



RadioOnkologie und Strahlentherapie  
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Technische Universität München

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HelmholtzZentrum münchen

ARI  
TUM

# Meningeome

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low

Progression / aggressive growth  
Treatment resistance

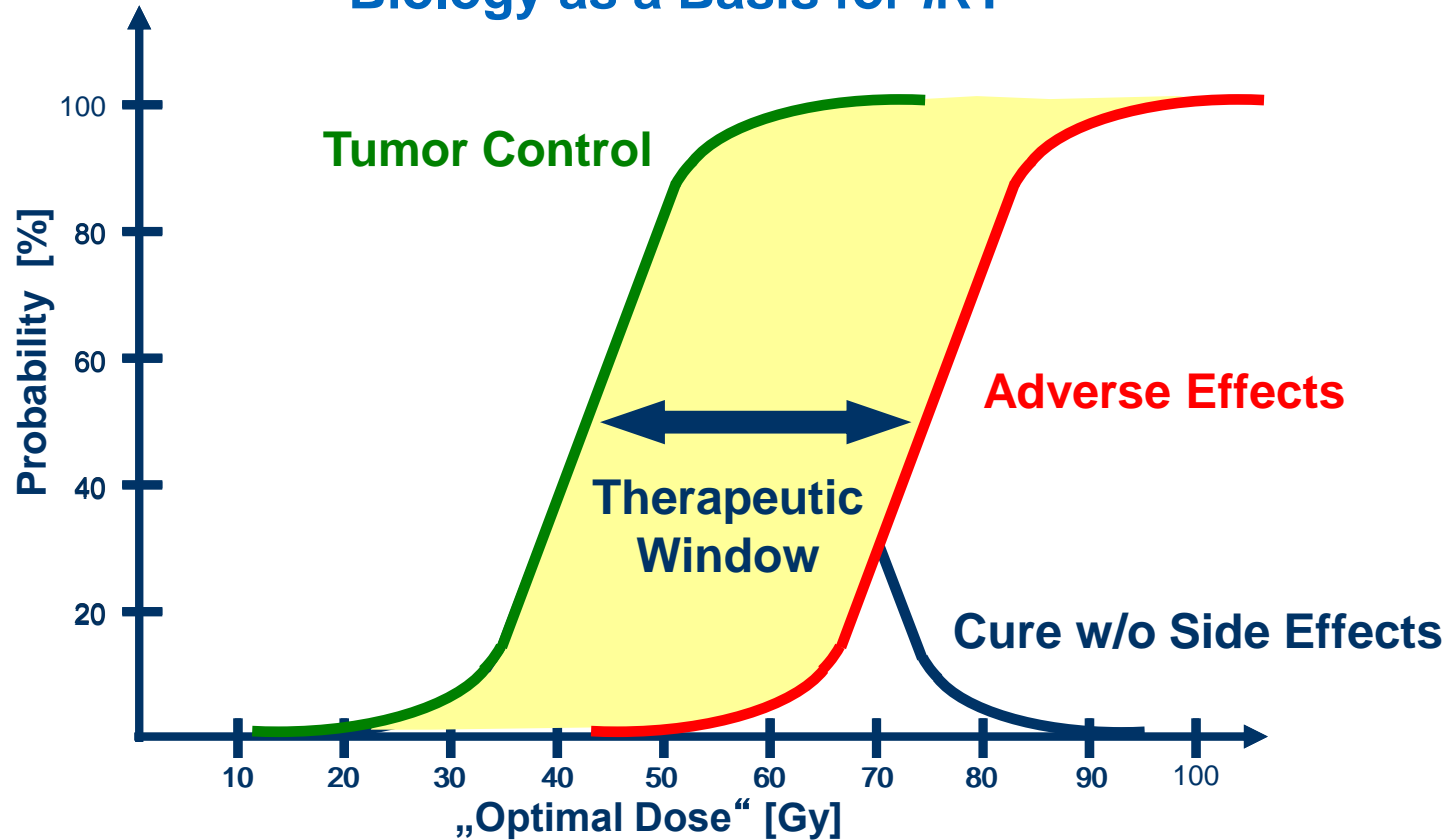
high

good

Prognosis

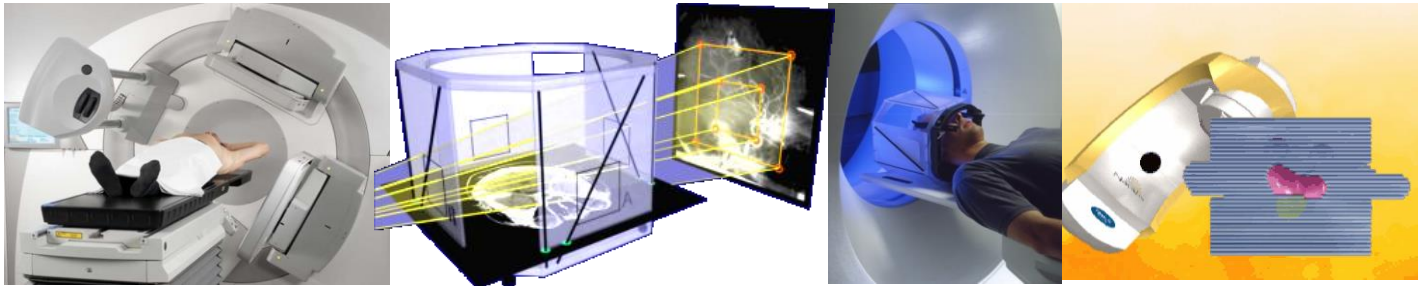
bad

## Holthusen-Curve: Dose-Response-Relationship Biology as a Basis for iRT

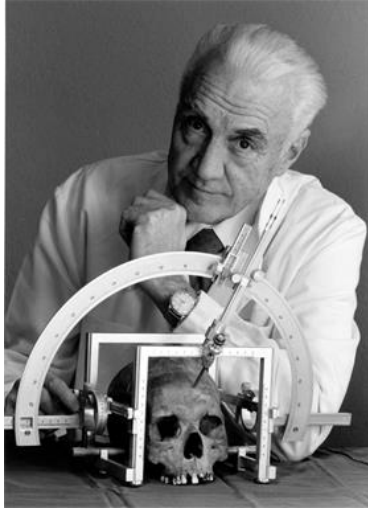


# Modern Techniques in Radiation Oncology *i*RT Concepts

- 3D - imaging – CT, MRI, PET etc.
- High Precision Radiotherapy (Radiosurgery, Fractionated Stereotactic....)
- Intensity Modulated Radiotherapy (IMRT)
- Particle Therapy (Protons, Carbon Ions, Neutrons and other)
- Image Guided Radiotherapy (IGRT)
- Adaptive Radiotherapy

