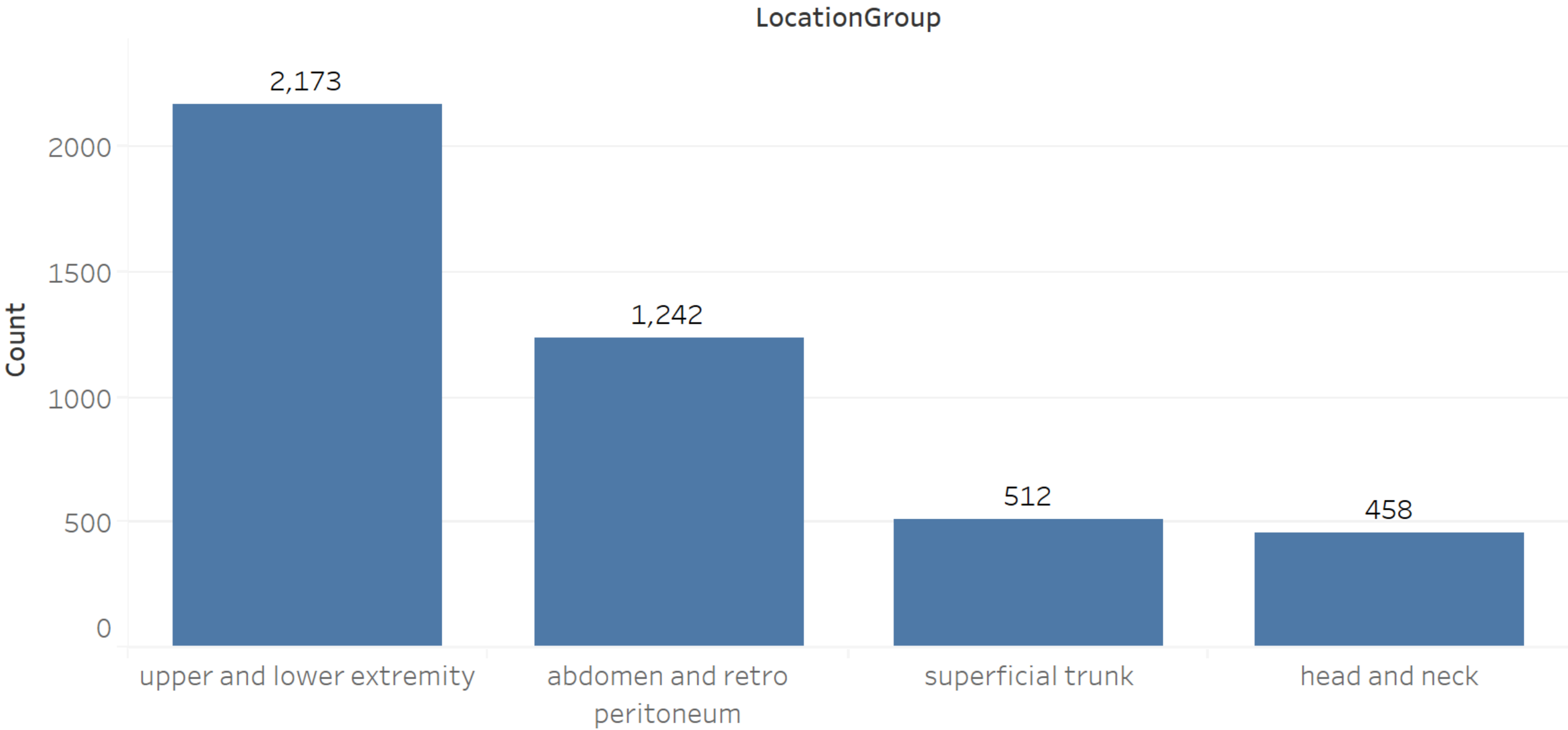

Grading-ASIR
ASIR
0.3
0.2
0.1
0.0
0
1
2
3
4
Null

# Location

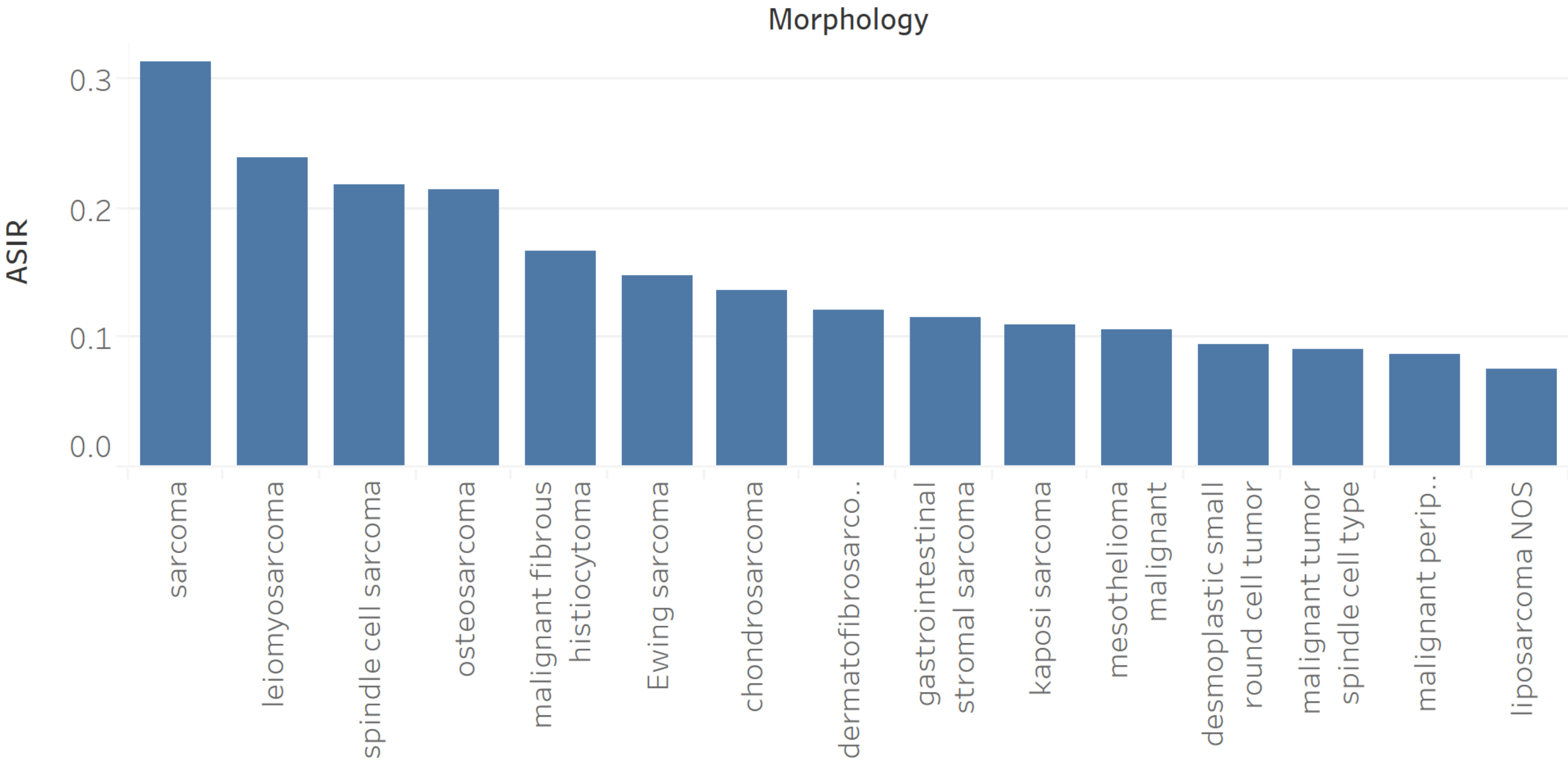

Location
Count
1500
1000
500
0
1,500
1,320
1,110
904
742
638
439
430
417
406
352
331
314
313
295
connective tissues of lower limb
long bone of lower limb
skin
uterus
unknown primary sites
connective tissues of upper limb
connective tissue of all of body
heart, mediastinum and pleura
connective tissue of pelvis
retro peritoneum
connective tissues of thorax
pelvic bones
long bones, joints and cart..
bone except limbs
bronchus and lung

