RadioOnkologie und Strahlentherapie
Fakultät für Medizin
Technische Universität München

Meningeome

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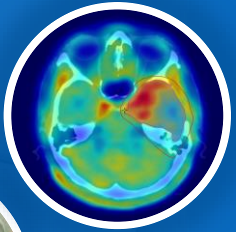
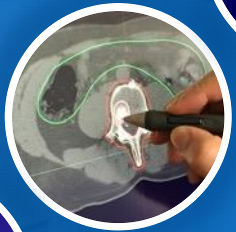
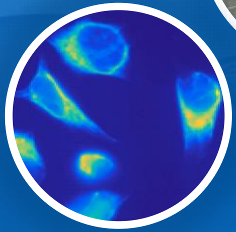
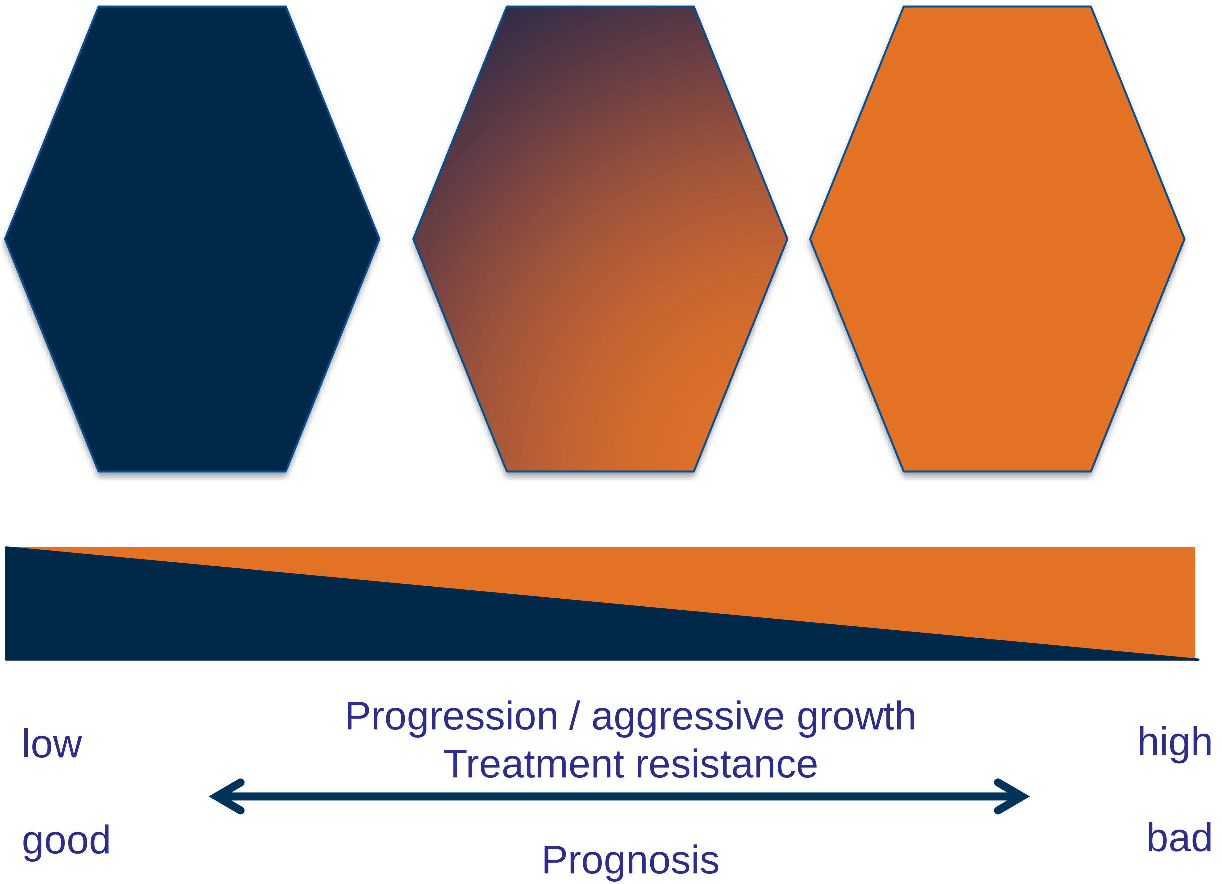
Institut für Strahlenmedizin (IRM)