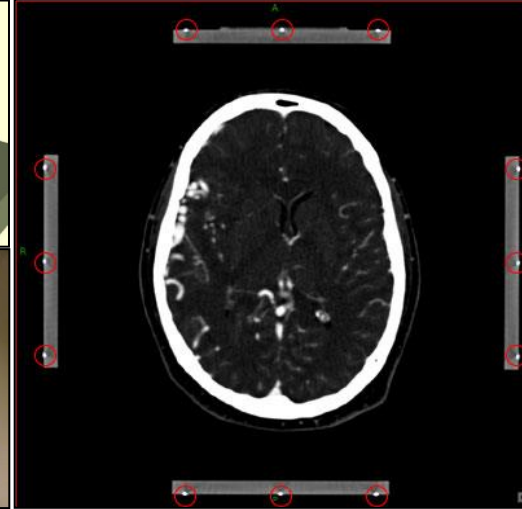
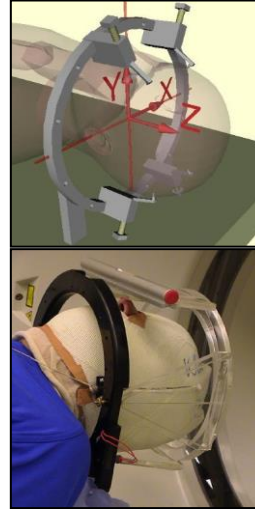


## 3D-Radiotherapy: Stereotactic Treatment

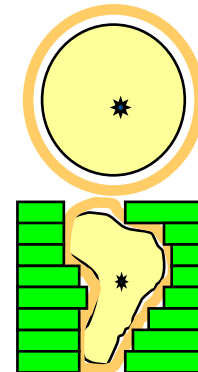


### Lars Leksell (1907–1986 )

- Neurosurgeon at the Karolinska in Stockholm, Sweden
- Cooperation with the Physicist Börje Larsson
- Development of the Gamma-Knife 1968
- *Leksell Gamma Knife*
- for stereotactic radiosurgery of brain tumors
- 201 Cobalt-60-sources



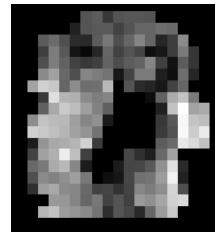
- invasive fixation, mask fixation
- dose application in a single fraction
- steep dose gradient towards surrounding normal tissue
- linear accelerator, Gamma-Knife/Cyber-Knife
- Limitation: Risk for side effect increases with treatment volume



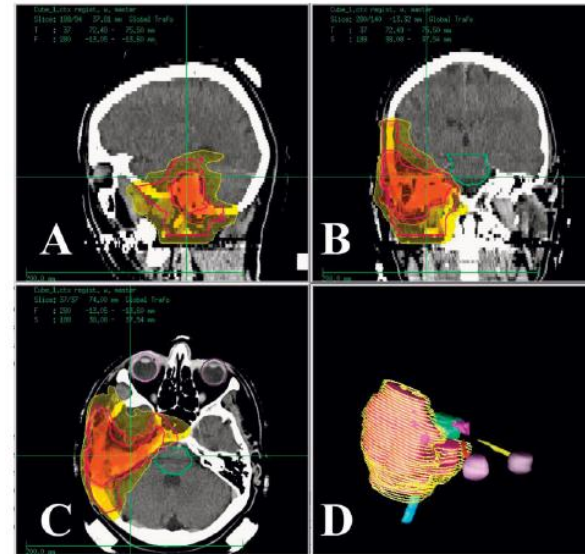
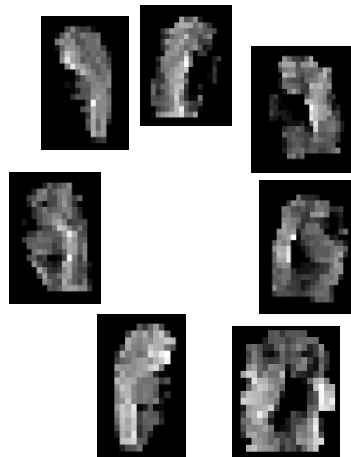
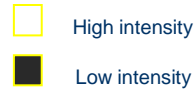
# 3D-Radiotherapy: Intensity Modulated Radiotherapy (IMRT)