# LocationGroup-ASIR

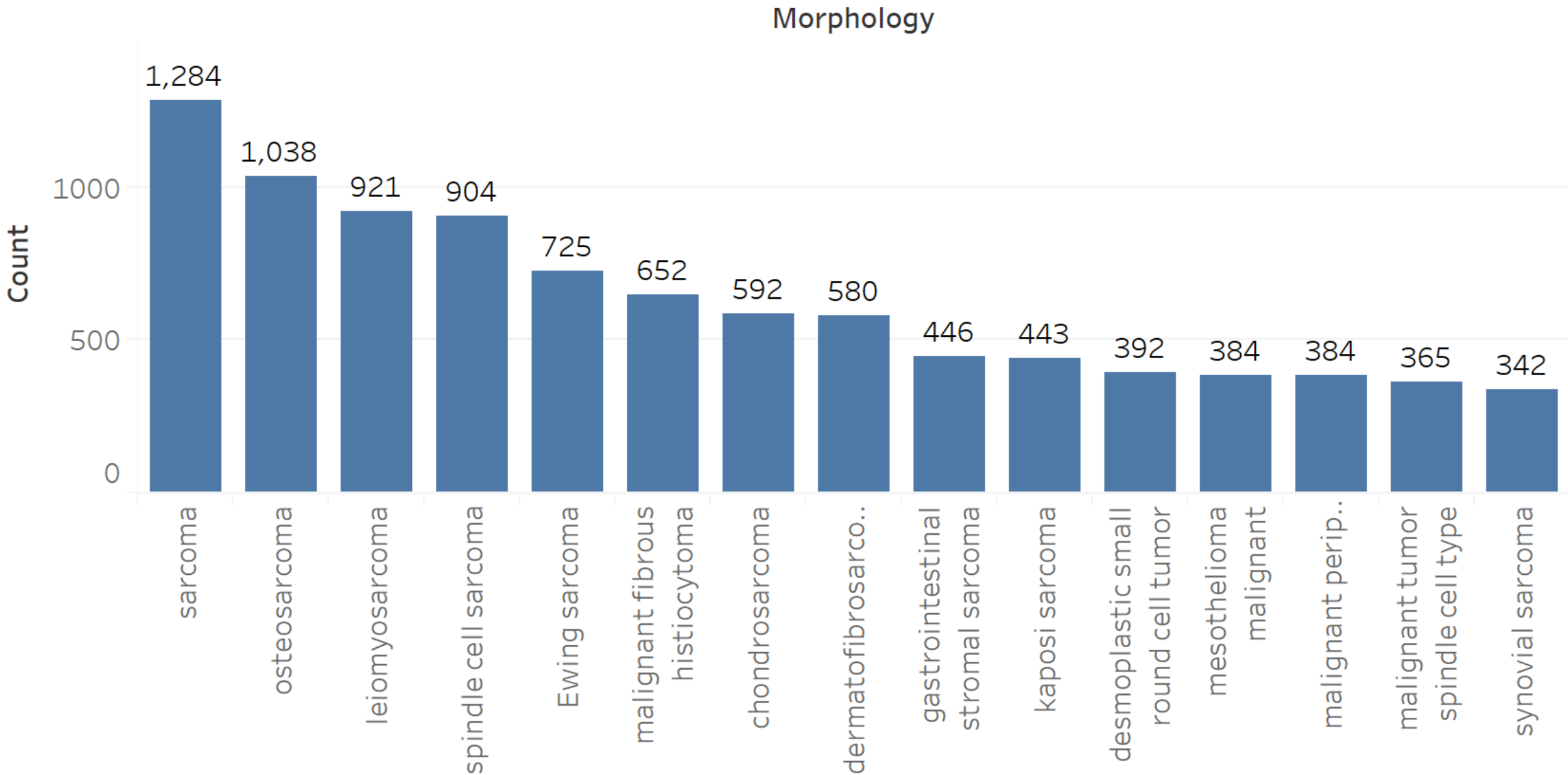



LocationGroup
Count
2000
1500
1000
500
0
2,173
1,242
512
458
upper and lower extremity
abdomen and retro peritoneum
superficial trunk
head and neck