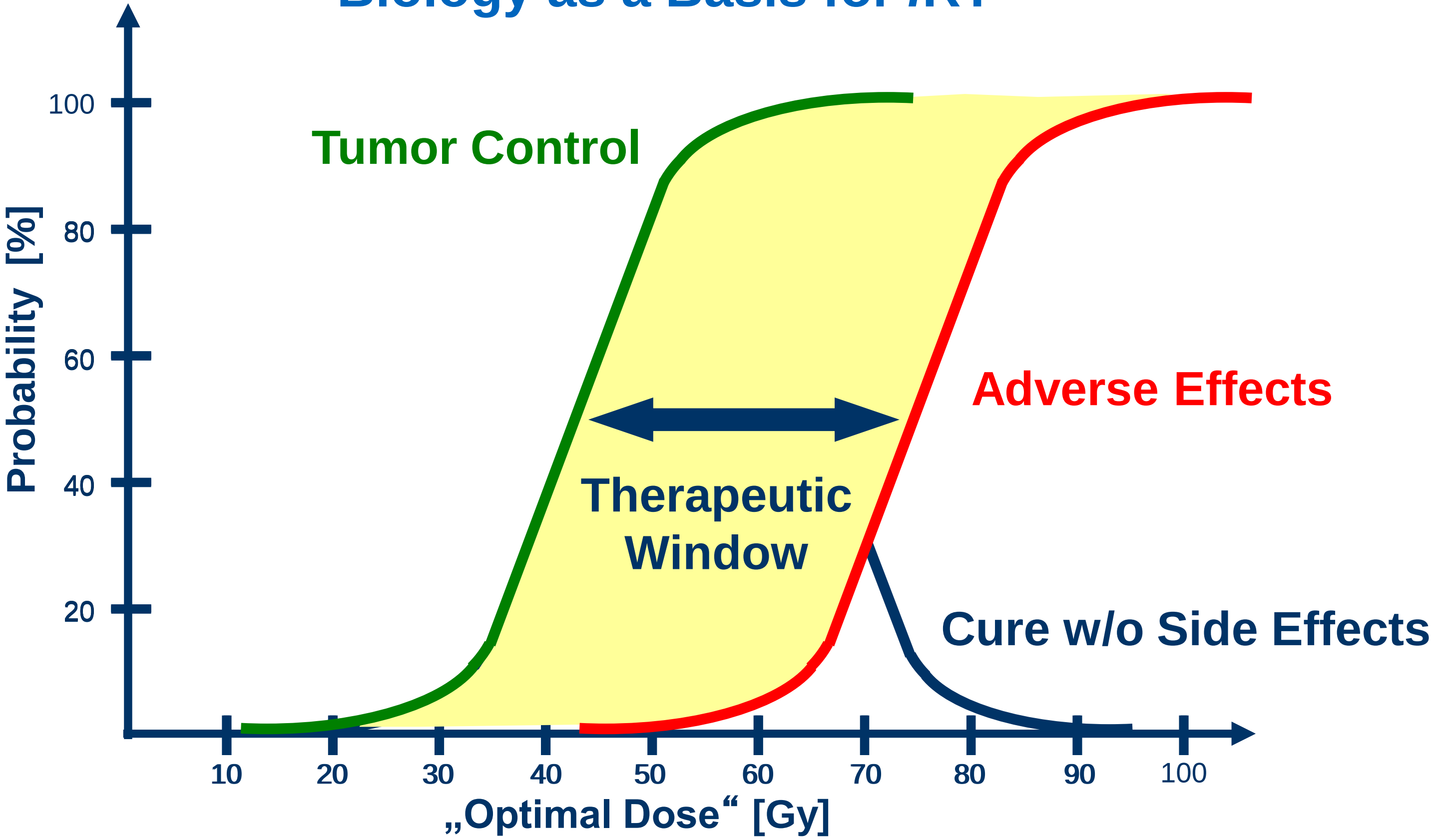





Progression / aggressive growth
Treatment resistance
low
high
good
bad
Prognosis

Holthusen-Curve: Dose-Response-Relationship

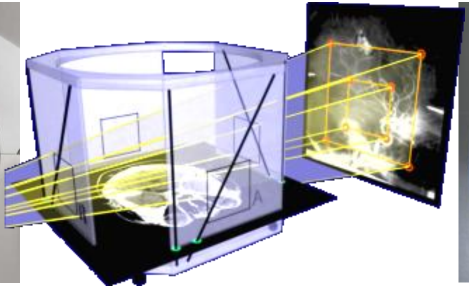
Biology as a Basis for *i*RT

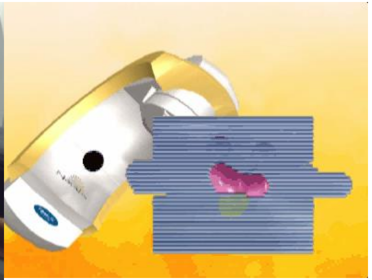


After: Holthusen, H. und Braun, R. (1933) :
Grundlagen und Praxis der Röntgenstrahldosierung, Thieme Verlag, Leipzig