Homogeneous  
Dose  
Application



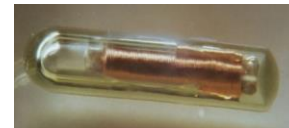
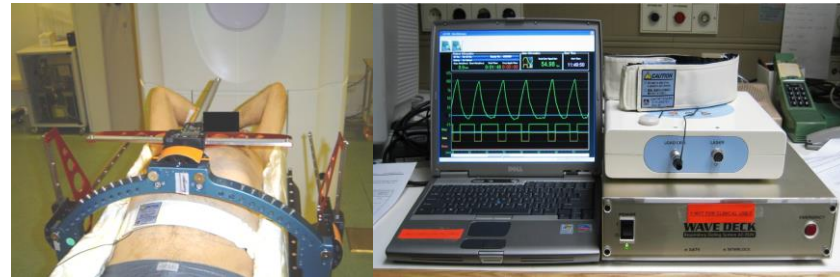
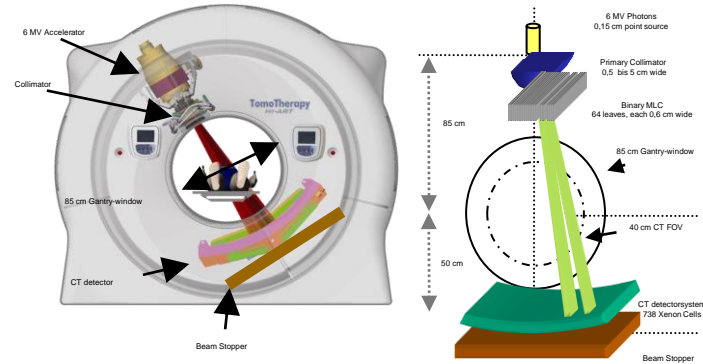
Inhomogeneous  
dose application



- treatment of complex targets
- vicinity to radiation-sensitive organs at risk
- e.g. Skull Base Tumors, Tumors of the Head-and-Neck Region, Paraspinal Tumors

# Image-Guided Radiotherapy (IGRT)

- Daily tailored treatment: Positioning verification prior to every treatment fraction
- combination of treatment and imaging in one machine
- treatment adapted to anatomical changes, tumor reponse during treatment...
- **Adaptive Radiotherapy (ART)**

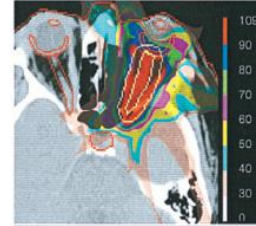




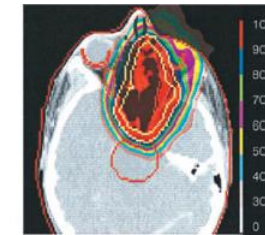
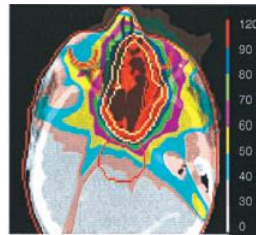
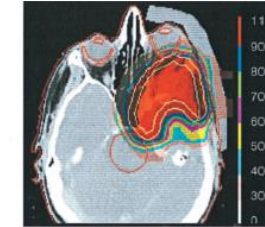
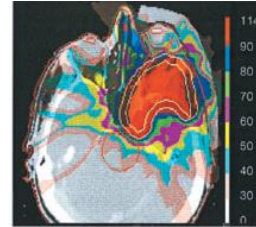
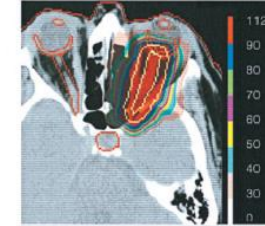
- 1946 Ion Therapy for Tumor Therapy
- 1954 Lawrence Berkeley Laboratory, USA starts Proton Therapy
- 1975 Lawrence Berkeley Laboratory, USA starts treatments with Heavy Ions
- 1990 Opening of the Protonen Facility Loma Linda (USA)
- 1994 Opening of the 1. Center for Carbon Ion Radiotherapy in Chiba (Japan)
- 1997 Protons Therapy in Villigen/Schweiz
- 1997 Carbon Ion Radiotherapy at GSI in Darmstadt
- 2009 Patient Treatment at the Heidelberger Ionenstrahl Therapiezentrum (HIT)



