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# ABSTRACT

## ISRS Educational Course "SRS/SRT in Management of Benign Intracranial Tumors, Skull Base Tumors, Genitourinary and Gynecological Cancers; Medical Physics and Imaging for Radiosurgery"

(April 21-23, 2022; Debrecen, Hungary)

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NATIONAL RESEARCH, DEVELOPMENT AND INNOVATION OFFICE HUNGARY
PROGRAM FINANCED FROM THE NRDI FUND

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The International Stereotactic Radiosurgery Society (ISRS) was founded as an international, non-profit organization in 1991 and is dedicated to advancing the field of stereotactic radiosurgery through research, education and multidisciplinary collaboration. It is the largest organization of its kind with over 800 members from more than 60 countries.

In furtherance of its mission to advance the field of focused radiation on an international basis through education and disseminating best practices, the ISRS has implemented a robust program of Educational Courses in collaboration with leading centers throughout the world.

The Department of Oncoradiology and Neurosurgery of the University of Debrecen has been in close contact with the organization for many years, since 2019 we have been participating in international events as regular invited instructors. In 2019, we hosted a successful event. The aim of the courses is to present the latest technologies and clinical applications to clinicians, physicists, radiographers and departments (surgery, oncology, pulmonary medicine) involved in the care of cancer patients. The program joins ISRS annual planned training and scientific program, the course to be held in Debrecen in 2022, besides discussing the clinical, physical, imaging and pathological background of the radiation surgery of benign intracranial space reservations, aimed at the radiation surgical aspects of urogential tumors. The fact that for the second time in Hungary we manage to bring the elite of the profession is of paramount importance. Internationally recognised rapporteurs ensure up-to-date education of the professions concerned, presentation of their research results and presentation of international research directions. It provides opportunities for international contacts, the establishment of cooperations and the construction of research programmes.

In 2019 the course focused on the field of stereotactic management of intracranial malignancies, with dominantly malignant indications. After the hard and difficult years of COVID pandemic the organizers had prepared a program focusing on state of art stereotactic management of benign intracranial tumors and genitourinary and gynecological malignancies.

The program is designed to give high attention to imaging, physics, and the treatment opportunities on this special fields of stereotactical interventions. To be able to transfer this knowledge, we invited many national and international experts. The educational faculty is multidisciplinary and has a wide range of professionals (radiology, radiation oncology, medical oncology, surgery, urology, gynecology, medical physics).



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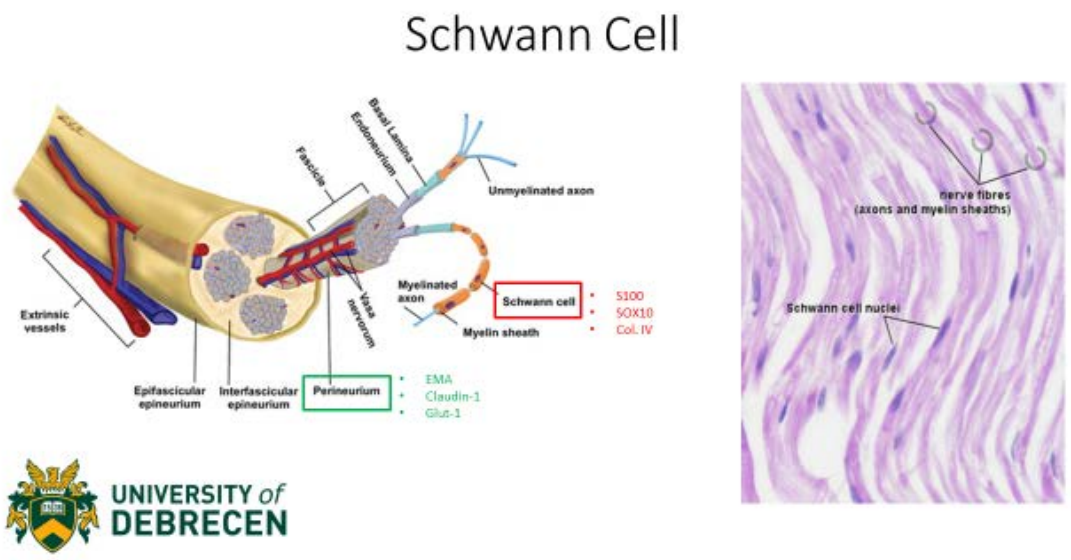
## SESSION I SRS/SRT IN MANAGEMENT OF VESTIBULAR SCHWANNOMAS

### VESTIBULAR SCHWANNOMAS: OVERVIEW - DR. CHANG-CHIEN YI-CHE (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)




Schwannoma (Acoustic Neuroma)

- Benign, encapsulated nerve sheath tumour composed **entirely** of well-differentiated Schwann cells (WHO grade I).
- 85% cerebellopontine angle, 29% spinal nerve root.
- Somatic *NF2* inactivation mutation in sporadic cases.
- $4^{th}$ to $6^{th}$ decades. No gender predilection.
- 90% solitary and sporadic, 4% from NF2.

Schwannoma-clinical aspects

- From asymptomatic to hearing loss/vertigo.
- Imaging:
  - Well-circumscribed.
  - “Ice-cream-cone” sign (tapered intraosseous cone).
  - Cystic change.
- Gross:
  - Globoid mass light-tan glistening cut surface.
  - May have cystic degeneration.



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Schwannoma-histology

- Surround by perineurium.
- Antoni A areas with Verocay bodies.
- Antoni B areas with hyalinized vessels.
- Typically diffuse positive for S100/SOX10
- Mitosis is usually low (<4/10HPF).
- Degeneration change:
    - Degenerative nuclear atypia.
    - Cystic change

Schwannoma subtypes:

- Cellular Schwanoma
    - Usually head and neck region.
    - Hyperceullular without nuclear atypia.
    - No brisk mitosis.
    - Diffuse S100/SOX10 positivity.
    - D.D.: MPNST, M. Melanoma
- Ancient Schwannoma
    - Smudgy nuclear feature
    - No brisk mitosis
    - Cystic change
    - Hemorrhage
- Degenerative atypia
- Plexiform Schwannoma
    - Typical morphological features retained
    - D.D. Plexiform neurofibroma, leiomyoma.

## RADIOSURGERY OF SPORADIC VESTIBULAR SCHWANNOMAS - DR. EDUARDO LOVO (INTERNATIONAL CANCER CENTER, SAN SALVADOR, EL SALVADOR)

**Learning objectives**

- To understand the natural history, and basic strategies such as surgery, SRS and combined approaches
- To understand the effectiveness of radiosurgery for small vestibular schwannomas
- To understand the effectiveness of radiosurgery for large vestibular schwannomas
- Hearing preservation, pseudoprogression
- Case examples and regional experience



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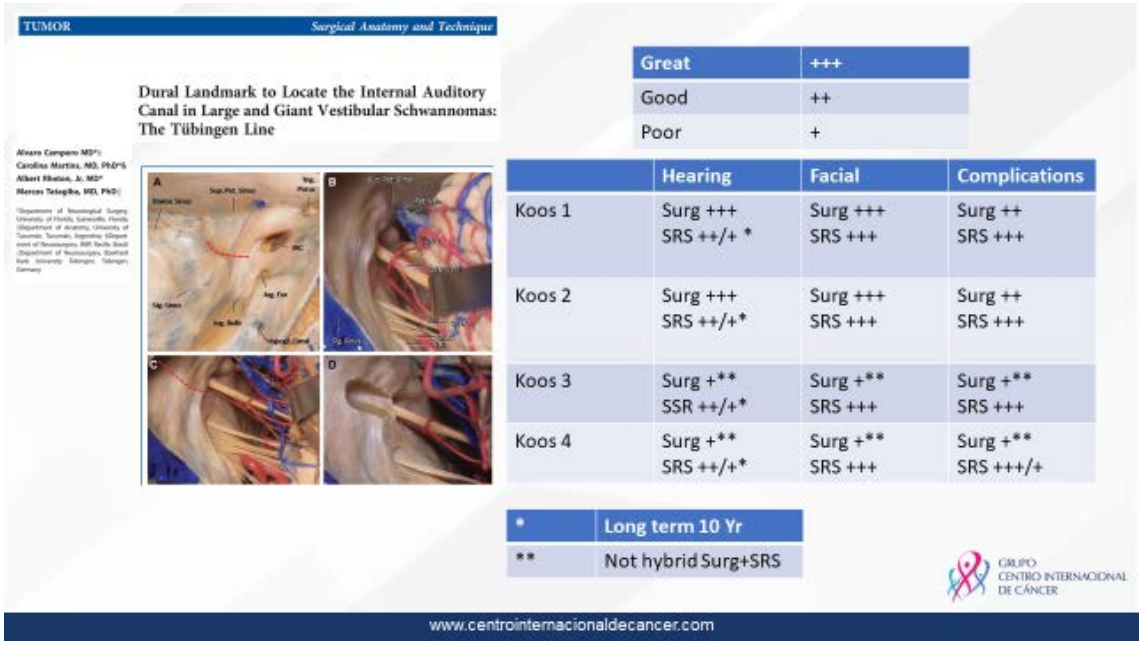
## Generalities

- Most common benign tumor of the cerebellopontine angle
- Tumor arising from the vestibular portion of the VIII
- Diagnosis after hearing loss, vertigo, tinnitus, disequilibrium
- Treatment strategies: Wait and see, surgery, radiosurgery, radiotherapy




- For small tumors (<1cm) Koos I and II **complete and safe** removal allows hearing preservation (Class A or B)
- Natural history 10 years 50% preservation (Long-term hearing preservation in vestibular schwannoma. Otol Neurotol 2010;31(02):271–275)
- Radiation 10 years 23% preservation
- Surgery (each center must measure their results) 70-85%