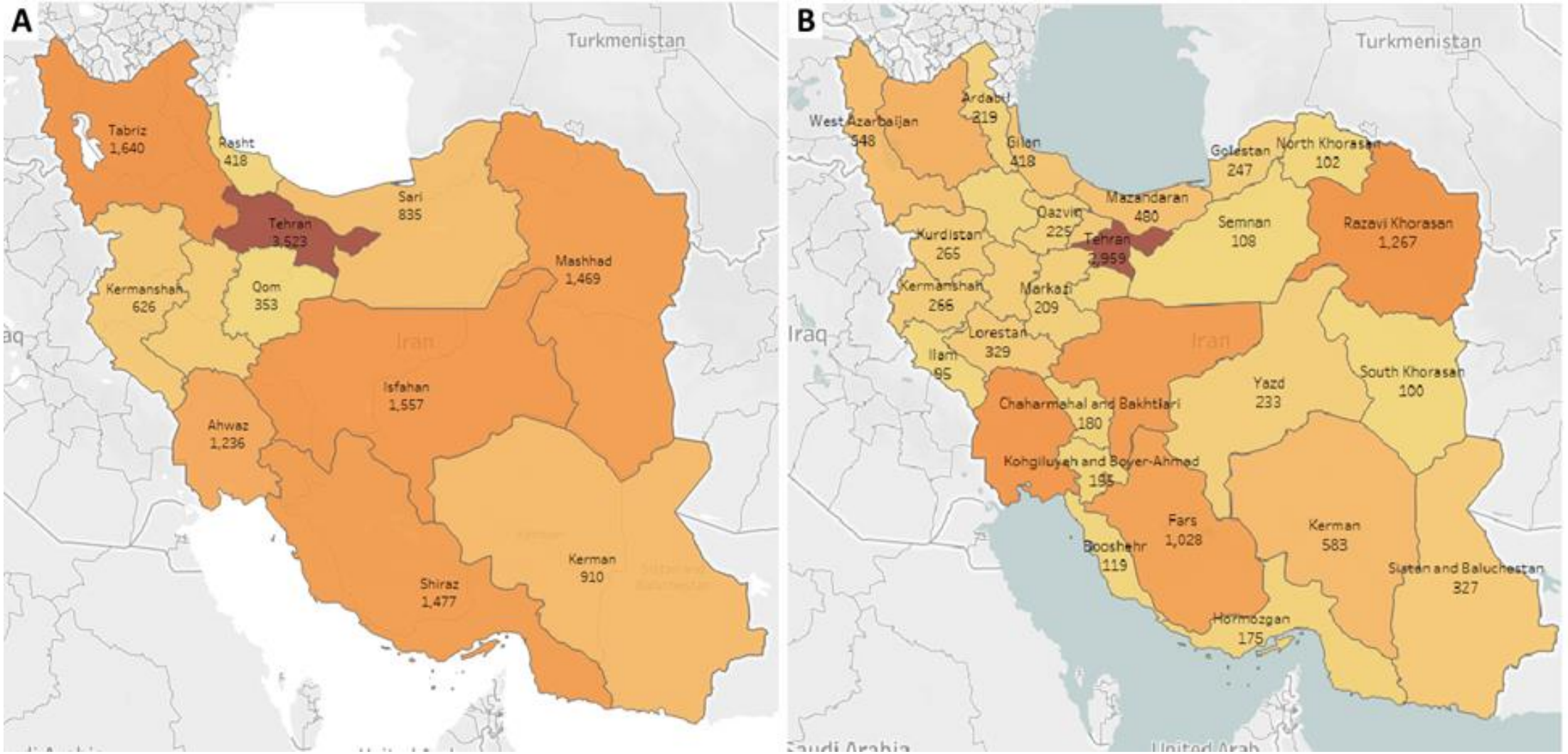
# Morphology-ASIR



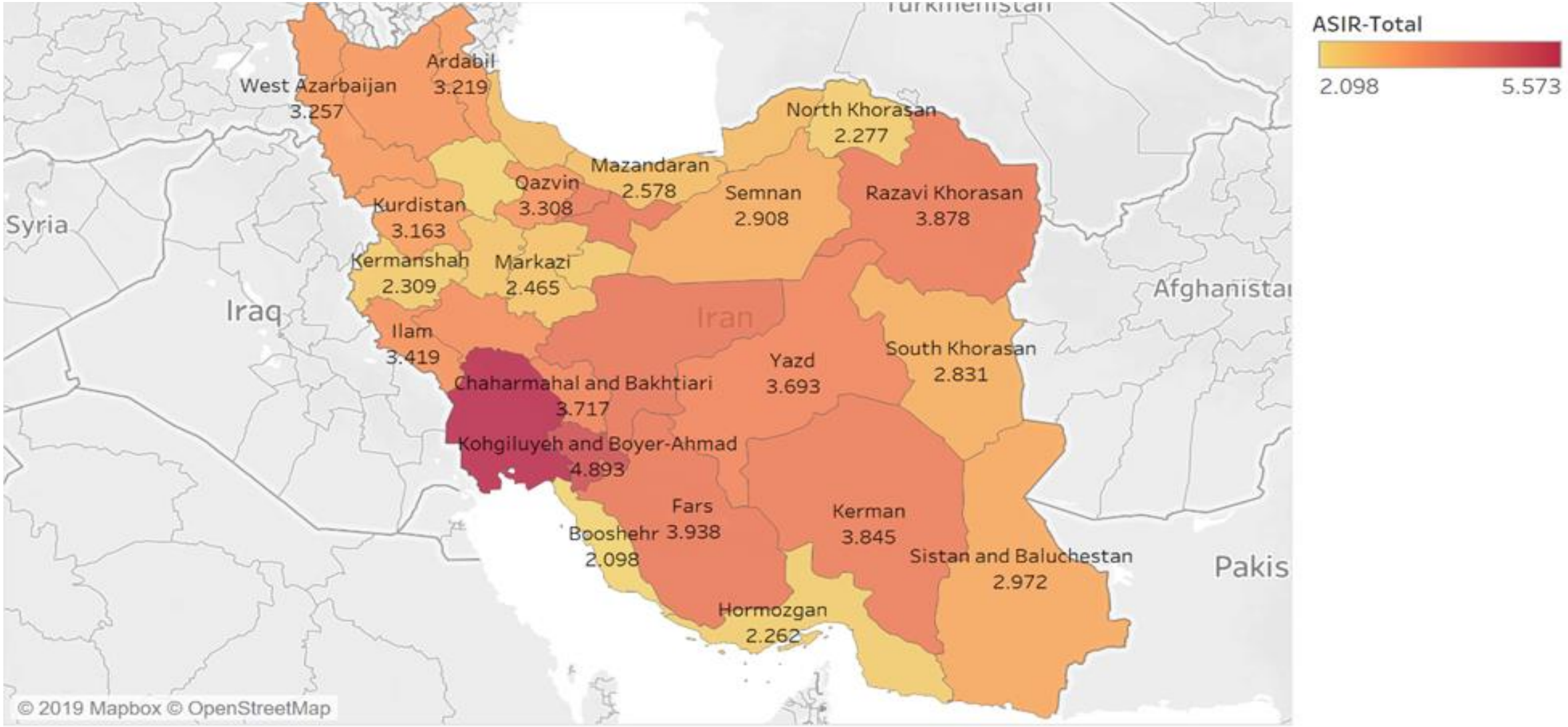
# Morphology


Morphology
Count
1000
500
0
1,284
1,038
921
904
725
652
592
580
446
443
392
384
384
365
342
sarcoma
osteosarcoma
leiomyosarcoma
spindle cell sarcoma
Ewing sarcoma
malignant fibrous histiocytoma
chondrosarcoma
dermatofibrosarco..
gastrointestinal stromal sarcoma
kaposi sarcoma
desmoplastic small round cell tumor
mesothelioma malignant
malignant perip..
malignant tumor spindle cell type
synovial sarcoma

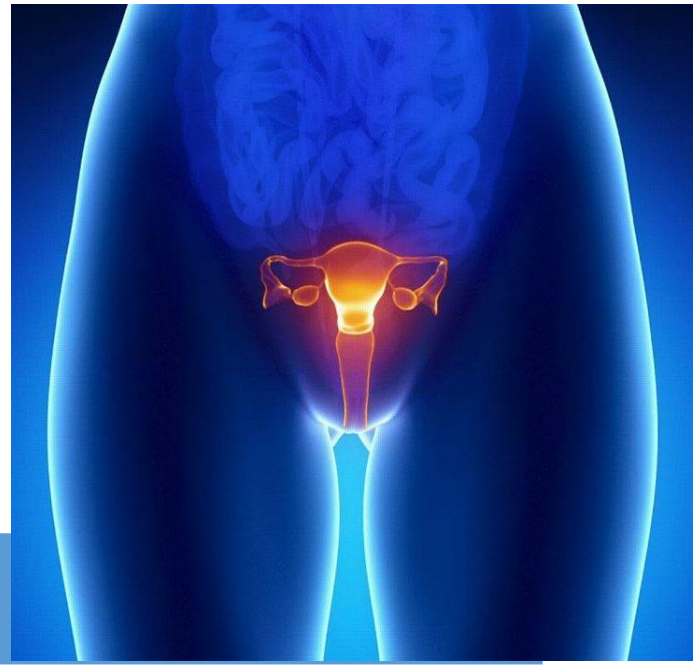
# Spatial distribution of the sarcoma patients identified in: (A) 12 Cancer Research Centers; (B) 33 provinces throughout Iran