IMRT

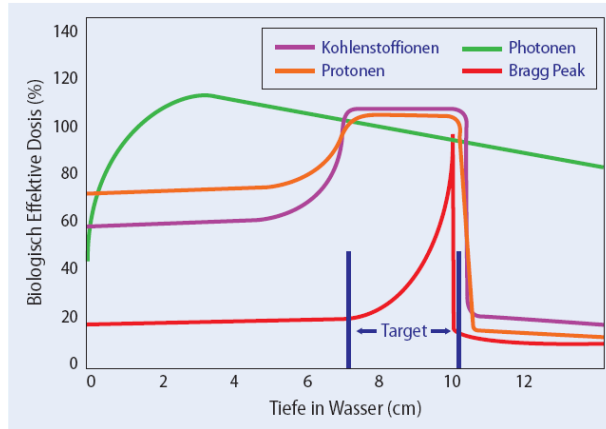


IMPT





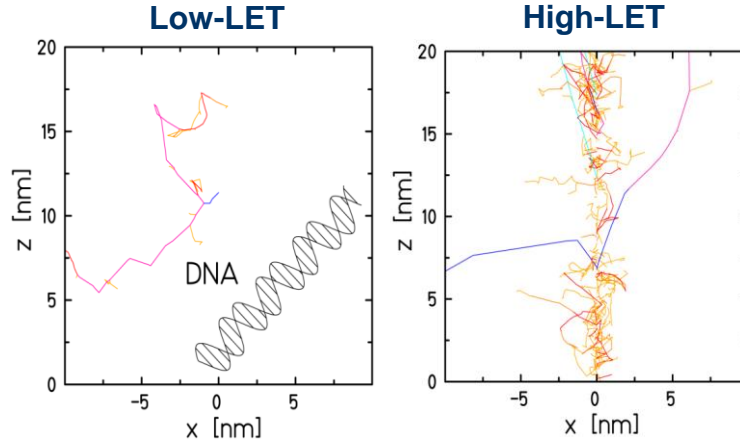
# Physical and Biological Benefit of Ion Beams



- inverse dose profile
- high local dose deposition in „Bragg Peak“
- sparing of normal tissue

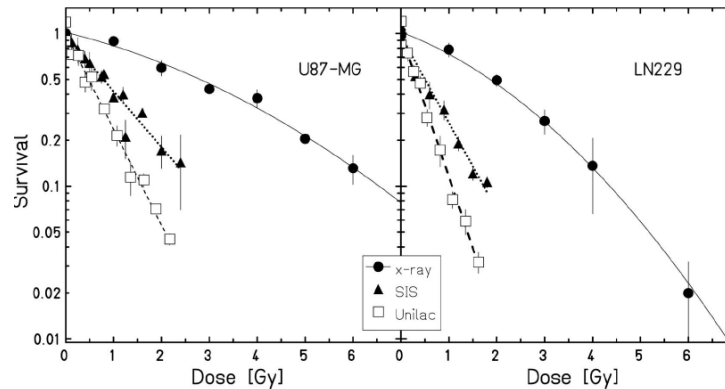
Combs SE et al. Chirurg, 2007

# Physical and Biological Benefit of Ion Beams



- carbon ions: higher relative biological effectiveness (RBE)
- difficult to repair radiation damage, i.e. double strand breaks
- correlation with repair proteins, e.g. p21

M. Scholz et al. Rad. Res. 2001



- higher RBE in glioblastoma cell lines
- independent of molecular markers, e.g. MGMT- promotor methylation



## Treatment Alternatives

- **Single fraction / radiosurgery**  
radiosurgery(Gamma knife / LINAC)
  - fast treatment time
  - non invasive
  - high biological effect
  - CAVE: increasing tox with volume and dose!
  
- **FSRT/fractionated treatments**
  - non-invasive treatment
  - beneficial for all volumes (small or large)
  - overall more forgiving risk-benefit ratio
  - down side: longer treatment times



# Schädelbasismeningiome

- gutartiger, langsam wachsender Tumor
- oder hohes Rezidivrisiko bei atypischen oder anaplastischen Tumoren
- oft im Bereich der Schädelbasis lokalisiert
- low-risk – Behandlungsindikation: Tumorwachstum oder -Rezidiv  
Klinische Symptomatik

## Behandlungsalternativen:

- „wait and see“
  - chirurgische Resektion
  - Radiochirurgie (Gamma knife / LINAC)
  - Fraktionierte stereotaktische Radiotherapie/IMRT
  - Proton Therapy / Schwerionentherapie
- 
- high-risk - Behandlungsindikation: postoperative Radiotherapie  
Tumorprogression

# Meningeome - Klassifikation

**Grad I:** etwa 70–80 %

**Grad II:** Atypische Tumore, zeigen eine schnellere Proliferation im Vergleich zu den benignen Läsionen und neigen zu höheren Rezidivraten.