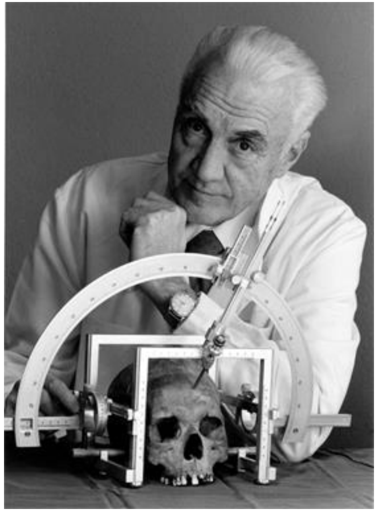
Modern Techniques in Radiation Oncology *i*RT Concepts

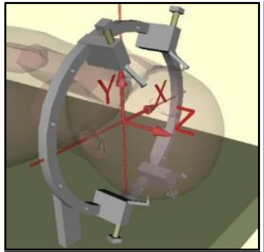
- 3D - imaging – CT, MRI, PET etc.
- High Precision Radiotherapy (Radiosurgery, Fractionated Stereotactic....)
- Intensity Modulated Radiotherapy (IMRT)
- Particle Therapy (Protons, Carbon Ions, Neutrons and other)
- Image Guided Radiotherapy (IGRT)
- Adaptive Radiotherapy

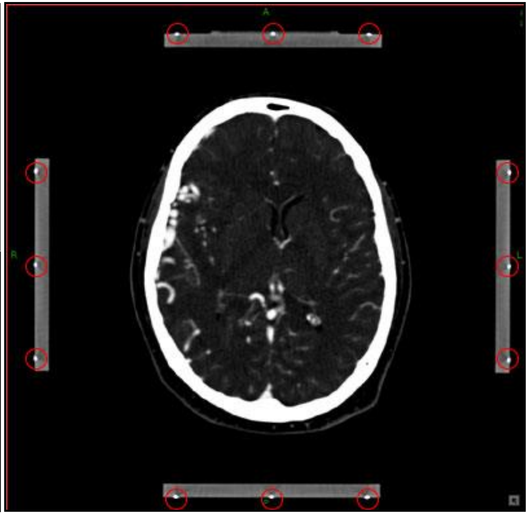





3D-Radiotherapy: Stereotactic Treatment



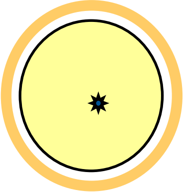


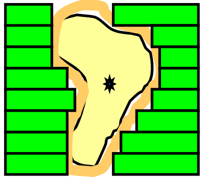


Lars Leksell (1907–1986)

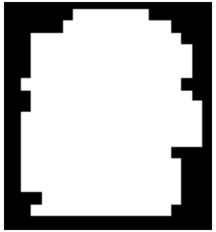
- Neurosurgeon at the Karolinksa in Stockholm, Sweden
- Cooperation with the Physicist Börje Larsson
- Development of the Gamma-Knife 1968
- *Leksell Gamma Knife*
- for stereotactic radiosurgery of brain tumors
- 201 Cobalt-60-sources

- 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

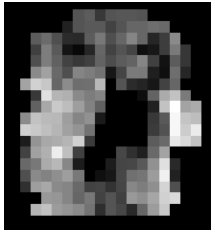




3D-Radiotherapy: Intensity Modulated Radiotherapy (IMRT)