# The overall age-standardized incidence rates (ASIR) of sarcoma throughout Iran from 2009 to 2015

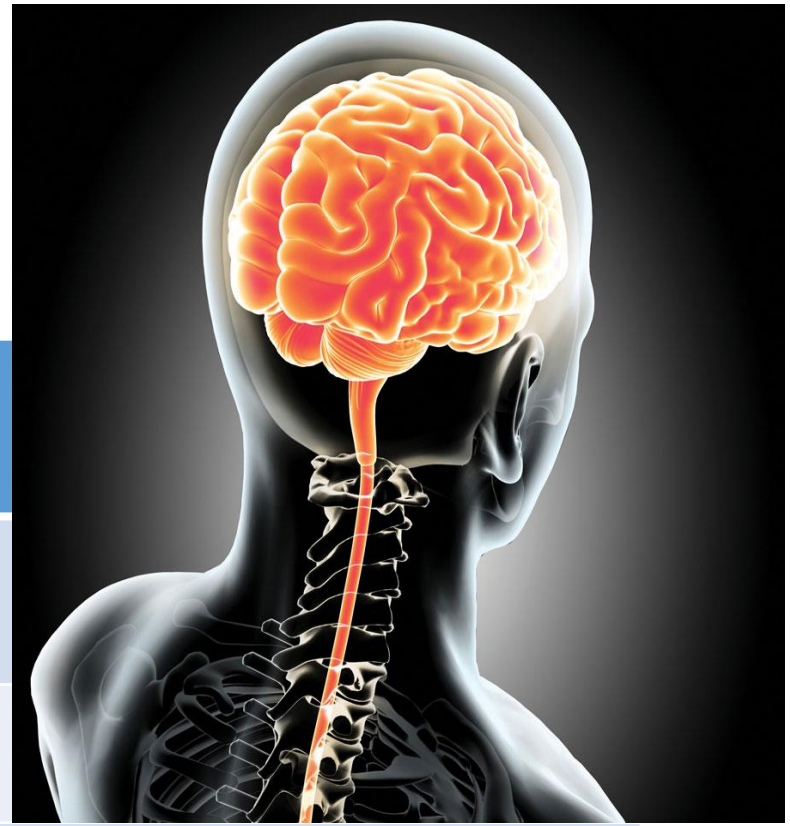


# Sarcoma of female genitalia & reproductive organs



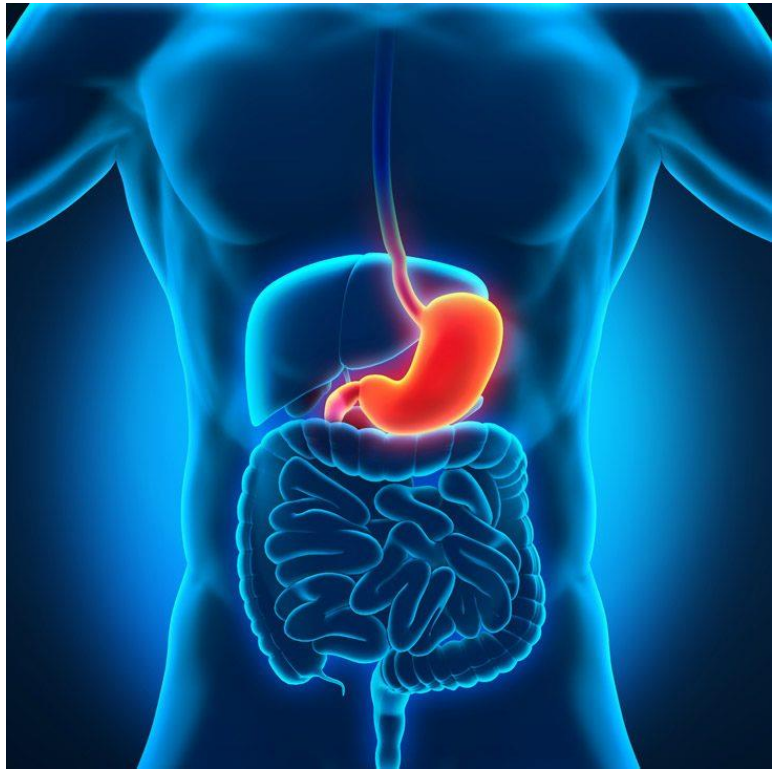
| | |
|---|---|
| Uterus | 904 |
| Cervix | 83 |
| ovary | 101 |
| vagina | 33 |
| vulva | 19 |
| Un specified female organ | 34 |

# CNS & Spinal cord Sarcoma



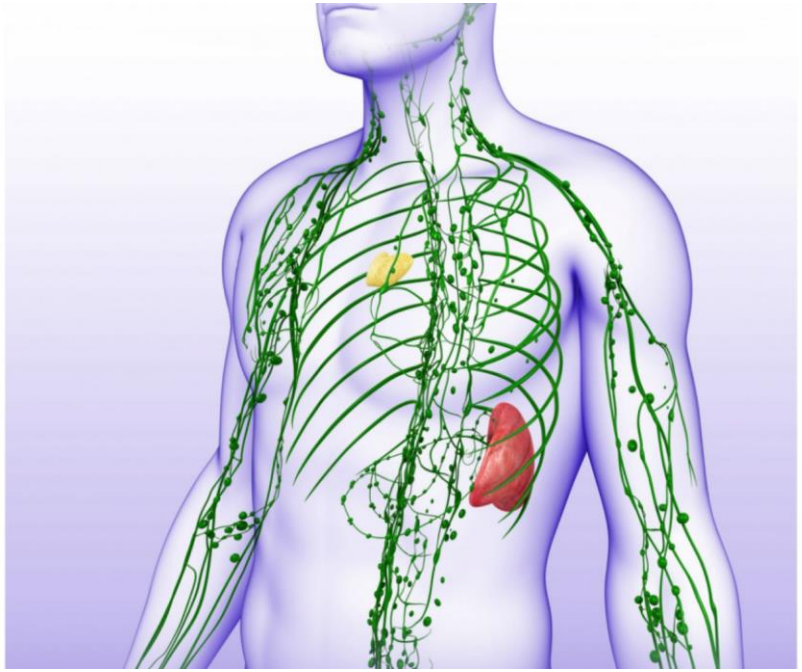
| | |
|---|---|
| brain | 193 |
| Spinal cord | 89 |
| Meninges | 14 |
| Pituitary gland<br>Pineal gland<br>Craniopharyngeal duct | 3<br>1<br>1 |

# GIST



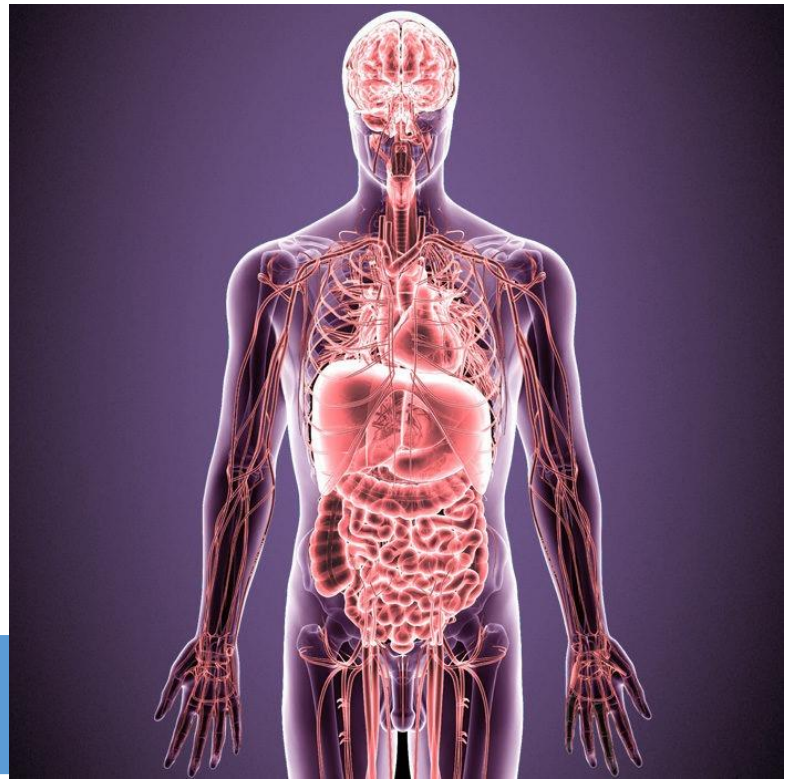
| | |
|---|---|
| gastrointestinal stromal sarcoma | 447 |
| | |

# Lympho Sarcoma



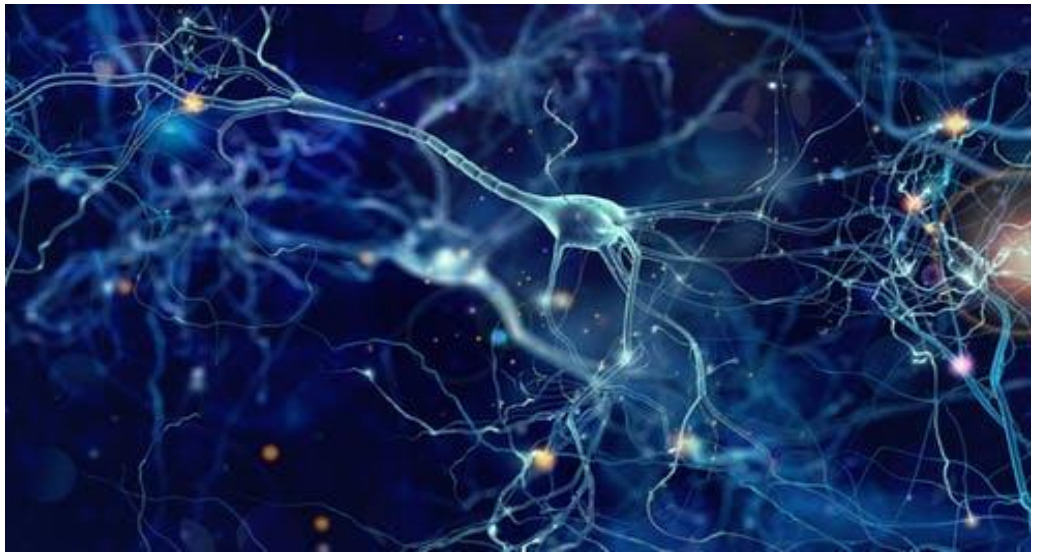
| | |
|---|---|
| Lymph node of head and neck | 23 |
| Lymph node of inguinal region and leg | 16 |
| Lymph node | 13 |
| Intra abdominal lymph node | 11 |
| Intra thoracic lymph node | 10 |
| Lymph nodes of axilla and arm | 10 |
| Pelvic lymph node | 6 |
| Multiple region lymph node | 1 |