## Early radiosurgery vrs wait and see

- Larger volumes are associated with worse hearing preservation
- Average growth rates 1-2.9mm/year, unpredictable. (Sughrue ME J Neurosurg. 2010)
- Up to 38% of Koos 1 present 20% increase/1year (Lees KA Otolaryngol Head Neck Surg. 2018, Akiyoshi Ogino J Neurosurg 2021)
- SRS performed early after diagnosis resulted in improved hearing preservation (Regis J Neurosurg. 2010)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# SURGERY FOR VESTIBULAR SCHWANNOMAS - DR. LÁSZLÓ NOVÁK (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)

**Strategic paradigms**

Shifted from merely saving lives (1895 – finger technique)

TO

Best possible cranial nerve outcome

Oncological control

Posttreatment quality of life

**Growth of vestibular schwannoma 1.**

Comprise over 80% in CPA

Various growth rates reported – 1-2 mm/year up to 17 mm/year

Proportion of tumors that continue to grow – 15-85%

Determination of treatment – current hearing status, comorbidity

If hearing status is good and tumor size is not too large – γ

Most cases no rapid growth and treatment accompanies some grade of morbidity

Only pts. presenting significant growth or intractable symptoms should be considered for active management

**Growth of vestibular schwannoma 2.**

Significant growth in almost half of the cases (41,3%) in 5 years

53,3% within 10 years

Extrameatal location and deteriorated hearing (>20dB)

Predictive of tumor growth

Delayed tumor growth can occur after 5 years (25%)

Continued follow-ups



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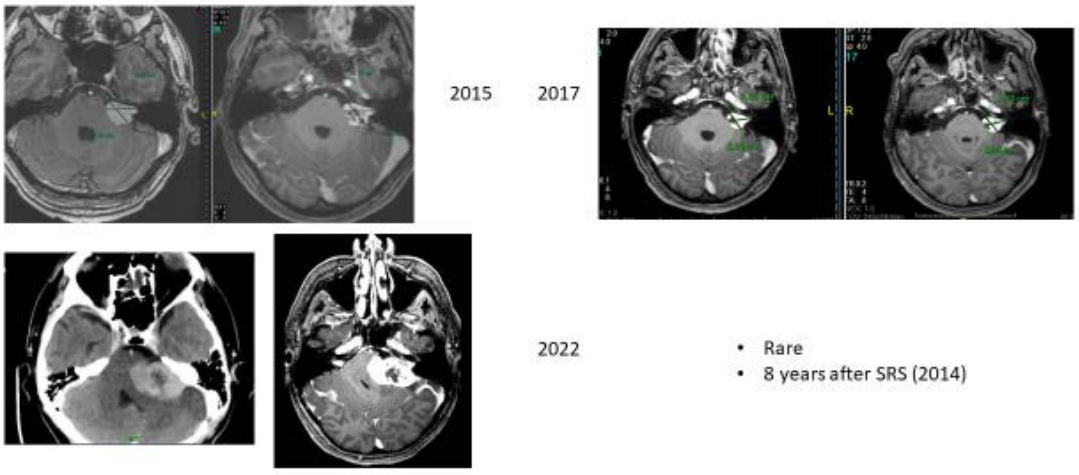
## Malignant transformation (PMNST)




**Guidelines of treatment**

- Level of evidence to provide treatment recommendations is low
- Observing VS – incidental, asymptomatic (SRS)
- Smaller VS – preservation of facial and hearing functions (SRS – microsurgery)
- Large VS – surgery (reduce mass effect)
    - Tumor characteristics
    - Surgeon's expertise
- Large VS – mass reduction is followed by SRS or observation
- Risk of regrowth rises with residual tumor volume

**Surgical approaches**

- Retrosigmoid
    - Panoramic CPA
    - Any size unrespectful of hearing
    - Pain, fistula
- Middle fossa
    - IAC, mainly for small, ensure hearing
- Translabirinthine
    - Lateral IAC, CN VII
    - Large tumors that grow towards to IAC
    - No hearing



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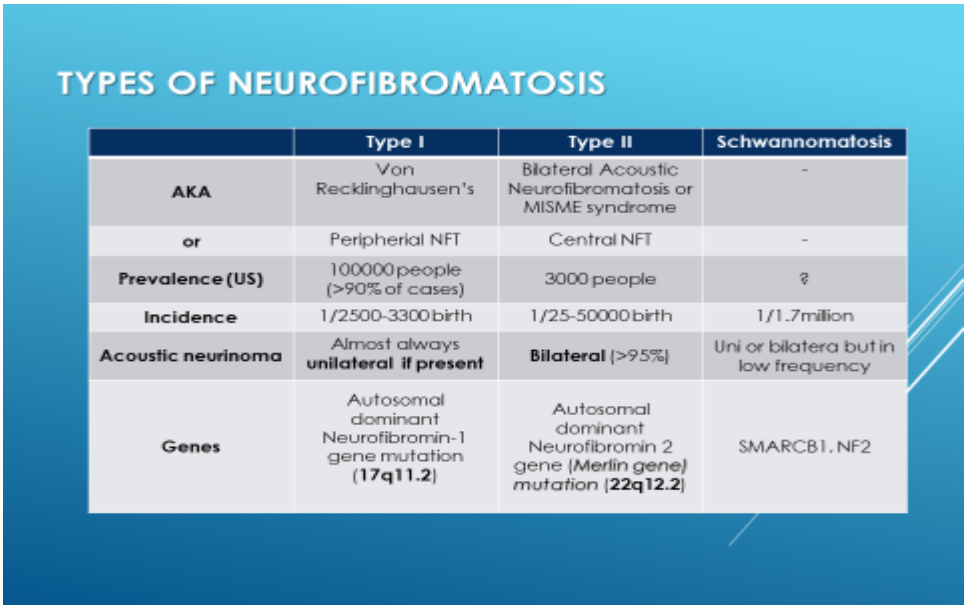
# RADIOSURGERY OF SCHWANNOMAS IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 2 - DR. JÓZSEF DOBAI (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)

## NEUROFIBROMATOSIS (DEFINITION)

The neurofibromatosis is a special group of genetic disorders. These changes cause tumor growth in the nervous system. The tumors called neurofibromas, are usually benign and grow on nerves in and outside the CNS. They produce abnormalities of the brain, skin, and many other organs.




| | Type I | Type II | Schwannomatosis |
|---|---|---|---|
| AKA | Von Recklinghausen's | Bilateral Acoustic Neurofibromatosis or MISME syndrome | - |
| or | Peripherial NFT | Central NFT | - |
| Prevalence (US) | 100000 people (>90% of cases) | 3000 people | ? |
| Incidence | 1/2500-3300 birth | 1/25-50000 birth | 1/1.7milion |
| Acoustic neurinoma | Almost always **unilateral if present** | **Bilateral** (>95%) | Uni or bilatera but in low frequency |
| Genes | Autosomal dominant Neurofibromin-1 gene mutation (**17q11.2**) | Autosomal dominant Neurofibromin 2 gene (*Merlin gene*) *mutation* (**22q12.2**) | SMARCB1, NF2 |

- **Wishart phenotype**: multiple cerebral and spinal lesions in people younger than 20 years and with rapid progression of the tumors
- **Feiling-Gardner-Phenotype**: single central tumors with slow progression after age of 20
- VS commonly develop at younger age
- VS behave more aggressively
- Greater number of associated cranial deficits
- Majority of NF2 pts acquire significant bilateral hearing loss
- For diagnosis of VS, histology not required
  - MRI crucial
- Tumor growth – compression of surrounding tissues, closing CSF pathway leads hydrocephalus, brain impactation
- **Congenital NF2**: bilateral schwannomas develope in the first days or in first month of life, but they remains asymptomatic for decades



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## NF2 TREATMENT OPTIONS

1. Observation (wait and see)
2. Microsurgery
3. Irradiation - SRS / FSRS /FRT
    a. SRS : 11-14Gy
    b. HfSRS : 5x5Gy, 3x6Gy, 5x4Gy,
    c. FSRT: 10x3-4Gy or 50-57,6Gy in 1,8-2Gy per fraction
4. Systemic therapy - Bevacizumab (Avastin) – VEGF monoclonal antibody-angiogenesis inhibitor and lapatinib (epidermal growth factor and ErbB2 inhibitor)
5. Hearing rehabilitation ( eg. sign language)
6. Mental healthcare
7. Fetal genetic screening
8. Supporting care

# PLENARY LECTURE

## RADIOSURGERY OF NON-VESTIBULAR SCHWANNOMAS SPEAKER: DR. VLADISLAV BURYK (SIGULDA RADIOSURGERY CENTER, SIGULDA, LATVIA)

- Schwannomas are typically benign tumors arising from Schwann cells making up the nerve's myelin sheath
-

## Non-vestibular Schwannomas pathogenesis

- Schwannomas may arise sporadically or in association with Neurofibromatosis type 2 (NF2) as a result of mutations involving tumor suppressor protein, merlin (schwannomin)
- Unilateral Schwannomas are usually sporadic
- Bilateral Schwannomas are associated with NF2
- Schwannomas may arise sporadically or in association with Neurofibromatosis type 2 (NF2) as a result of mutations involving tumor suppressor protein, merlin (schwannomin)
- Neoplastic proliferation of Schwann cell differentiation leading to tumor cells growing diffusely within and along the nerves affecting the neural elements
- Schwannomas originate most frequently from the sensory cranial nerves. In the absence of neurofibromatosis, the motor nerves are involved extremely rare



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**Non-vestibular Schwannomas genetic**

- Schwannomas may arise sporadically or in association with Neurofibromatosis type 2 (NF2) as a result of mutations involving tumor suppressor protein, merlin (schwannomin)
- Schwannomas only common and constant genetic alteration, regardless of their location, is the loss of part of chromosome 22 which can be found in up to 50% of these tumors
- Schwannomas associated with NF2 are due to deletion of NF2 locus (22q12.2) which encodes a tumor suppressor protein, merlin (schwannomin)