**Grad III:** Werden auch als anaplastische Meningeome bezeichnet, die eine hohe Tendenz zu Lokalrezidiven nach einer Therapie aufzeigen. Etwa 3 % der Meningeome

## Grade I

- Low mitotic rate, less than four per ten high-power fields (HPFs)
- Absence of brain invasion
- Nine subtypes

## Grade II (atypical)

- Mitotic rate four to 19 per HPF
- Or brain invasion
- Or three of five specific histologies: spontaneous necrosis, sheeting, prominent nucleoli, high cellularity, and small cells

## Grade III (anaplastic)

- Mitotic rate more than 20 per HPF
- Or specific histologies: papillary or rhabdoid meningioma

# Meningeome – Simpson`s Grade

1928-1954		
<u>GRADE</u>	<u>DEFINITION OF EXTENT OF RESECTION</u>	<u>10 y LF</u>
I	Gross total resection of tumor, dural attachments and abnormal bone	10%
II	Gross total resection of tumor, coagulation of dural attachments	20%
III	Gross total resection of tumor without resection or coagulation of dural attachments, or extradural extensions (e.g. invaded or hyperostotic bone)	30%
IV	Partial resection of tumor	44%
V	Simple decompression (biopsy)	N/A

Simpson, J Neurol Neurosurg Psychiat 20, 1957



# Schädelbasismeningeome

## Indikation zur Strahlentherapie:

benigne Histologie: Größenprogredienz oder Zunahme Klein.  
Symptomatik  
„Elektiv“ nach Teilresektion bei ganz kritischer  
Lokalisation u/o großem Restbefund

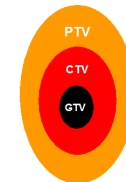
**Zielvolumen GTV:** T1-KM-Aufgenommene Läsionen (Makroskopischer Rest)  
DOTATOC-PET positive Areale  
cave: Knocheinfiltration im MRT oft nicht gut sichtbar  
– CT!!  
Meningeale Ausdehnung – sog. Dural Tail

CTV + 1-2 mm, PTV je nach Technik

**Gesamtdosis:** ca. 57.6 Gy in 1.8 Gy ED

**Technik:** FRST, IMRT, Protonentherapie

GTV – Gross Tumor Volume  
makroskopischer Tumor  
CTV – Clinical Target Volume  
mikroskopische Ausbreitung  
PTV – Planning Target Volume  
geometrische Unsicherheiten  
(Setup-Variation, Organbewegung)





# Schädelbasismeningeome

## Indikation zur Strahlentherapie:

High-risk Histologie: nach Diagnose, postoperativ

## Zielvolumen GTV:

T1-KM-Aufgenommene Läsionen (Makroskopischer Rest)

cave: Knocheinfiltration im MRT oft nicht gut sichtbar

– CT!!

Meningeale Ausdehnung – sog. Dural Tail

CTV + 1-2 cm, PTV je nach Technik

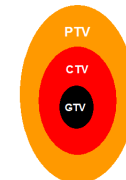
## Gesamtdosis:

ca. 60 Gy in 2 Gy ED, ggf. Dosisescalation in Studien

## Technik:

FRST, IMRT, Protonentherapie

GTV – Gross Tumor Volume  
makroskopischer Tumor  
CTV – Clinical Target Volume  
mikroskopische Ausbreitung  
PTV – Planning Target Volume  
geometrische Unsicherheiten  
(Setup-Variation, Organbewegung)



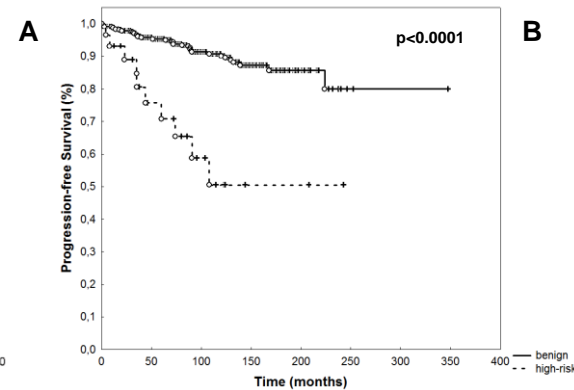
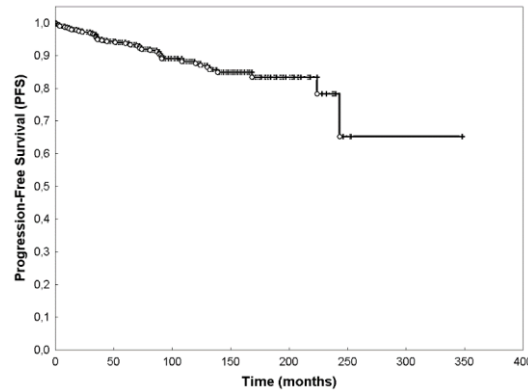


## Low-Grade Meningiomas

FSRT or IMRT well established

Long-term Results in 507 Patients with skull base meningiomas

- local control 91% at 10 years for low-grade histology
- neurocognitive function and QOL preserved





# Background

## **Skull base Meningiomas:**

- data from smaller (or larger) series
- few multicentric analysis
- value of pooled data shown in other indications

**To evaluate large-scale clinical results we evaluated outcome in 927 patients with skull base meningiomas treated with either Radiosurgery (RS), Fractionated Stereotactic Radiotherapy (FSRT) or Intensity Modulated Radiotherapy (IMRT).**