# Hematopoietic Sarcoma



| | |
|---|---|
| Myeloid sarcoma | 30 |
| Histiocytic sarcoma | 7 |
| Mast cell sarcoma | 5 |
| Hodgkin sarcoma | 2 |
| Malignant mastocytosis | 1 |

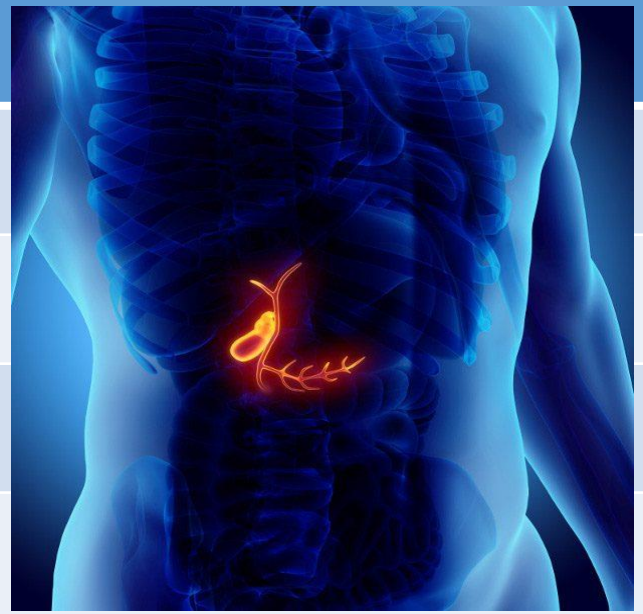
# Parotid & major salivary gland sarcoma



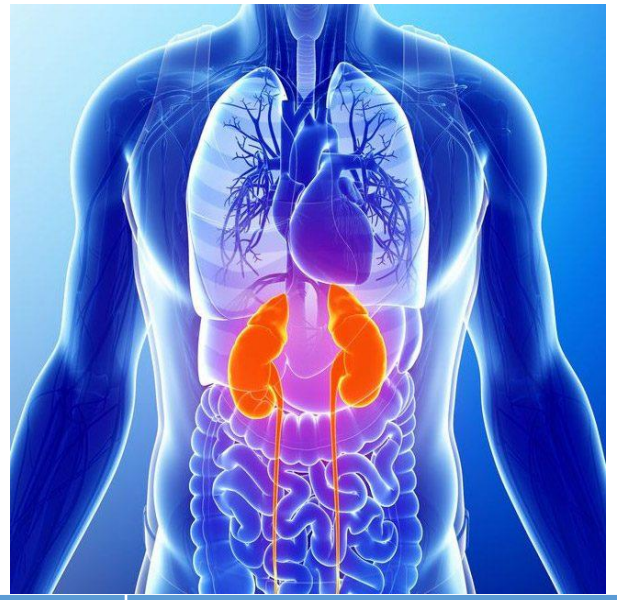
| | |
|---|---|
| Parotid gland | 53 |
| Major salivary gland | 17 |

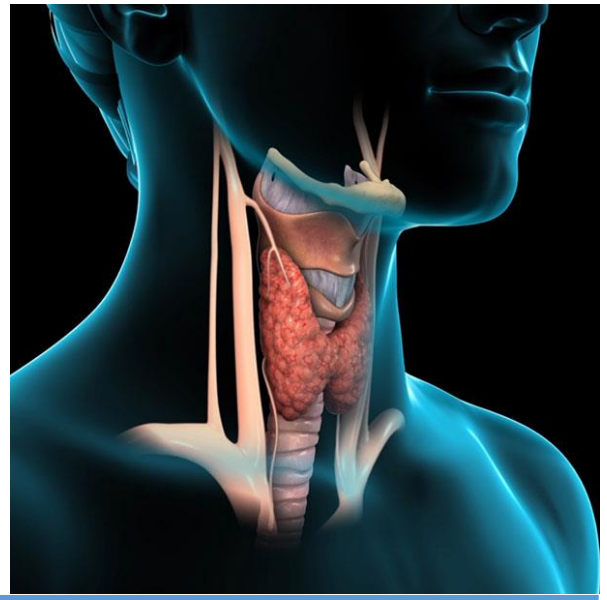
# Pancreato Hepato Biliary sarcoma

| | |
|---|---|
| Liver and intrahepatic bile duct | 95 |
| gallbladder | 9 |
| pancreas | 16 |
| Head of pancreas | 5 |
| Body of pancreas | 2 |
| Other part of biliary tract | 6 |