**Non-vestibular Schwannomas gross and microscopic pathology**

- Schwannomas are composed of spindle cells which demonstrate two growth patterns:
- Antoni type A pattern: elongated cells are densely packed and arranged in fascicles. Palisades are sometimes seen; when prominent these form Verocay bodies
- Antoni type B pattern: cells are less compact and are prone to cystic degeneration

Schwannoma Variants:

- Ancient Schwannoma
- Cellular Schwannoma
    - predominantly composed of Antoni A tissue
    - no Verocay bodies
    - most commonly found in a paravertebral location, or trigeminal nerves (CN V)
- Melanotic Schwannoma : dense melanin pigment
- Plexiform Schwannoma
    - usually arise from skin or subcutaneous tissues
    - usually diagnosed at birth or childhood
    - usually sporadic, but rarely associated with NF2
    - should not be confused with plexiform neurofibromas
        - associated with NF1
        - may undergo malignant change



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# SRS/SRT OF BENIGN INTRACRANIAL MENINGIOMAS - SPEAKER: DR. AMR EL-SHEHABY (CAIRO GAMMA KNIFE CENTER, NASSER INSTITUTE, CAIRO, EGYPT)

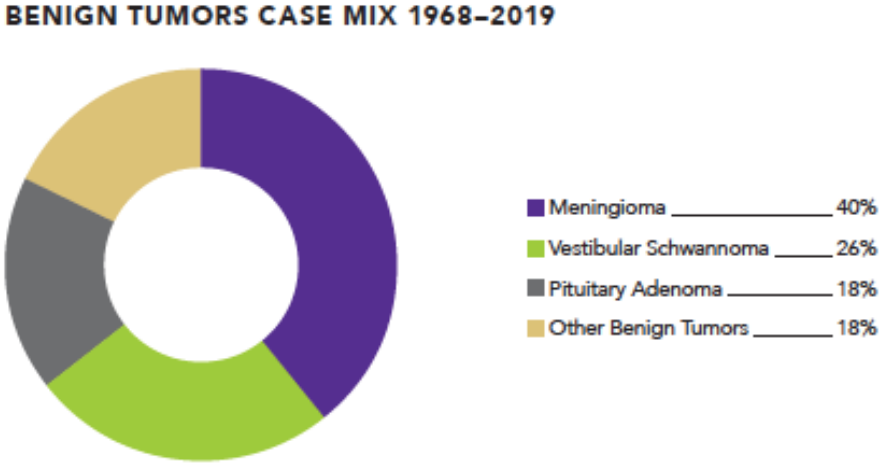
## Outline

- Epidemiology
- Basal/Non-Basal Meningiomas
- Non-Basal Meningiomas
- Basal Meningiomas
    - Anterior Fossa (Parasellar/Perioptic)
    - Posterior Fossa (Special Attention To Cpa, Fm)
- Incidental Meningiomas
- Stereotactic Fractionated Radiotherapy (Srt) For Meningiomas (Single-Session, Srt, Hsrt, Staged)

## Epidemiology

- Second most common CNS neoplasm
- ~18 % of all intracranial tumors
- Incidence of meningiomas is estimated to be 8.6 per 100,000
- According to the central Brain Tumor Registry of the United States estimates that there will be approximately 34,210 new meningioma cases in the United States in the year 2020
- Majority are benign
- Of the histologically identified meningiomas diagnosed between 2013 and 2016 in the United States, 79.3% were classified as WHO grade I, 17.7% as grade II, and 1.7% as grade III

***Ostrom QT, Cioffi G, Gittleman H, et al.*** *CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. Neuro Oncol. 2019;21(Suppl 5):v1-v100.*



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## Basal/non-basal meningioams

- Skull base/basal meningiomas are often suitable for GK because of the higher incidence of surgical complications after microsurgery for many skull base meningiomas
- Convexity or falcine meningiomas may be suitable for GK as well, but most patients with symptomatic larger tumors generally are considered for craniotomy and resection as the first line option in patients eligible for general anesthesia and resection
- The ratio of non-basal to basal meningiomas is 2.3/1
- SRS ratio for non-basal to basal meningiomas is 1/3

*Pinzi V, Biagioli E, Roberto A et al (2017) Radiosurgery for intracranial meningiomas: a systematic review and meta-analysis. Crit Rev Oncol/Hematol 113:122–134*

## Problem with benign meningiomas

- Locally compressive
- Can invade brain tissue and surrounding structures
- Recur after resection
- Multiplicity
- 10 - 20 % are atypical or anaplastic (malignant) and clinically associated with significant morbidity and mortality
- Even among WHO grade1 meningiomas varying degrees of proliferation index (MIB-1)



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# SRS/SRT OF ATYPICAL AND ANAPLASTIC MENINGIOMAS - SPEAKER: PROFESSOR ELITSA ENCHEVA (MEDICAL UNIVERSITY VARNA, VARNA, BULGARIA)

## Meningioma

- The most common primary CNS tumors
- Heterogeneous group of tumors and outcomes vary with
  - Histological type
  - Molecular genetic findings
  - Location
  - Tumor size/volume
  - Presenting clinical characteristics
  - Treatment

## WHO classification system

- **WHO grade I benign meningiomas** - the most common type (80%) with 9 subtypes and slow growing in nature- longer follow up needed
- **WHO grade II (20-35%)- atypical,** chordoid and clear cell meningioma-higher rate of local recurrence
- **WHO grade III (3%)- anaplastic (malignant)**, papillary and rhabdoid meningioma- rapid growth and higher mortality

## World Health Organization (WHO) 2000 classification system

- 314 meningiomas resected between 1994 and 2003 (archives of the Western General Hospital's neuropathology unit in Edinburgh)
- On reclassification
  - 78% grade I
  - 20.4% grade II
  - 1.6% as grade III
  - With regard to grade II meningiomas classified by using the WHO 2000: **Atypical meningiomas are diagnosed more frequently under the current WHO classification system than they were under the previous classification systems**
  - 38.1% had originally been classified as grade I prior to 2000
  - 13.6% had originally been classified as grade I after 2000
  - In most cases, reclassification was **due to formal counts of mitotic figures**
  - interobserver variability is likely to remain because of the subjective nature of some of the criteria



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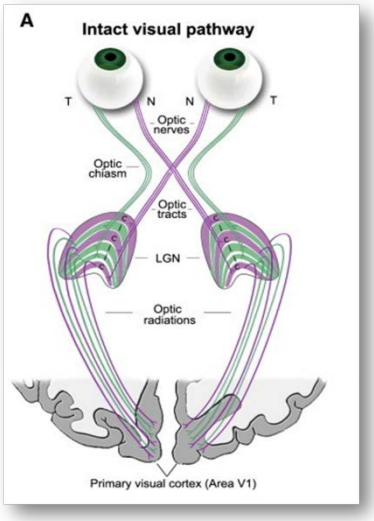
## SESSION II SRS/SRT OF SELLAR TUMORS

### SRS/SRT IN VICINITY TO ANTERIOR OPTIC PATHWAYS - DR. VLADISLAV BURYK (SIGULDA RADIOSURGERY CENTER, SIGULDA, LATVIA)

Visual Pathway

- Optic Nerves
- Optic Chiasm
- Optic Tracts
- Lateral Geniculate Nucleus
- Optic radiations
- Primary visual cortex




**BRIEF ANATOMY OF OPTIC PATHWAYS**

Visual pathways consist: OPTIC NERVE, OPTIC CHIAZM, LATERAL GENICULATE NUCLEUS, OPTIC RADIATIONS, PRIMARY VISUAL CORTEX

The VISUAL PATHWAY originates from the RETINAL PHOTORECEPTORS.

The AXONS OF RETINAL GANGLION CELLS gather together and FORM THE OPTIC NERVE.

THE ANTERIOR OPTIC APPARATUS comprises the OPTIC NERVES, CHIASM, AND OPTIC TRACTS;

these structures are typically defined on NEUROIMAGING STUDIES and CONTOURED APPROPRIATELY.

OPTIC NERVES pass through the approximate CENTER OF EACH ORBIT and are encompassed by the rectus muscles and periorbital fat.

From each globe, they angle rostrally to pass THROUGH THE OPTIC CANALS and EXIT NEAR THE ANTERIOR CLINOID PROCESS.

Both nerves MEET AT THE CHIASM.

Typically, the CHIASM lies ABOVE THE DIAPHRAGMA sellae and the pituitary gland, CROSSING JUST ANTERIOR TO THE PITUITARY STALK

However, ~ 30% of patients demonstrate either a pre- or postfixed chiasm.

A prefixed chiasm overlies the tuberculum sellae;

a postfixed chiasm, above the dorsum sellae.