**3 Centers:** Heidelberg, Freiburg and München/TUM

## Patients and Methods

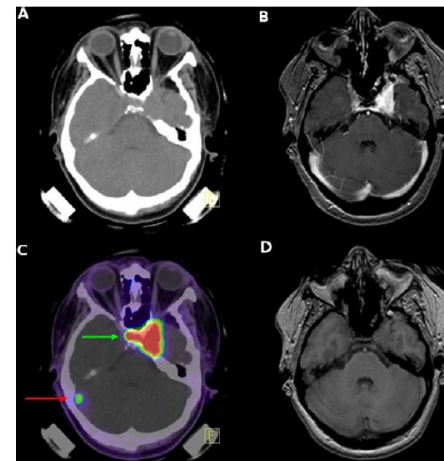
- 928 patients with skull base meningiomas
- Heidelberg (n=507)
- Freiburg (n=207)
- Munich/TUM (n=213)
- median age was 58 years
- the median follow-up time was 81 months (range 1-348 months)

### Target Volume Definition:

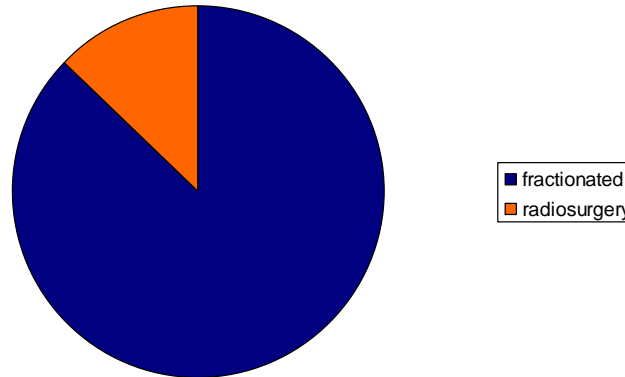
**GTV** – contrast-enhancement on MRI DOTATOC-PET

**CTV** – GTV plus 1-2mm for low-grade meningiomas

**PTV** – center and technique dependent



## Patients and Methods



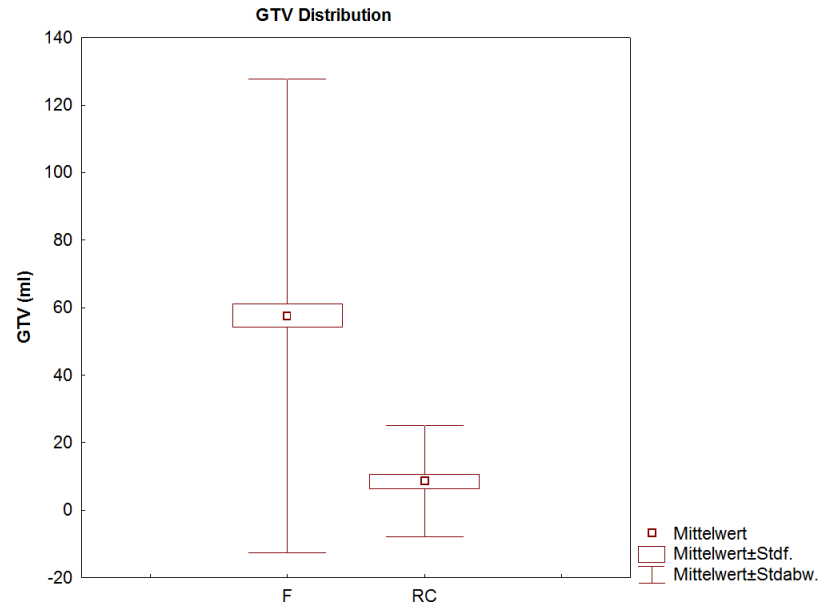
**FSRT/IMRT:** median total dose of 54 Gy/one center generally 57.6 Gy (HD)  
median single fractions of 1.8 Gy

**RS:** median single dose of 13 Gy

## Results - I

Comparing both groups, GTV volumes were significantly smaller  
in the RS group compared to the fractionated group:

**median 3,7 ml vs. 30,25 ml;  $p < 0.001$ .**

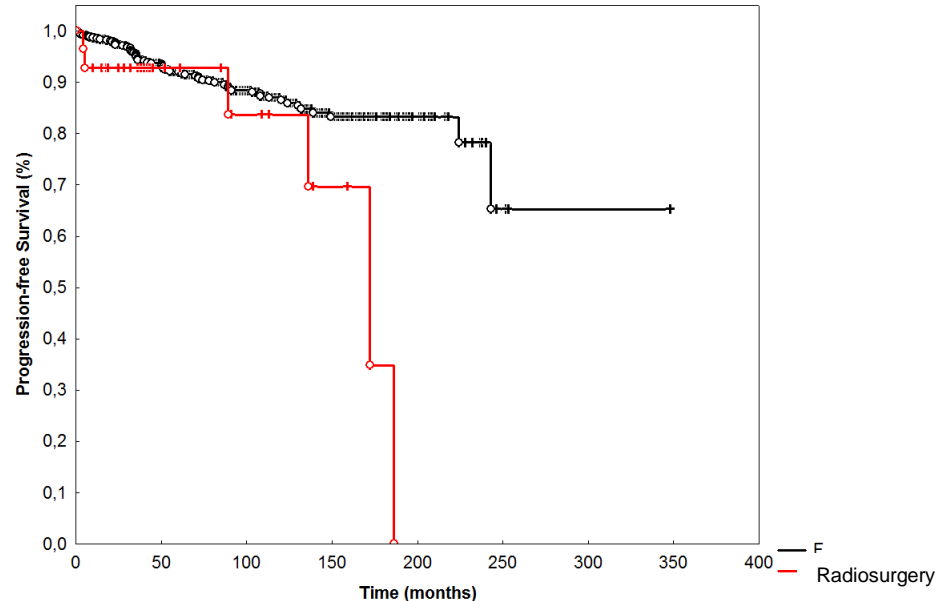


## Results - II

**Local control (LC) was not significantly different between both groups:**

**For RC, LC was 91% and 5 years, and 81% at 10 years.**

**For the fractionated group, LC was 94% at 3, 93% at 5 and 87% at 10 years.**





## Results of Proton Therapy for Patients with Meningiomas

<i>Author</i>	<i>Institute</i>	<i>No. of Pts.</i>	<i>Radiation Modality</i>	<i>Overall Survival</i>	<i>Local Control</i>	<i>Toxicity</i>
Wenkel et al.	MGH, USA	46	Protons and Photons, 59.0 GyE	95% and 77% at 5 and 10 years	100% and 88% at 5 and 10 years	20% severe toxicity
Vernimmen et al.	Tygerberg, SA	27	Protons 54 Gy E - 61.6 GyE, 16 - 27 fractions	-	88%	11% (2 patients) late toxicity : ipsilateral partial hearing loss, temporal lobe epilepsy
Noël et al.	CPO, Orsay, F	51	Protons and Photons 60.6 GyE	100% at 4 years	98% at 4 years	2/51 Grade III toxicity. Unilateral hearing loss, complete pituitary deficiency
Boskos et al.	CPO, Orsay, F	24	34.05 GyE Photons and 30.96 Gy E Protons (total dose 65.01 GyE)	53.2% and 42.6% at 5 and 8 years	46.7% at 5 and 8 years	1/24 radiation necrosis at 16 months after RT
Halasz et al.	MGH, USA	50	10 -15.5 Gy E Radiosurgery	Not reported	94% at 3 years	5.9% (3/51 patients) severe toxicity
Weber DC et al.	PSI, Switzerland	39	Protons 52.2 - 66.6 Gy E	81.8%% at 5 years	84.8% at 5 years	15.5% ≥ Grade III

# Meningeome - Adj. RT bei WHO °II?

Rogers et al  
ASTRO 2016  
RTOG 0539

- Prospektive Phase II-Studie (244 Pat.)
- Gruppe 1 = low risk (total/subtotal reseziert, WHO I)  
→ Observation
  - **Lokalrezidivrate 12,5% nach 5 J., 40% wenn STR**
- Gruppe 2 = intermediate risk (WHO II nach GTR oder WHO I-Rezidiv)  
→ RT 54 Gy
  - Lokalrezidivrate 14% nach 5 J.
- Gruppe 3 = high risk (WHO III oder WHO II-Rezidiv/ STR)  
→ RT 60 Gy

Schlechte Ergebnisse nach STR bei WHO I → adj. RT?  
Gute Ergebnisse mit RT in Gruppe 2



# Meningeome – Zielvolumen und Dosierung

## RTOG 0539 – Phase II Meningioma

- Low Risk: Observation
- Intermediate: 54 Gy to GTV + 1.0 cm CTV + 0.3-0.5 cm PTV  
– CTV may be reduced to 0.5 cm at natural barriers
- High Risk: 54 Gy to GTV + 2.0 cm CTV + 0.3-0.5 cm PTV  
60 Gy to GTV + 1.0 cm CTV

No edema or dural tail included in GTV

## RTOG 0539 – Phase II Meningioma

- Low Risk: Grade I: GTR (Simpson I-III)  
STR (Simpson IV-V)
- Intermediate: Grade I: Recurrent  
Grade II: GTR
- High Risk: Grade II: Recurrent  
STR  
Grade III: new, recurrent, GTR, STR



# Meningeome – Zielvolumen und Dosierung

## NCCN Guidelines:

**WHO grade I:** radiotherapy with doses of **45–54 Gy**.

WHO grade I SRS doses of 12–16 Gy in a single fraction when appropriate. **ZV Konzept??**

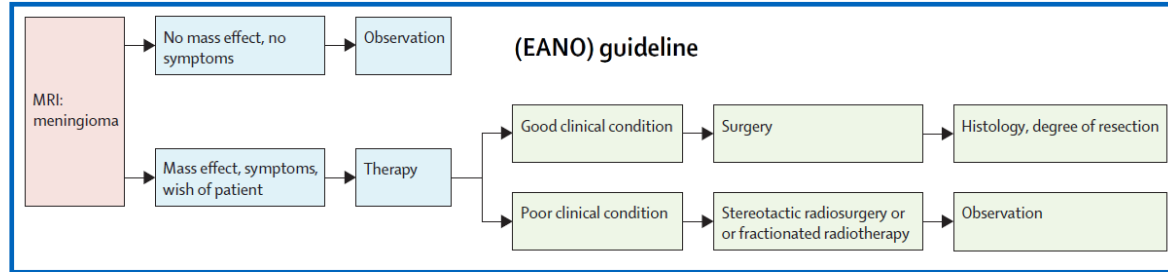
**WHO grade II:** if present **GTV** + surgical bed (**CTV1**) + a margin **1–2 cm CTV2** + **PTV** to a dose of **54–60 Gy** in **1.8–2.0 Gy** fractions.