# Thyroid & Adrenal gland Sarcoma



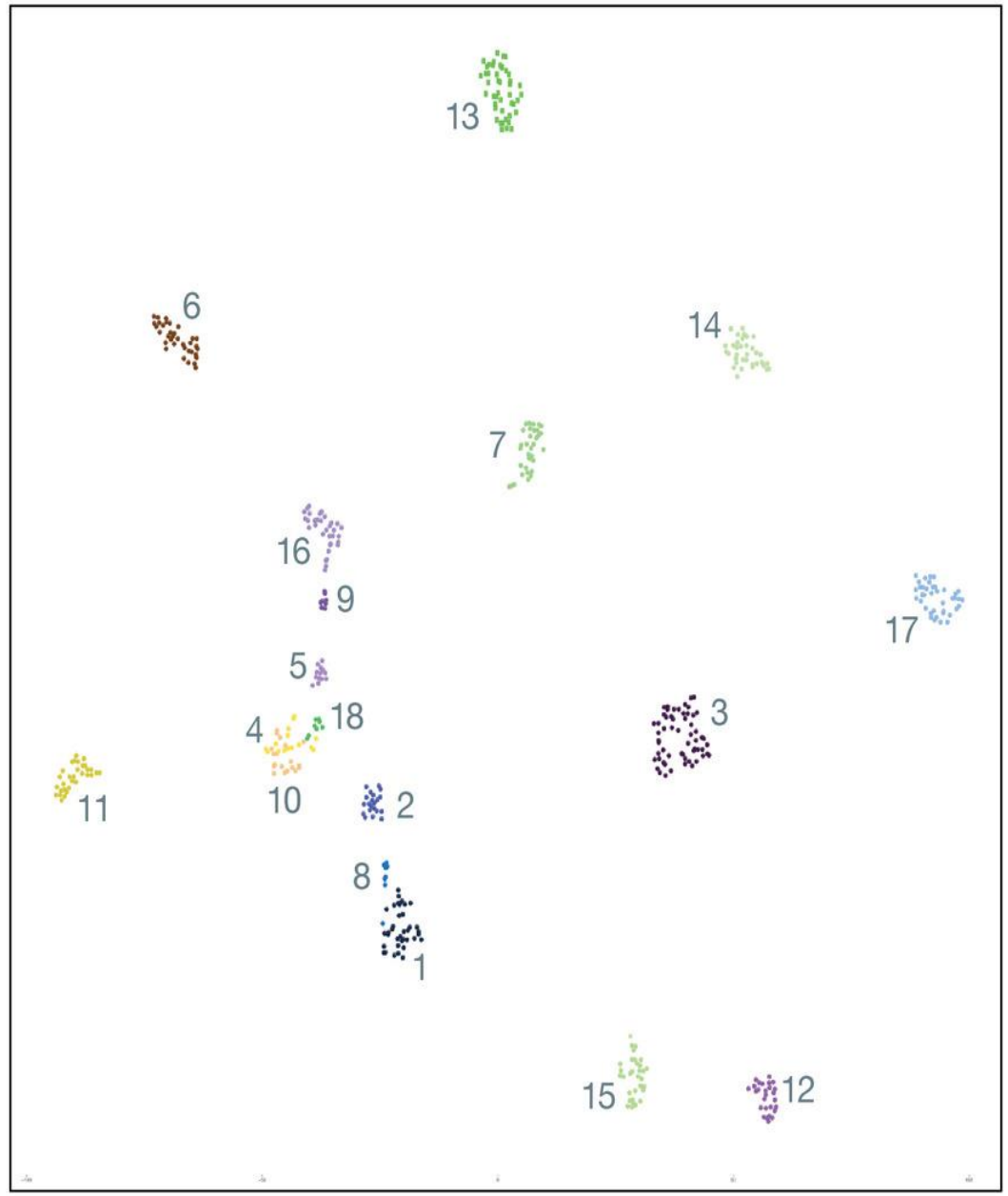


| | |
|---|---|
| thyroid | 19 |
| Adrenal gland | 13 |

- **Potential risk factors are ionizing radiation, lymphatic edema (secondary angiosarcoma of the breast), viral infections (HHV8 and Kaposi sarcoma), exposure to chemical factors (vinyl chloride and hepatic angiosarcoma).**
- **Genetic susceptibility plays a role in a minority of cases. However, mutations in TP53, ATM and ATR genes are associated with enhanced susceptibility to radiation.**

- **Genetic alterations observed in sarcomas could be divided into three major groups characterized by: (1) chromosome translocations; (2) simple karyotype and mutations; (3) variably complex karyotypes.**
- **A large part of sarcomas belong to the first group and the specific chromosal translocations could be utilized in the diagnostic process.**

## DNA-methylation-based clustering of sarcoma subtypes




1 Angiosarcoma
2 Alveolar soft part sarcoma (ASPS)
3 Chordoma
4 Liposarcoma (LPS; dediff.)
5 Dermatofibrosarcoma protuberans
6 Ewing sarcoma (EwS)
7 Gastrointestinal stromal tumor (GIST)
8 Kaposi sarcoma
9 Fibromyxoid sarcoma (low-grade)
10 Leiomyosarcoma (LMS)
11 Liposarcoma (LPS; myxoid)
12 Malignant peripheral nerve sheath tumor (MNPST)
13 Osteosarcoma (OS; high-grade)
14 Alveolar rhabdomyosarcoma (ARMS)
15 Embryonal rhabdomyosarcoma (ERMS)
16 Solitary fibrous tumor (SFT)
17 Synovial sarcoma (SS)
18 Undifferentiated pleomorphic sarcoma (UPS)

- **second group ( simple karyotype ): desmoids fibromatosis (CTNNB1 or APC mutations) and GIST (KIT, PDGFRA, or less frequently BRAF, SDH, NF1).**

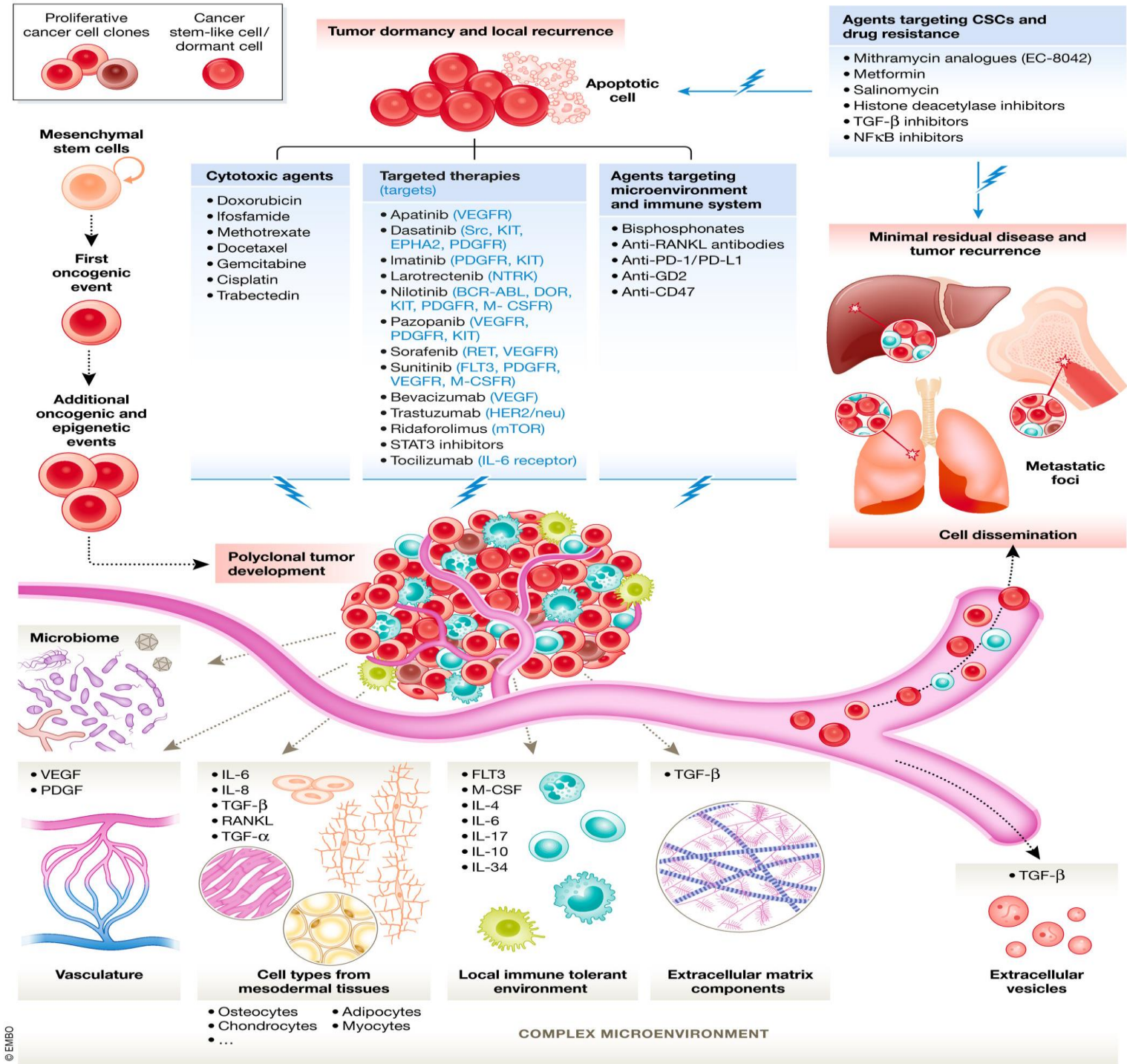
- In well-differentiated liposarcoma there is an amplification of MDM2, CDK4 and HMGA2 genes or sarcoma-specific chromosomal break regions present in the CHOP gene in Myxoid liposarcoma and FKHR in alveolar rhabdomyosarcoma.