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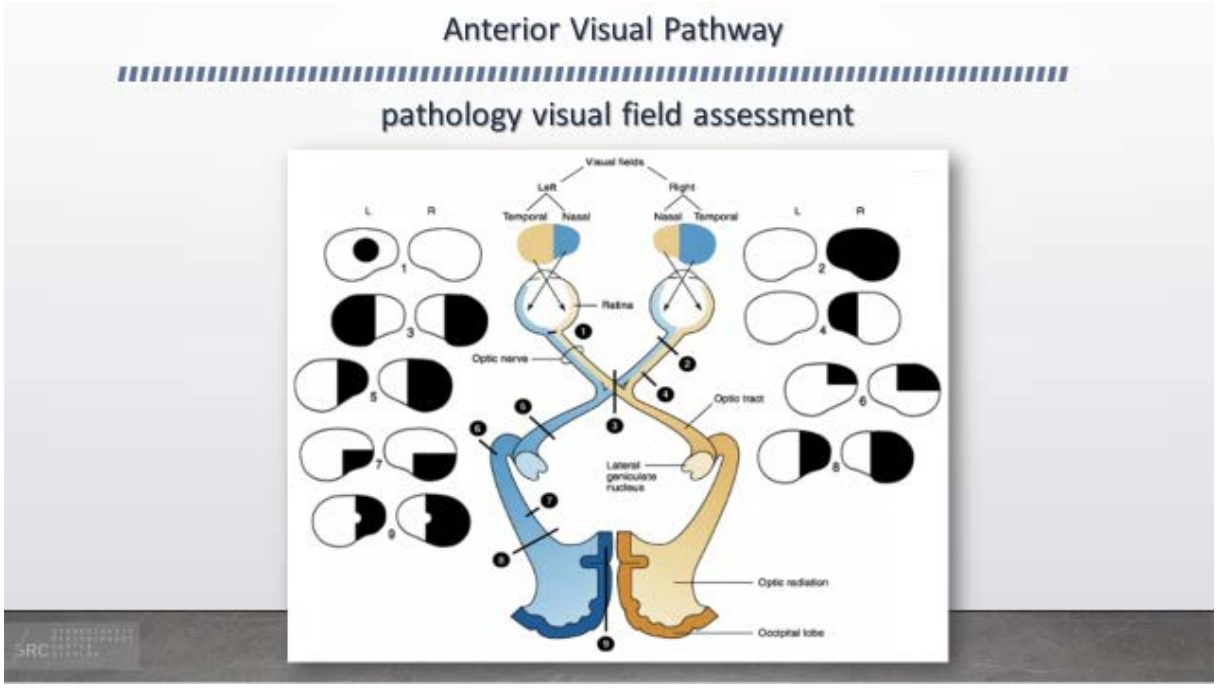


MEDIALLY LOCATED FIBERS cross to the CONTRALATERAL OPTIC TRACT, whereas LATERALLY LOCATED FIBERS remain in the IPSILATERALLY LOCATED TRACT.

The optic tracts represent the visual projections just beyond the chiasm

**Anterior Visual Pathway neighboring structures:**

There are neighboring structures around ANTERIOR VISUAL PATHWAY,

ANTERIORLY : ANTERIOR CEREBRAL ARTERIES and their communicating artery

POSTERIORLY: pituitary gland stalk, hypothalamus

SUPERIORLY: 3rd ventricle

INFERIORLY: Sphenoid Sinus, Pituitary gland

LATERALLY: Cavernous Sinus, CN III, IV, V1, V2, VI , ICA

and these structures can be a place of origin of pathological processes involving anterior visual pathways

**Anterior Visual Pathway pathology:**

- tumors of the eye globe
- orbital tumors/ optic nerve sheath meningioma, optic nerve glioma, metastases, cavernoma
- tumors of the optic canal, superior orbital fissure and sphenoid wing, sella turcica, ACF, MCF



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**Anterior Visual Pathway pathology clinical symptoms**

- Visual acuity impairment
- Ophtalmoparesis
- Exophtalmus
- Headache
- Hypopituitarism
- Trigeminal neuralgia
- Epileptic seizures

## ROLE OF SRS/SRT IN MANAGEMENT OF PITUITARY ADENOMAS - DR. JÓZSEF DOBAI (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)

Central location in head – near to critical structures (optic pathway, brain stem, temporal lobe, hypothalamus, cranial nerves, vascular elements (Internal Carotid Artery)

Benign tumors arise from cells of anterior pituitary gland

Represent 10-20 of all primary tumors of CNS

**Types:**

- non- functioning adenoma ( 1/3 ) – absence of hormone secretion
- secreting adenoma (2/3) – intensive hormone production by tumor cells
  - prolactinoma ≈ 20-30%
  - GH ≈ 50%
  - ACTH ≈ 40-65%

**Historically**

– 1968 January, Sophiahemmet Hospital, Stockholm Sweden - first SRS treatment of pituitary adenoma

**Treatment options**

- Regular follow up with MRI
- Conservative management – pharmacological treatment
- Surgery
- Irradiation

Primary treatment is usually pharmacologic or surgery but in selected cases radiosurgery acceptable also

When initial treatment fails irradiation treatment can use SRS/SRT.



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**SRS/SRT**

- Initial treatment (in selected cases – eg. medically inoperable patient, patient refuse other treatment)
- Adjuvant treatment – who had subtotal resection
- Salvage treatment – growth of residual

**Treatment options**

- Regular follow up with MRI
- Conservative management – pharmacological treatment
- Surgery
- Irradiation

Primary treatment is usually pharmacologic or surgery but in selected cases radiosurgery acceptable also

When initial treatment fails irradiation treatment can use

**SRS/SRT**

**SRS/SRT delivery systems**

- Gamma Knife
- Linear accelerator sytems
- Cyberknife (robotic LINAC)
- Proton therapy

**Goals of radiosurgery**

- Stop tumor growth, stabilization
- Shrinkage may occure,but it is not necessary
- Normalize hormonal hypersecretion
- Minimize loss of normal hormonal secretion
- Avoid radiation injury to adjacent structures
    1. Brainstem
    2. Optic apparatus
    3. Temporal lobes



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# ROLE OF SRS/SRT IN MANAGEMENT OF CRANIOPHARYNGIOMAS - DR. AMR EL-SHEHABY (CAIRO GAMMA KNIFE CENTER, NASSER INSTITUTE, CAIRO, EGYPT)

- Craniopharyngioma management is a nightmare
- Why?
  - Surgery
  - Radiotherapy
  - Intracavitary irradiation/chemotherapy
  - Interstitial brachytherapy
  - Stereotactic radiosurgery
- No single treatment mode has been found to provide effective LONG-TERM CONTROL with minimal complications

## Surgical results

- Tumor control
  - Complete resection rate (45-90%)
    - 5 year control 90%
  - Partial resection
    - 5 year control as low as 15%
- Mortality rate
    - Partial resection 4%
    - Aggressive resection 17%
- Morbidity rate 80%
    - pituitary dysfunction, hypothalamic dysfunction, and visual and neurocognitive deficits

## Radiotherapy results

In external beam radiotherapy (EBRT), photon beam radiation was delivered using a limited number of fixed fields, usually two to six, on a target defined on the base of two-dimensional (2D) conventional and more recently three-dimensional (3D) conformal radiotherapy planning

Because of this limited number of fields used, the final radiation dose was less conformal to the target. This, together with the lack of image guidance, determines that large portions of normal tissues receive potentially harmful radiation doses

10-year recurrence-free survival rates of 81 to 91% after subtotal tumor removal followed by RT, with 46 to 58% of the survivors living a normal independent life

Hetelekidis S, Barnes PD, Tao ML, et al: 20-year experience in childhood craniopharyngioma. Int J Radiat Oncol Biol Phys 27:189–195, 1993



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*Rajan B, Ashley S, Gorman C, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. Radiother Oncol 26:1–10, 1993*

Radiotherapy is not without hazards. There are reports of radionecrosis, optic neuritis, malignancies and cognitive disturbances in young children following RT

Serious morbidity after RT is reported in 6 to 18% of patients

*Rajan B, Ashley S, Gorman C, et al: Craniopharyngioma—a long-term results following limited surgery and radiotherapy. Radiother Oncol 26:1–10, 1993*

The American study with the longest follow up (median 17 years) in the treatment of craniopharyngioma with combined surgery and RT reports radiation-related complications in 58% of the children and 46% of the adults

The deaths of 41% of the adult patients, in whom further tumor growth did not occur, were related to complications from RT

*Regine WF, Mohiuddin M, Kramer S: Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. Radiother Oncology 27:13–21, 1993*



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# SESSION III IMAGING FOR STEREOTACTIC RADIOSURGERY

## IMAGING PROTOCOLS FOR RADIOSURGERY: STANDARD OPTIONS AND BEYOND - PROFESSOR ERVIN BERÉNYI (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)

**Information provided by the imaging**

- CT
  - X-ray absorption
- MRI
  - T1 and T2 relaxation properties
  - Diffusion characteristics of the water molecule
    - Independent of spatial direction (DWI - trace, ADC)
    - Depending on spatial direction (DTI - FA, MD, etc.)
  - MRS, MRSI
  - Molecular imaging - metabolic imaging (NAA, Cho, Cr, Lac, etc.)
  - fMRI
  - OxyHb/DeoxyHb ratio - active cortical areas (sensory, motor, speech, memory, etc.)
- PET, PET-CT, PET-MRI
  - Metabolic imaging depending on the positron emitting tracer (F18-FDG, F18-DOPA, F18-PSMA, C11-Cho, C11-Met, etc.) – and the imaging properties of the hybrid imaging system.

**Properties and usefulness of different modalities in terms of therapy-guidance**

- CT
  - The most accurate tool for the defining of the therapeutic space, practically without any distortion, and it is characterized by high resolution
- MRI
  - Modality, which provides various extremely valuable information about soft tissues,
  - very important to know the distortion of spatial mapping, which is not only vendor dependent, but also specific to the equipment.
- PET
  - Modality that provides valuable metabolic information with low resolution

**Distortion of MR imaging affecting brain radiation surgery**

- Sequence independent distortion
  - Non-linear distortion depending on the X, Y and Z gradients
  - constant
  - vendor dependent
  - Manufacturer's 2D or 3D optimization required



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    - for radiation therapy planning routine manufacturers 3D correction would be optimal
- Sequence dependent distortions
    - Caused by (standard) inhomogeneity of the main magnetic field (B0)
    - B0 inhomogeneity may be higher at higher field strength
    - Different sequences are sensitive to it to varying degrees.
    - The harsh distortion at the air-bone boundaries caused by large differences in susceptibility
    - A chemical shift occurs at the boundary of high-fat and high-water content areas - due to the different resonance, faulty spatial localization is created along the frequency coding gradient

**Main logical points of the design of stereotactic brain radiation surgery**

- 3D space without any distortion is defined by the CT – therefore the CT is the main determinant of the planning coordinate system. This is the reference space.
- Information's from MRI and PET should be registered into the CT's 3D reference space with appropriate modifications
- Different MRI samplings (T1W, T2W, DWI, DTI, fMRI) have different distortions, but if any MRI information is registered into the 3D T1W space, then the resulting common information space can be combined with CT reference space in the second step.