Consider limiting margin expansion into the brain parenchyma

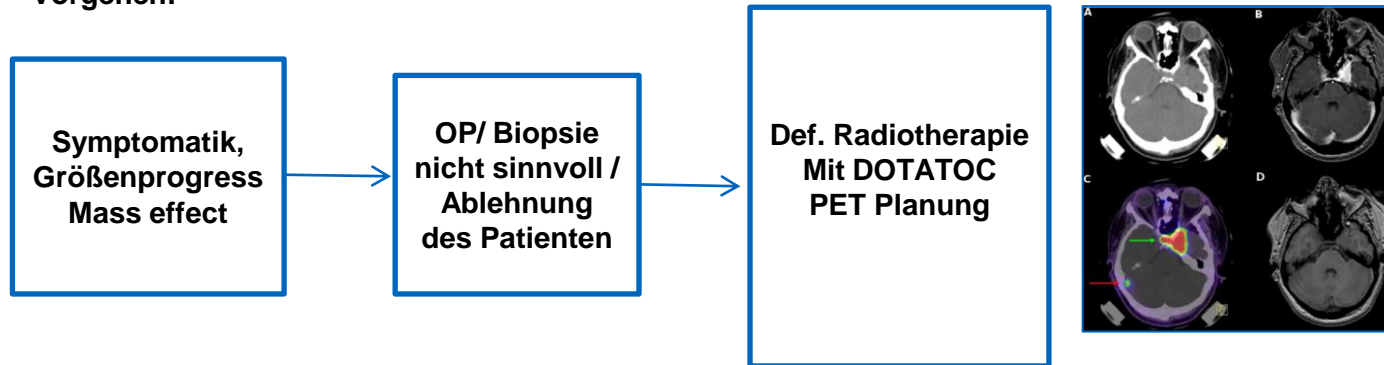
**WHO grade III:** should be treated as malignant tumors:

**GTV** (if present) + surgical bed (**CTV1**) + a margin 2–3 cm (**CTV2**) + **PTV**  
receiving **59.4–60 Gy** in **1.8–2.0 Gy** fractions.

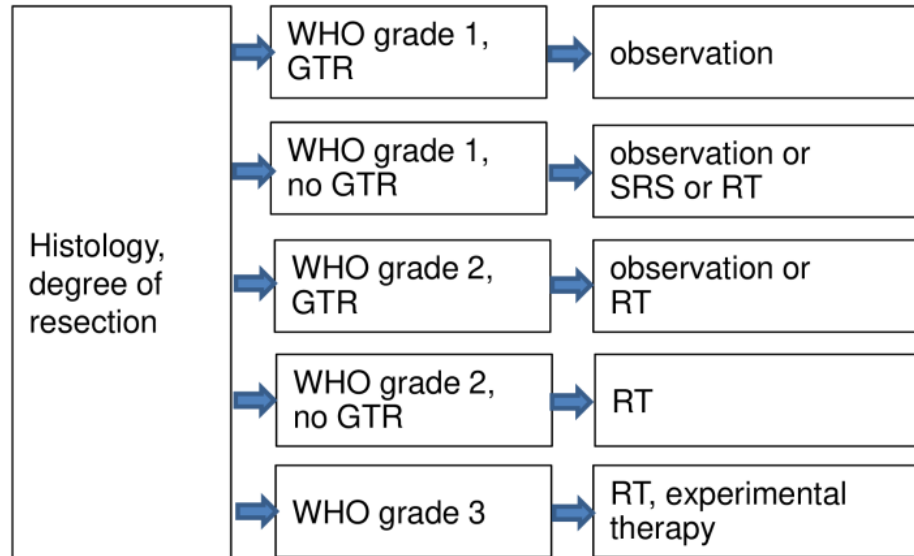
# Meningeome – ED ohne histologische Sicherung



## Vorgehen:



# Meningeome – histologische Sicherung vorhanden



**EANO guideline on the diagnosis and management of meningiomas , 2021**

GTR = gross total resection  
SRS = radiosurgery  
RT = fractionated radiotherapy



# Meningeome - Nachsorge

## **Aufklärung**

Ödembildung möglich, insbesondere nach RC. Dann auch Strahlennekrose möglich. Hypophyseninsuffizienz, Optisches System, bei SRS auch Fahrtauglichkeit

## **Nachsorge**

NU nach 3 Monaten, 6 Monaten, dann ggf. jährlich (Grad1)

cMRT: 1. cMRT 3 Monate nach RTx

1x jährlich augenärztliche Untersuchung

1x jährlich endokrinologische Kontrolle



# Indikationsstellung

- Tumorgröße (Volumen, Durchmesser)
- Anatomie: Kompression von Risikoorganen, Nähe zu Risikoorganen
- Klinische Symptomatik (z.B. Hören, Hirnnervenbeeinträchtigung)
- Vorbehandlung: Operation – ggf. Defizite durch die Operation
- Nebendiagnosen: Diabetes...
- Patientenalter
- Wunsch/Präferenz der Patienten