# Impact of the tumor microenvironment on the stemness and behavior of sarcoma cells:

- **Similar to the "seed and soil" theory described for other malignancies, sarcoma cells evolve in a permissive milieu favoring their quiescence and drug resistance or their proliferation and aggressiveness.**

- **Sarcoma cells are embedded in a highly heterogeneous tissue context composed of immune cells, endothelial cells, pericytes, mesenchymal stem cells (MSCs), cancer-associated fibroblasts (CAFs), and nerve fibers, all of which may influence their behavior and favor “stemness” properties.**

- **Cancer stem cells (CSCs) usually represent only a very small fraction of the tumor cell mass, yet their eradication is critical for improving drug response. Indeed, CSCs have a great potential for self-renewal and develop protective mechanisms against conventional anti-tumor treatments, thereby causing sarcoma relapse and metastasis.**


Proliferative cancer cell clones
Cancer stem-like cell/ dormant cell
Tumor dormancy and local recurrence
Apoptotic cell
Agents targeting CSCs and drug resistance
• Mithramycin analogues (EC-8042)
• Metformin
• Salinomycin
• Histone deacetylase inhibitors
• TGF-β inhibitors
• NFκB inhibitors
Mesenchymal stem cells
First oncogenic event
Additional oncogenic and epigenetic events
Cytotoxic agents
• Doxorubicin
• Ifosfamide
• Methotrexate
• Docetaxel
• Gemcitabine
• Cisplatin
• Trabectedin
Targeted therapies (targets)
• Apatinib (VEGFR)
• Dasatinib (Src, KIT, EPHA2, PDGFR)
• Imatinib (PDGFR, KIT)
• Larotrectenib (NTRK)
• Nilotinib (BCR-ABL, DOR, KIT, PDGFR, M- CSFR)
• Pazopanib (VEGFR, PDGFR, KIT)
• Sorafenib (RET, VEGFR)
• Sunitinib (FLT3, PDGFR, VEGFR, M-CSFR)
• Bevacizumab (VEGF)
• Trastuzumab (HER2/neu)
• Ridaforolimus (mTOR)
• STAT3 inhibitors
• Tocilizumab (IL-6 receptor)
Agents targeting microenvironment and immune system
• Bisphosphonates
• Anti-RANKL antibodies
• Anti-PD-1/PD-L1
• Anti-GD2
• Anti-CD47
Minimal residual disease and tumor recurrence
Metastatic foci
Cell dissemination
Polyclonal tumor development
Microbiome
• VEGF
• PDGF
Vasculature
• IL-6
• IL-8
• TGF-β
• RANKL
• TGF-α
Cell types from mesodermal tissues
• Osteocytes
• Chondrocytes
• …
• Adipocytes
• Myocytes
• FLT3
• M-CSF
• IL-4
• IL-6
• IL-17
• IL-10
• IL-34
Local immune tolerant environment
• TGF-β
Extracellular matrix components
• TGF-β
Extracellular vesicles
COMPLEX MICROENVIRONMENT

- **Sarcoma development results from a complex biological process. Their natural history combines the emergence of a first oncogenic hit followed by secondary oncogenic and epigenetic events with a conjuncture of a permissive microenvironment composed by cell types from mesodermal tissues, immune infiltrate, vascular, and extracellular matrix components.**

- **Sarcoma cells are characterized by a phenotypic and genetic heterogeneity coming from the successive oncogenic/epigenetic events occurring during tumor development and by cancer cells acquiring stemness properties that become progressively quiescent.**

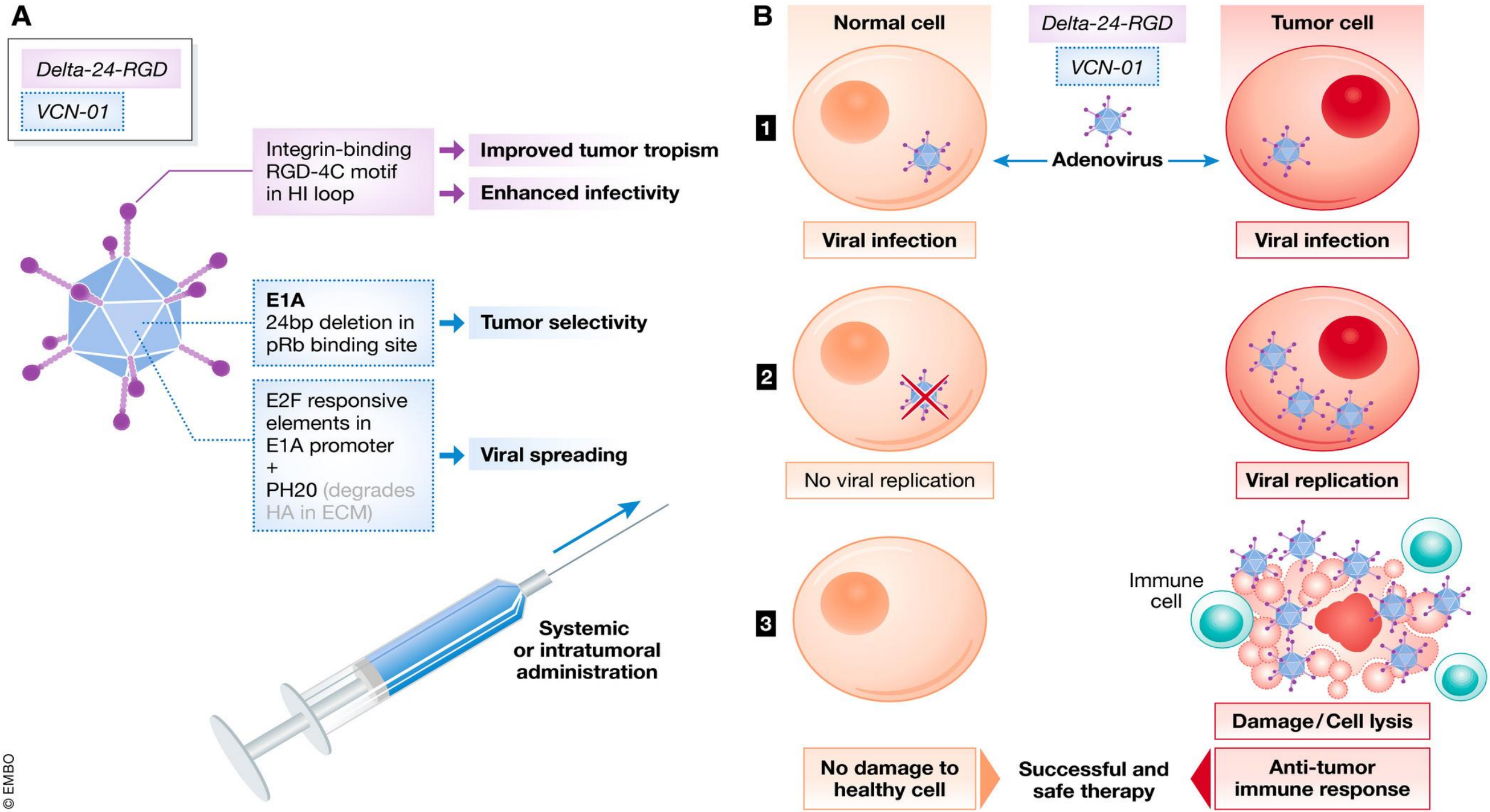
- Sarcomas are prone to induce distant metastatic foci spread by circulating tumor cells and invading after extravasation appropriate metastatic niches.
- Cancer cells installed in distant organs can spread again and enrich other metastatic sites increasing the tumor heterogeneity and potentially drug resistances.

- **Persisting cells after resection of the primary tumor or dormant cancer cells located in distant organs characterize the minimal residual disease and are responsible of tumor recurrences.**

- **The expression of these factors in sarcomas is oncogene-driven and triggered by a combination of mutational and epigenetic events or by developmental programs.**
- **These events ultimately result in the deregulation of pathways that control stemness and differentiation, such as Hedgehog, Notch, Wnt/β-Catenin, Hippo, or ALK.**

- **sarcoma TME may contain a specific microbiome (Nejman et al, 2020): A recent study described that bacterial DNA can be found in most CHSs. Bacteria were mostly intracellular and were detectable in immune and tumor cells.**

- **Interestingly, metabolic functions related to Intratumoral bacteria appeared tumor type-specific; that is, degradation of hydroxyprolines by bacteria was enriched in CHSs**