**Conditions and characteristics of registration**

- Correct resolution (thin slices with isotropic voxels)
- Appropriate image quality (ROI, properly selected registration algorithm with parameters correctly configured by the user landmarks, thresholds, etc.)
- Rigid or non-rigid registration: in stereotaxic radiosurgery, rigid registration is commonly used
- Extracranially, different anatomical regions have different challenges (physiological triggering, insertion of fiducial markers, unique registration methods)
- Registration must be validated, repeatable and robust
- Registration can be automatic
- In this case, well-defined anatomical points, fiducials are fundamental
- Initially semiautomatic registration can become automatic with manual correction in a self-learning environment
- At the same time, the "goodness" of registration is a necessary check
- At different points in the registration process, algorithms of artificial intelligence can be useful
- It is recommended to establish an institutional registration protocol



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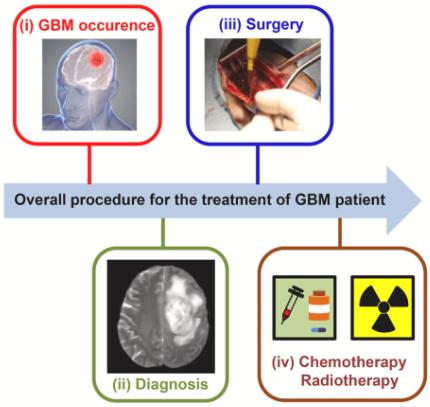
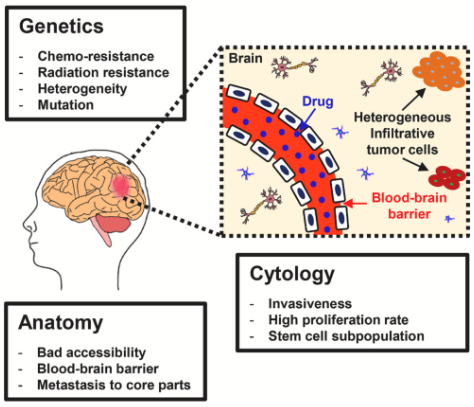
## ROLE OF FUNCTIONAL AND METABOLIC MRI IN RADIOSURGERY - DR. TAMÁS KINCSES (UNIVERSITY OF SZEGED, SZEGED, HUNGARY)

# Standard care of gliomas

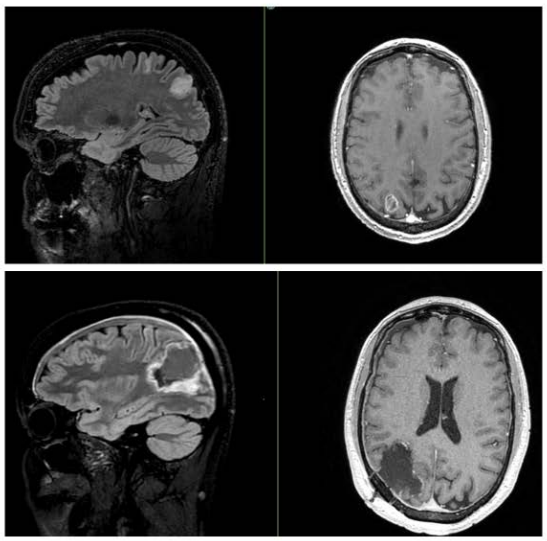


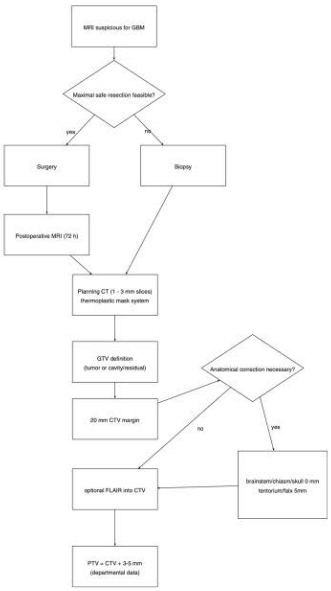




**Unresolved issues**

- Noninvasive diagnosis is not possible
- Identification of best biopsy site
- Avoiding eloquent regions
- Follow up of recurrence
- Prognostic factors

# Target delination of GBMs — ESTRO-ACROP







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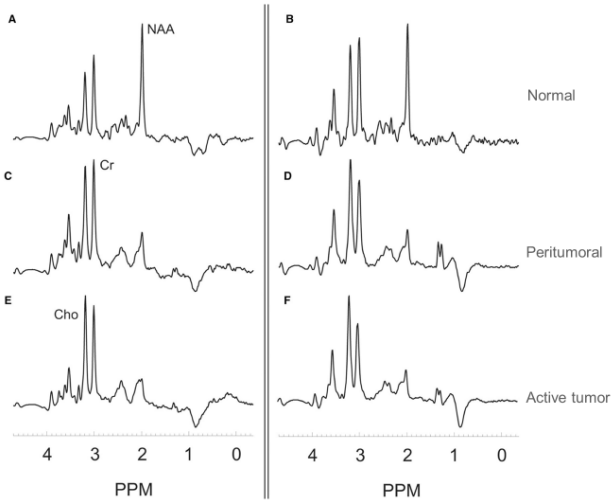
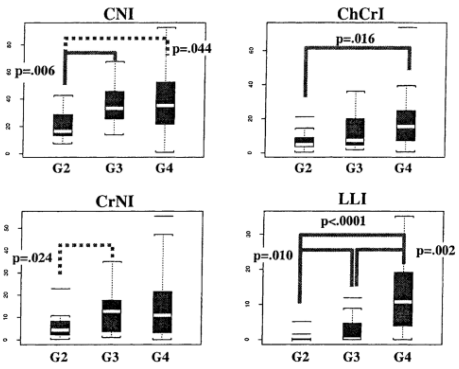
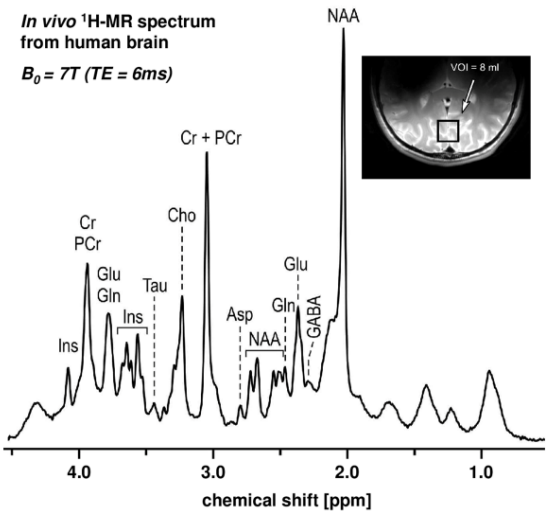
# MRS: signature of malignancy

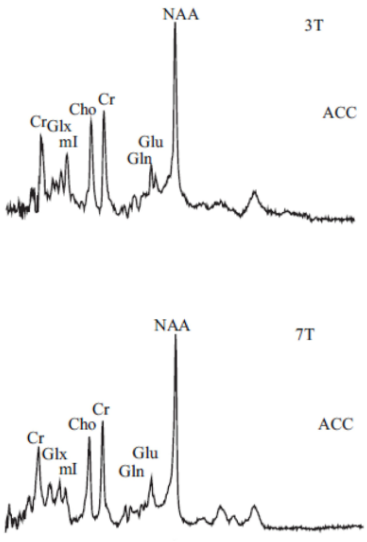



*Li et al., 2002*

# MR spectroscopy



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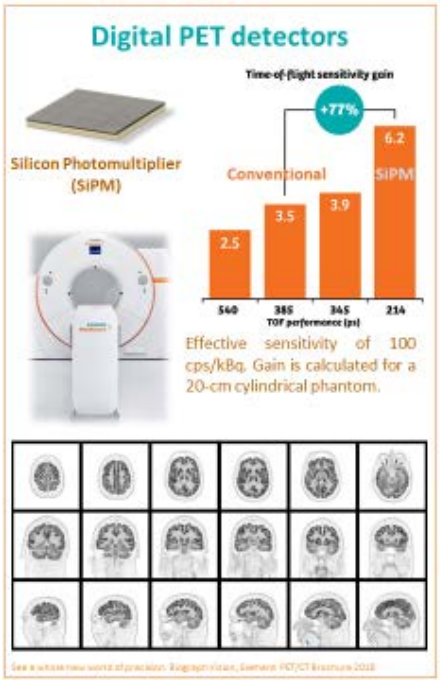
# PET IMAGING FOR RADIOSURGERY - DR. ILDIKÓ GARAI (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)

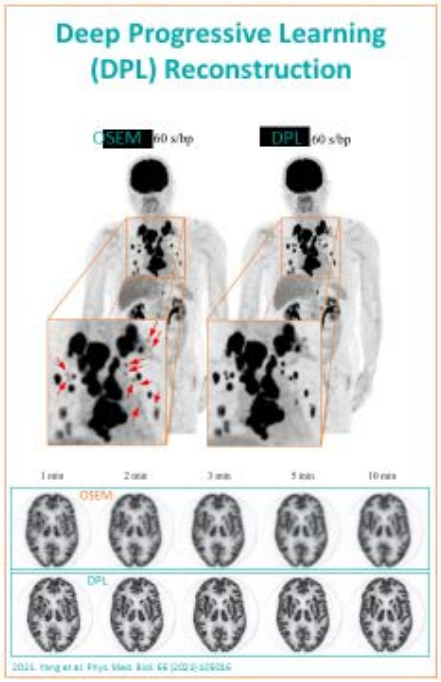
## SRS as a modality of precision medicine

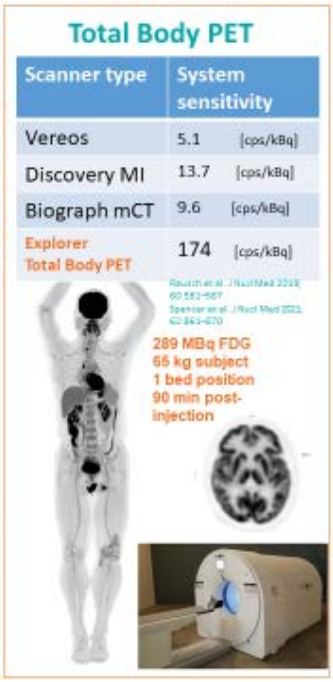
Non-surgical radiation therapy used to treat functional abnormalities and small tumors of the brain.