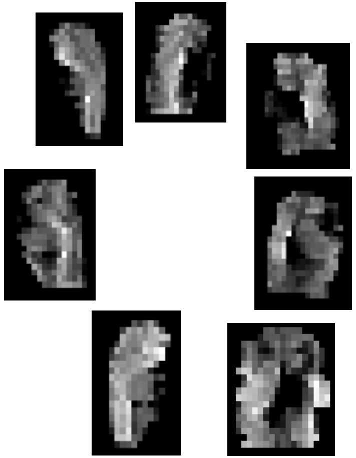
Homogeneous Dose Application

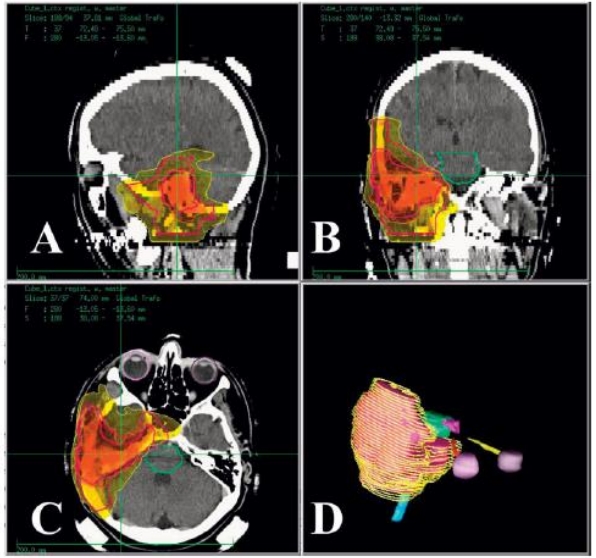


Inhomogeneous dose application

High intensity

Low intensity



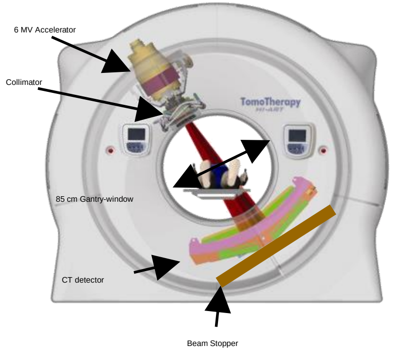


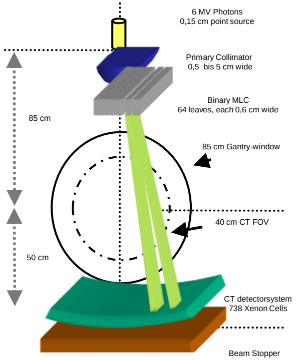
- treatment of complex targets
- vicinity to radiation-sensitive organs at risk
- e.g. Skull Base Tumors, Tumors of the Head-and-Neck Region, Paraspinal Tumors

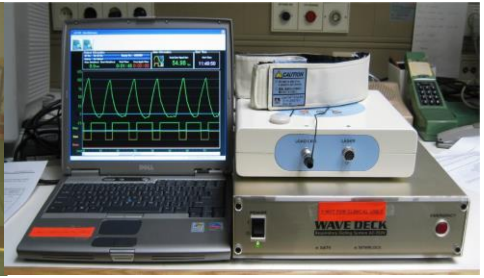
Combs SE et al., Cancer, 2005; **Combs SE** et al., Radiat Onkol 2006; **Combs SE** et al., Strahlenther Onkol 2007

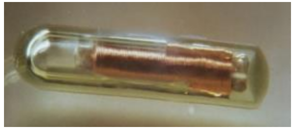
Image-Guided Radiotherapy (IGRT)

- Daily tailored treatment: Positioning verfication 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)**