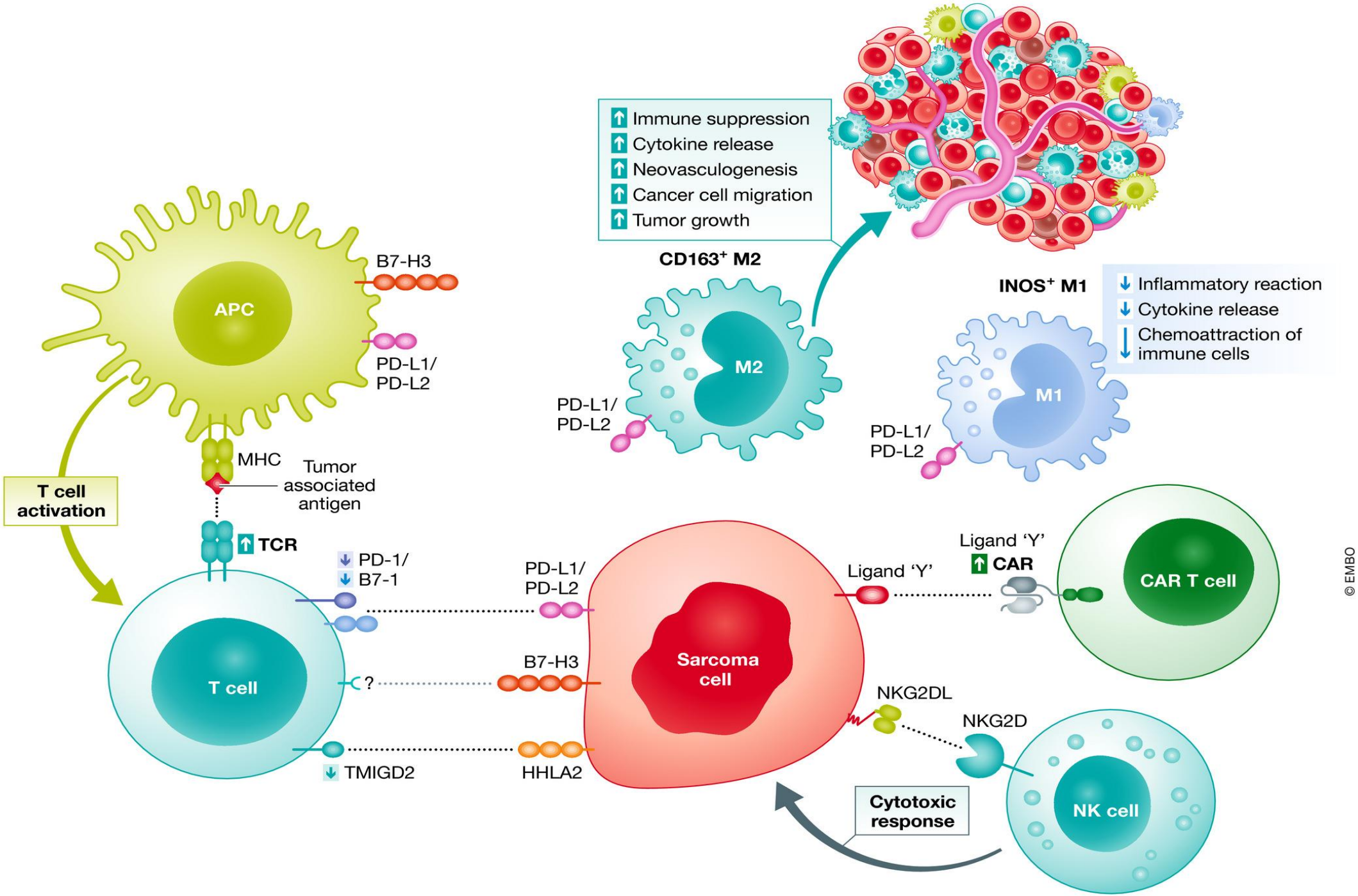

A
Delta-24-RGD
VCN-01
Integrin-binding RGD-4C motif in HI loop
Improved tumor tropism
Enhanced infectivity
E1A
24bp deletion in pRb binding site
Tumor selectivity
E2F responsive elements in E1A promoter + PH20 (degrades HA in ECM)
Viral spreading
Systemic or intratumoral administration
B
Normal cell
Delta-24-RGD
VCN-01
Adenovirus
Tumor cell
1
Viral infection
Viral infection
2
No viral replication
Viral replication
3
Immune cell
Damage/Cell lysis
No damage to healthy cell
Successful and safe therapy
Anti-tumor immune response

- **Sarcomas driven by reciprocal fusion oncoproteins, such as EwS, generally exhibit a low immune infiltrate, constituting so-called “cold” tumors. Few available studies have demonstrated that TILs and dendritic cells are quite rare (immune desert) and that programmed death-ligand 1 (PD-L1) expression is usually low (Spurny et al, 2018).**

- **The presence of infiltrating macrophages has been associated with poorer overall survival (Vakkila et al, 2006), and elevated levels of circulating proinflammatory factors (e.g., interleukin 6, IL-6) correlate with tumor-associated fever at advanced stages (Lissat et al, 2015) implying the recruitment of immunosuppressing myeloid dendritic cells, macrophages, and other inflammatory cells at the tumor site.**

- For STSs, only a very few recent reports have aimed to determine the "hot" or "cold" tumor immunophenotypes and their potential as biomarkers for response to therapy (Galon & Bruni, 2019). Kim et al reported the presence of PD-1+ and PD-L1+ TILs at rates of 65% and 58%, respectively, in various STS subtypes (Kim et al, 2013a).

- **The infiltrations of PD-L1-expressing macrophages and lymphocytes were observed in 58% and 30%, respectively, of 50 analyzed STS samples (D'Angelo et al, 2015), and the PD-L1 expression was associated with a higher density of CD3+ PD-1+ TILs, a higher tumor grading, and a lower overall survival (Orth et al, 2020)**


Immune suppression
Cytokine release
Neovasculogenesis
Cancer cell migration
Tumor growth
CD163+ M2
INOS+ M1
Inflammatory reaction
Cytokine release
Chemoattraction of immune cells
M2
M1
PD-L1/
PD-L2
APC
B7-H3
PD-L1/
PD-L2
MHC
Tumor associated antigen
T cell activation
TCR
PD-1/
B7-1
T cell
?
TMIGD2
PD-L1/
PD-L2
B7-H3
HHLA2
Sarcoma cell
Ligand 'Y'
Ligand 'Y'
CAR
CAR T cell
NKG2DL
NKG2D
NK cell
Cytotoxic response
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- **The cornerstone of bone sarcoma and STS management is surgical resection of the primary tumor, which is typically accompanied by neoadjuvant and/or adjuvant chemotherapy and/or irradiation.**

- **Radiation therapy contributes to local control of tumor growth with positive margins or high-grade STS (Kim et al, 2008). Chemotherapy regimens of bone sarcomas (e.g., OS, EwS) combine doxorubicin, cisplatin, methotrexate, and ifosfamide administered before and/after surgery for 6–12 months (Brown et al, 2018). Similarly, systemic treatments of STSs are mainly based on anthracyclines (e.g., doxorubicin) alone or in combination with an alkylating agent (e.g., ifosfamide) (Judson et al, 2014; Gómez & Tsagozis, 2020; Smrke et al, 2020). Interestingly, the use of adjuvant chemotherapy or radiotherapy may be defined by biological risk factors in high-risk STSs (Sundby Hall et al, 2018).**

- Although systemic therapy is the treatment of choice in metastatic disease (Meyers, 2015), resection of the primary tumor may still be performed with palliative intent, or rarely, in combination with resection of oligometastatic disease (Blakely et al, 2015). Wide margin surgery then remains the crucial technical approach in sarcoma treatment (Patrikidou et al, 2011).

- **For bone sarcomas, studies have demonstrated that oncologic outcomes of OS and EwS are similar between limb salvage and amputation when wide margins are achieved (Simon et al, 1986; Rougraff et al, 1994; Alamanda et al, 2012; Jauregui et al, 2018). Thus, the current standard of care is limb salvage surgery if preservation of neurovascular structures allows reconstruction of a functional extremity (Yang et al, 2017)**

- **Next study will revealed:**

- **What would be the reason or reasons of these types of Sarcoma's distribution in Iran?**

# So be aware about SARCOMA!

- **Thank you!**