It deliver precisely –targeted radiation in fewer high –dose treatments than conventional RT.

Requirement: high-resolution imaging to determine precisely coordinates of target(s)




## Conventional and investigational PET tracers in brain tumours

- F-18 FDG
- Aminoacid tracers
  - C11 MET
  - F18 FET (fluoroethyltyrosine)
  - F18 DOPA
- Hypoxia tracers: F18 MIZO, FAZA
- Others: FLT, somatostatine analogues, choline



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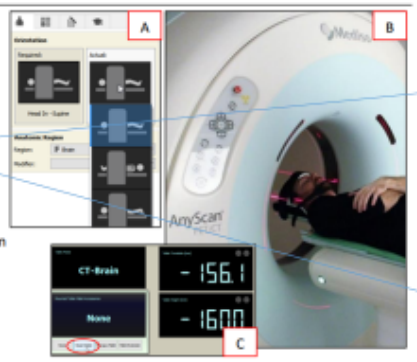
# Brain PET/CT protocol

## Brain FDG

1. **Scanner preparation:**
   Standard **Daily QC** before patient scan
2. **Patient preparation**
   - **6 hours fasting** before PET scan
   - Injected activity: **3.7 MBq***body weight (kg)
   - PET acquisition start time:
     **40 minutes** after **$^{18}$F-FDG** injection
3. **Patient positioning**
   - Head holder on patient bed
   - Head holder stripes on patient head, arms down
   - Positioning with laser in the CFOV transaxially
   - Patient Orientation: **Head In – Supine**
   - Head holder selection in Nucline



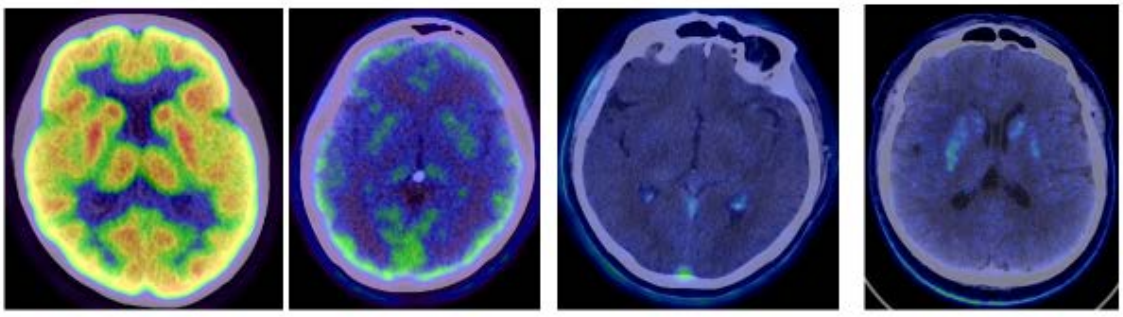

## Brain amino acid tracers

2. **Patient preparation**
   - **4 hours fasting** before PET scan
   - Injected activity: **3.7** MBq*body weight (kg)
   - PET acquisition start time:
     **10 minutes** after $^{11}$C-MET injection

2. **Patient preparation**
   - **4 hours fasting** before PET scan
   - Injected activity: **180-200 MBq**
   - PET acquisition start time:
     **20 minutes** after $^{18}$F-FET

# Normal tracer distribution in a healthy brain

18F-FDG-PET/ CT | 11C-MET | 18F-FET | 18F-DOPA





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## PLENARY LECTURE

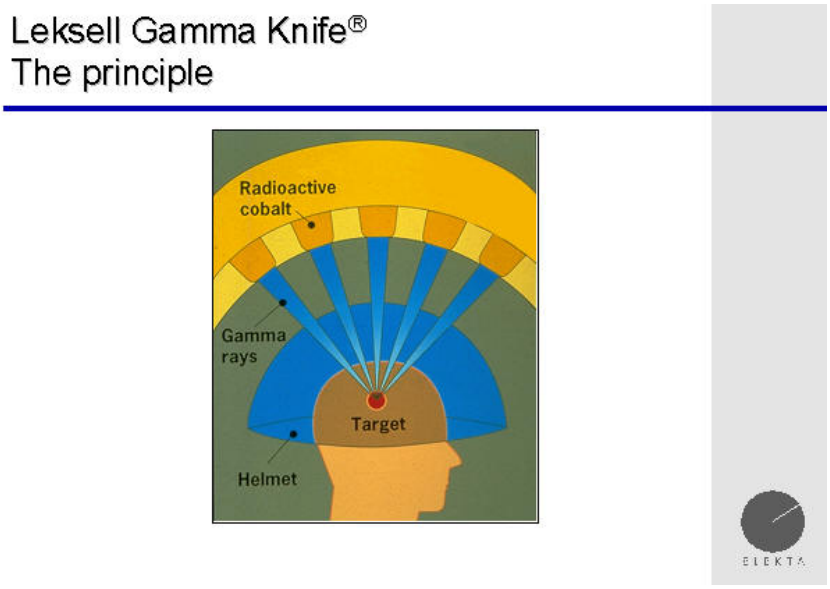
# GAMMA KNIFE VS. CYBERKNIFE VS. LINAC: ADVANTAGES AND LIMITATIONS - SPEAKER: MR. MIHÁLY SIMON (UNIVERSITY OF DEBRECEN, DEBRECEN, HUNGARY)

**Outline**

- Technical specifications
- Comparison
    - Patient immobilization
    - Margins
    - Dosimetry, planning

**Gamma knife**

- Highly focused gamma radiation from Cobalt 60 sources
- 192 individual beams
- Frame and frameless patient positioning
- Intracranial targets only
- Lesion size mostly limited to 35 mm, above that the effectiveness begins to decrease
- Onboard CBCT
- Infrared motion management system



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**CyberKnife**

- 6 MV
- 1000 MU/min dose rate
- Different collimation systems
  - Cones
  - MLC
  - IRIS
- Intra- and extracranial targets
- Orthogonal kV pair verification

**LINAC**

- 3D image verification (4D)
- 6 DoF tabletop
- SGRT capable
- FFF mode
- HD MLC

**Minimum requirements**

- Collimation, beam directions
  - SRS – MLC with ≤ 5mm leaf width or equivalent cone size
  - FSRT – MLC with ≤ 6.5 mm leaf width or equivalent cone size
- Treatment unit accuracy
  - SRS – 1mm
  - FSRT – 1.25 mm in head
- Positioning
  - SRS – invasive or non-invasive
  - FSRT – non-invasive



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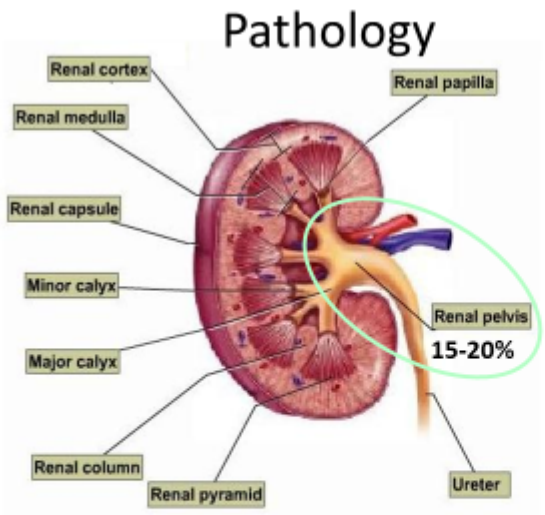
# SESSION IV_SRS/SRT OF RENAL AND ADRENAL GLAND CANCERS

## RENAL CANCER: OVERVIEW - PROFESSOR KATALIN HIDEGHÉTY (UNIVERSITY OF SZEGED, SZEGED, HUNGARY)

**Incidence of malignant tumors**

- Breast + prostate cancer ca. 20-30%
- Lung cancer. 15-20%
- Colorectal cc. 10-12%
- Gynacological tumors. 6-8%
- Head and neck tumors ca. 3-10%
- Bladder cancer. 3-4%
- Stomach, pancreas tumors. 2-3%
- Melanoma malignum. 2-3%
- Renal cc. 3%
- Brain tumors 2-3%
- 40 % incidental, asymptomatic (rutin abd. USG, CT, MRI)
- Haematuria, back pain, palpable mass, anaemia, fatigue
- Male-female 2:1




- **85% clear cell/renal cell cc.** (adenocc., hypernephroma, Grawitz-tumor)
- 12-14% papillar, sarcomatoid
- 4-6% chromophob
- 2-4% oncocytoma, - 1% Bellini chanel

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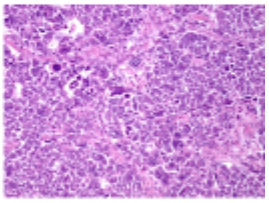
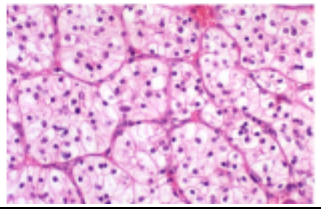
Etiological factors

Smoking (x4)
Obesity
Chemical exposure
Ionizing Radiation
VHL disease (2-3%, clear cell RCC)
MET germline mutations (80% papillary type RCC)
Familial (hereditary leiomyomatosis, etc.)

Wilms tumor-nephroblastom is rare, but 6% of all childhood tumors







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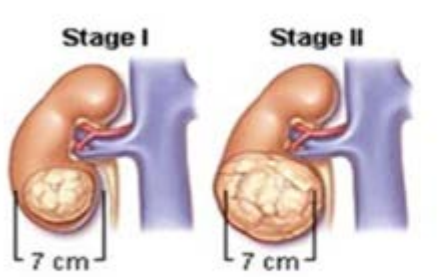
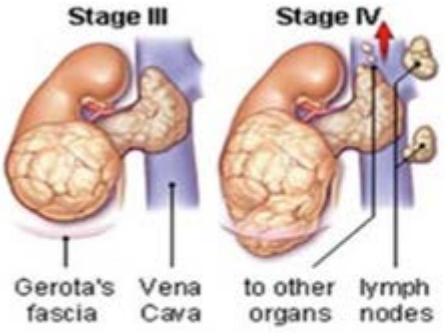
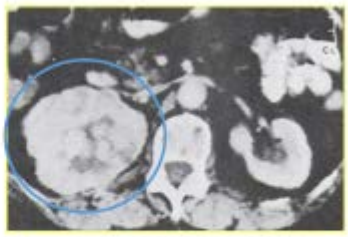
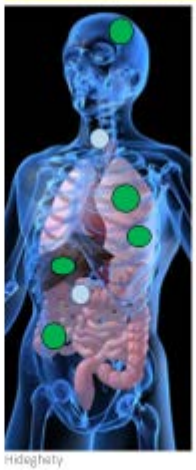



Kásler Miklós: Az onkológia alapjai





30 % metastatic at the diagnosis

| | |
|---|---|
| lung | 50-70% |
| lgl, bone, liver | 20-30% |
| suprarenal | 15-20% |
| brain | 5-8% |

Atypic
- Pancreas
- Thyroid

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## Pathomechanism

- Clear cell cc. (70–85%) → -**hypoxia induced pathway**

- Papillary II → - mTOR signal pathway
- papillary I (7–15%) → -cMet-RAF-MEK-ERK patway error

- chromophob (5–10%) → -mTOR

- Other collective duct, medullary

Escudier et al. Ann Oncol. 2012, 23: 65-71

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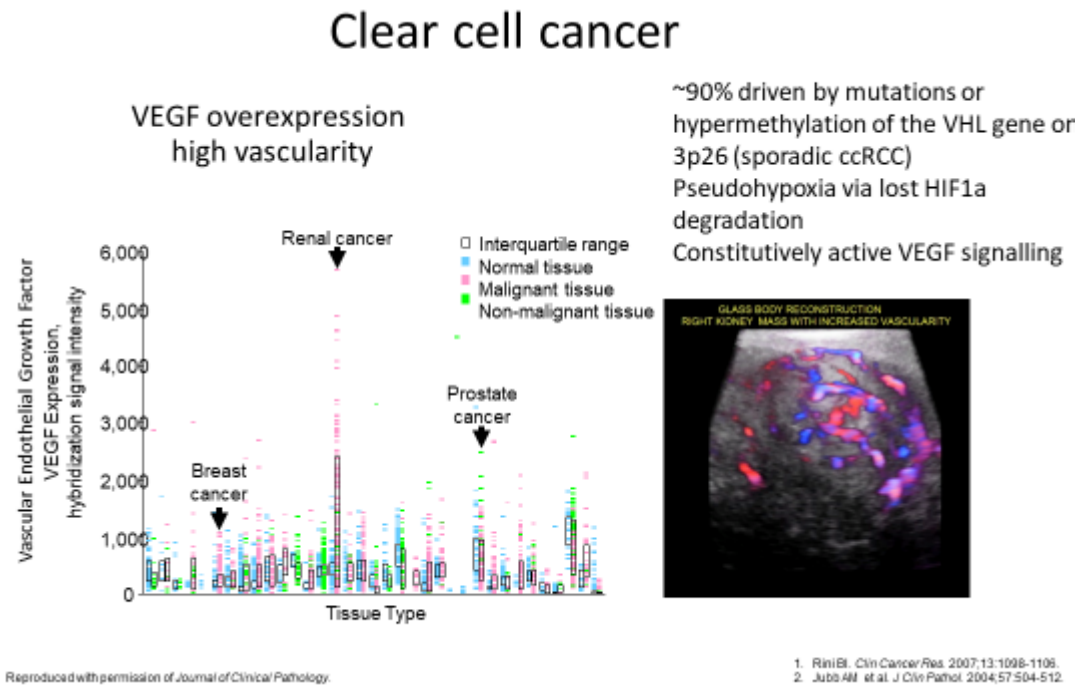


## RADIOSURGERY OF RENAL CANCER: INDICATIONS AND RESULTS - DR. ZSOLT CSELIK (VESZPRÉM COUNTY HOSPITAL, VESZPRÉM, HUNGARY)

### Epidemiology

- Kidney cancer incidence rates increased up to 4.1% in men per year and 3.3% in women between 2004 and 2008
- RCC is one of the ten most common malignancies in the developed world
- Majority of findings (90%) is adenocarcinoma - renal cell carcinoma (RCC)
- The rest of are urothelial (transitiocellular) carcinoma and Wilms tumour
- Appears predominantly in the older population (median age at diagnosis of 65 years)

### Diagnosis

- Could comes from lab diagnosis (blood and urine tests)
- Imaging:
  - US
  - or more accurate cross sectional imaging as CT, MRI (staging and therapy planning)
  - metabolic imaging - PET/CT* mainly for detecting recurrence, metastasis as the tracer excretion masks the tumour in the kidney (sensitivity of conventional CT vs. PET for detection of RCC is 91.7% vs. 60%**)
- Pathology



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** Yiyan Liu, The Place of FDG PET/CT in Renal Cell Carcinoma: Value and Limitations PMID: 27656421 PMCID: PMC5012103 DOI: 10.3389/fonc.2016.00201*

***Kang DE, White RL, Jr., Zuger JH, Sasser HC, Teigland CM. Clinical use of fluorodeoxyglucose F 18 positron emission tomography for detection of renal cell carcinoma. The Journal of urology 2004; 171(5): 1806-9*

**TNM**

- T1
  - T1a: tumor confined to kidney, <4 cm
  - T1b: tumor confined to kidney, >4 cm but <7 cm
- T2: limited to kidney >7 cm
  - T2a: tumor confined to kidney, >7 cm but not >10 cm
  - T2b: tumor confined to kidney, >10 cm
- T3: tumor extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota's fascia
  - T3a: tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
  - T3b: spread to infra diaphragmatic IVC
  - T3c: spread to supra diaphragmatic IVC or invades the wall of the IVC
- T4: involves ipsilateral adrenal gland or invades beyond Gerota's fascia
- *N*
  - *N0: no nodal involvement*
  - *N1: metastatic involvement of regional lymph node(s)*
- *M*
  - *M0: no distant metastases*
  - *M1: distant metastases*

**Standard therapy**

- Focusing on RCC
- Gold standard management for primary RCC is still surgery
- But cryotherapy and radiofrequency ablation (RFA) are also available (≤ 4 cm and limited by central location)
- Both of these procedures are invasive which can be problematic in the patients who may have a number of contraindications (eg. anticoagulative medications)
- In this cohort surgical procedures could generate further de novo chronic kidney disease or advancement of pre-existed renal dysfunctions



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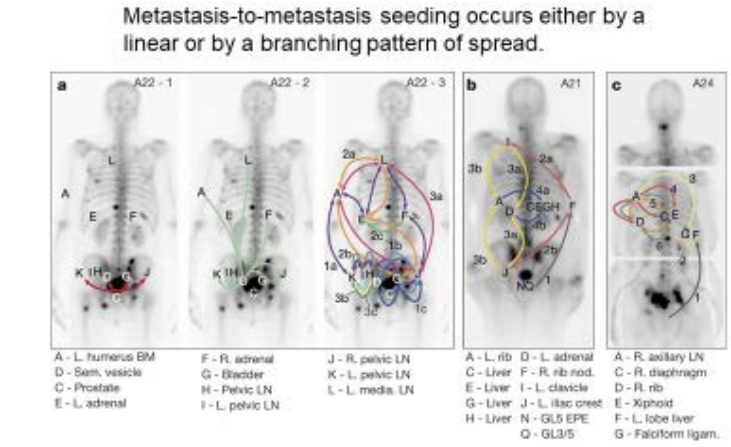
# IRRADIATION OF ADRENAL GLAND METASTASES - DR. ZOLTÁN LŐCSEI (UNIVERSITY OF PÉCS, PÉCS, HUNGARY)

## Theory

- Halstead (1894)
  - Tumor directly spreads from primery site to the lymph nodes and than to distant sites
- „Systemic Theory”
  - Cancer is a widespread disease from the beginning and the tumor is only a manifestation of the systemic disease
- Hellmann and Weichselbaum (1995)
  - Oligometastatic disease
  - Intermediate stage (limited number and site)
  - Not enough genetic changes for rapid spread
  - Only involving one or two sites




G Gundem *et al. Nature* **000**, E1-E5 (2015) doi:10.1038/nature14347

nature

## One definition of Oligometastases

Oligometastases can be defined clinically as a limited number of metastatic lesions ≤ 5 in a limited number organs ≤ 3, generally identified bí imaging.

## Presentation and definition of Oligometases

Syncronous oligometastases a clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour.



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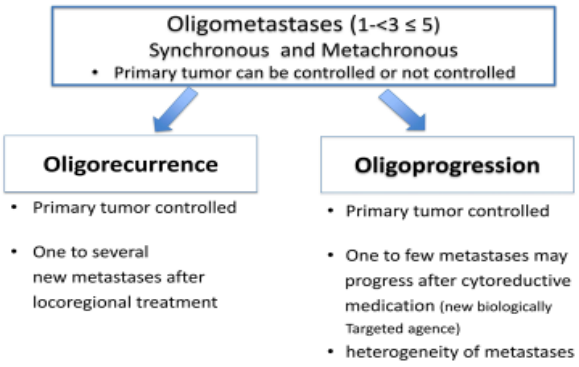
Metachronus oligometastasis the development of oligometastatic disease after treatment of the primary tumour. The interval for classification of metachronous versus synchronus is not standardized.



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# SESSION V RADIOSURGERY OF PROSTATE CANCER

## RADIOSURGERY OF PRIMARY AND RECURRENT PROSTATE CANCER: RESULTS - DR. MARIS MEZECKIS (SIGULDA RADIOSURGERY CENTER, SIGULDA, LATVIA)

- Work plan for ISRS Prosate cancer working group:
- Focus of interest: intermediate unfavorable, high- and very high-risk prostate cancer (NCCN classification)
    - Literature review - completed
    - Data base → publication of original data
        - In progress:
            - RedCap data base has been created
            - 196 records has been inserted, QoL data has been collected
            - 83 records (interm&high risk) from 2 clinics needs update to comply with minimum requirements
                - Spizenko clinic (Kyiv)
                - M. Skłodowskiej-Cuerie Oncology centr (Gliwice)
    - Guideline project
        - In progress

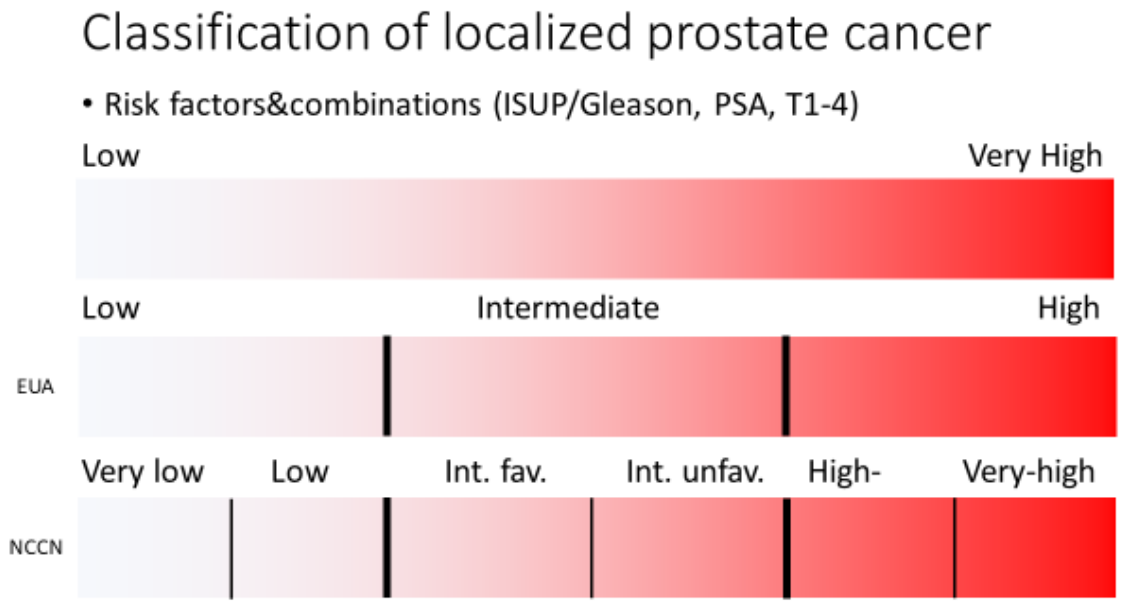




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**Table 4.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer**

| Definition | | | |
|---|---|---|---|
| **Low-risk** | **Intermediate-risk** | **High-risk** | |
| PSA < 10 ng/mL | PSA 10-20 ng/mL | PSA > 20 ng/mL | any PSA |
| and GS < 7 (ISUP grade 1) | or GS 7 (ISUP grade 2/3) | or GS > 7 (ISUP grade 4/5) | any GS (any ISUP grade) |
| and cT1-2a | or cT2b | or cT2c | cT3-4 or cN+ |
| **Localised** | | | **Locally advanced** |

*GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.*

**Table 4.3: International Society of Urological Pathology 2014 grade (group) system**

| Gleason score | ISUP grade |
|---|---|
| 2-6 | 1 |
| 7 (3+4) | 2 |
| 7 (4+3) | 3 |
| 8 (4+4 or 3+5 or 5+3) | 4 |
| 9-10 | 5 |

- Challenges of risk stratification
- PSA – high-grade tumor and low PSA
- Biopsy related problems
    - Biopsy often represents small volume of cancer
    - Routine practice: Double sextant biopsy→diagnosis→mpMRI
    - Best practice: suspicion of cancer (elevated PSA, DRI+)→ mpMRI →double sextant&targeted biopsy from suspicious areas on mpMRI
    - Accessibility of fusion/MRI guided biopsy
- Gleason score
    - describes phenotype not genotype of the cancer
    - Subjective (second opinion in pathology may give different Gleason score)



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# RADIOSURGERY OF PROSTATE CANCER: COMPLICATIONS AND THEIR AVOIDANCE - PROFESSOR ELITSA ENCHEVA (MEDICAL UNIVERSITY VARNA, VARNA, BULGARIA)

## Localized Prostate Cancer
## Treatment Options

- Watchful waiting
- Active surveillance
- Surgery
- Definitive radiotherapy +/- ADT
  - Conventionally fractionated RT
  - Brachytherapy
  - EBRT + Brachytherapy
  - Moderate Hypofractionated RT
  - SBRT (Ultrahypofractionated, Extreme hypofractionated)

## Prostate SBRT

- Only a decade ago SBRT for localized prostate cancer was considered as an experimental
- SBRT efficacy and safety proved in Phase III trials
  - PACE B
  - HYPO-RT PC

## Rationale for SBRT in Prostate Cancer

- Low alpha/beta ratio of 1.5-1.8
- Increased patient convenience
- Increased patient access
- More cost-effective than MHRT and EBRT

## Indications for SBRT in Prostate Cancer

- ASTRO, ASCO and AUA 2018
  - low
  - Intermediate risk disease
- NCCN 2022



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- COVID19 pandemic recommendation 2020
  - 5- to 7- fraction SBRT is preferred

**Complications/Side effects/Toxicity**

- Acute or early-during course of SBRT till 3 months
- Late- after 3 months post SBRT
- GI
  - Diarrhea
  - Bleeding
  - Bowel cramps
  - Flatulence
  - Fistula
- GU
  - Early -“urinary bother” symptoms, including frequency, urgency, reduced flow, and dysuria
  - Late-dysuria, frequency, urgency, stricture , spasm, reduced flow, hematuria, and rarely, fistulization, necrosis, ulceration, and incontinence
- Erectile dysfunction



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## PLENARY LECTURE

### IRRADIATION OF GYNECOLOGICAL CANCERS - SPEAKER: DR. FERENC LAKOSI (KAPOSI MÓR TEACHING HOPITAL, KAPOSVÁR, HUNGARY)

**Indications**

- Primary tumors- boost
- Pelvic/vaginal vault recurrences
- Nodal recurrences
- Oligometastatic disease
- Upcoming indications:
- Technical revolution, adaptive workflows, improved image quality
- BUT: limited number of series, mainly retrospective, SABR COMET trial (2pts)
- Need for prospective trials

C-ARM LINAC WITH IGRT

CYBERKNIFE

MRI-LINAC



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**Primary treatment:LACC-boost**

- MRI/CT- guided IC/IS BT is the standard of care

Upcoming SABR reports for patients not suitable for BT

Reasons:

- Medically unfit-Anaesthesia/Comorbidity
- Volume
- Technical insufficiency: no cervical os or rigid closed cervix, uterine malformation
- Non-available BT unit with advanced IS experience
- Fistula
- Patient refusal
- Limited number of publications with few patients

**Challenging situation:**

- Complex movement of the primary tumor-could be related to OARs filling status, pelvic floor muscle contraction
- Very close vicinity of OARs
- Inter-intrafractional variability of OARS (filling status, position), need for adaptation
- BT is a „best case scenario", at least for the primary, bladder and rectum
- N:31
- Indications: uterus bi-collis and bi-cornis (n= 1), refusal of Smit sleeve insertion (n= 3), refusal of brachytherapy (n= 7) and inability to find the cervical os and implant the Smit sleeve or loss of Smit sleeve and refusal of reinsertion (n= 22)
- Dose: 5x5-6Gy (27), 3x5 (N:2) (70% isodose line) (same as for BT pts)
- 30/31 completed CK boost therapy.
- 4 fiducials, no adaptation
- Predominant stage: IIB, 58%
- The median follow-up time was 40 months (range 5–84 months).
- The 1-, 3-, and 5-year OS rates were 89, 60, and 57% respectively
- Mean PFS was 41 months (range 2–84 months).
- 7 patients showed progression (28%)
- Only two LF (8%), LC rate of 92% after 3 and 5 years.
- Only 1 Gr.3 diarrhea
- 15 pts (48%) underwent intracervical curettage 3 months after completion of treatment of which 14 (93%) had complete pathologic response.



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