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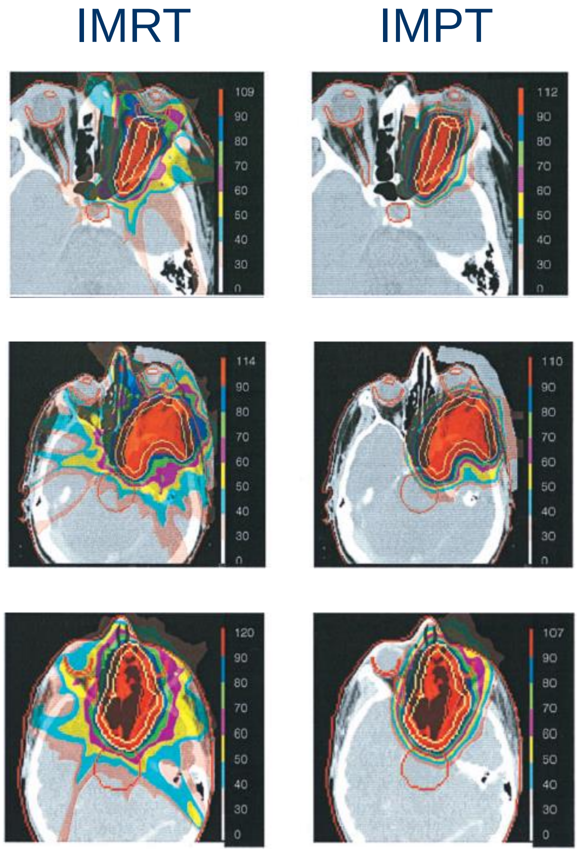
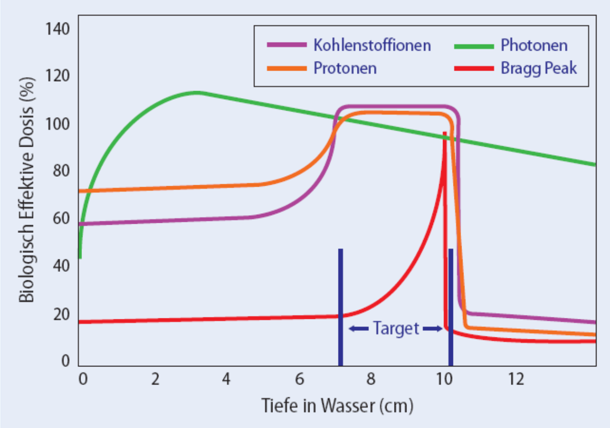
5D Radiotherapy: Ion Beams

1946 Ion Therapy for Tumor Therapy
1954 Lawrence Berkeley Laboratory, USA starts Proton Therapy
1975 Lawrence Berkeley Laboratory, USA starts tretments 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)



Miralbell et al., IJROBP 2000

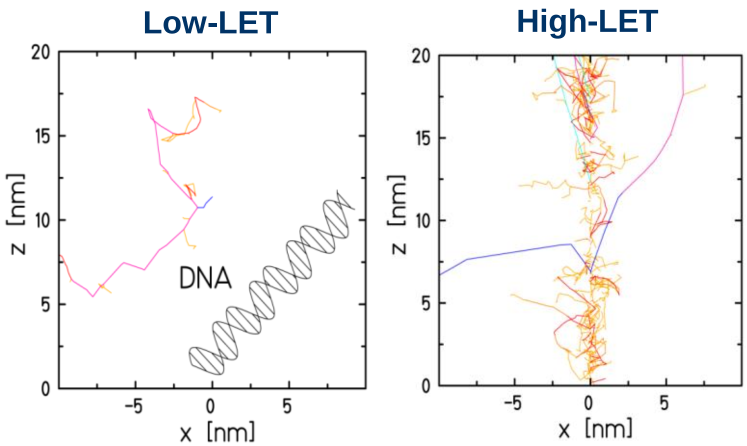
Physical and Biological Benefit of Ion Beams



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

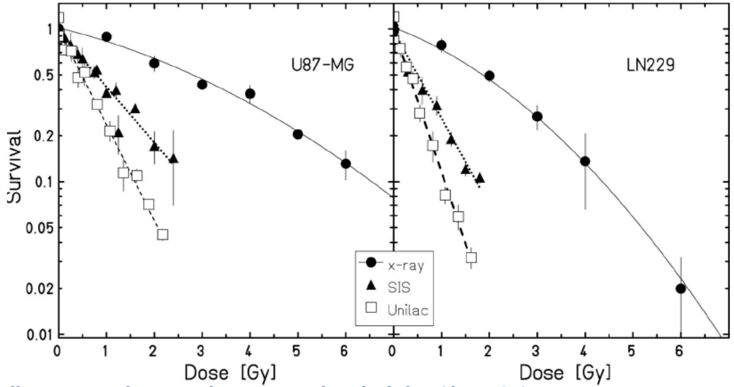
Combs SE et al. Chirurg, 2007

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

Funding: Deutsche Forschungsgemeinschaft (DFG), KFO 214

Combs SE et al. Int J Radiat Biol, 2009

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 foregiving 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

GRADE	DEFINITION OF EXTENT OF RESECTION	10 y LF
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-Aufnehmene 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

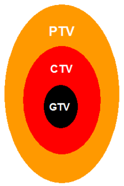
Gesamtdosis: ca. 57.6 Gy in 1.8 Gy ED

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-Aufnehmene 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

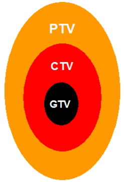
Gesamtdosis: ca. 60 Gy in 2 Gy ED, ggf. Dosiseskalation in Studien

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)



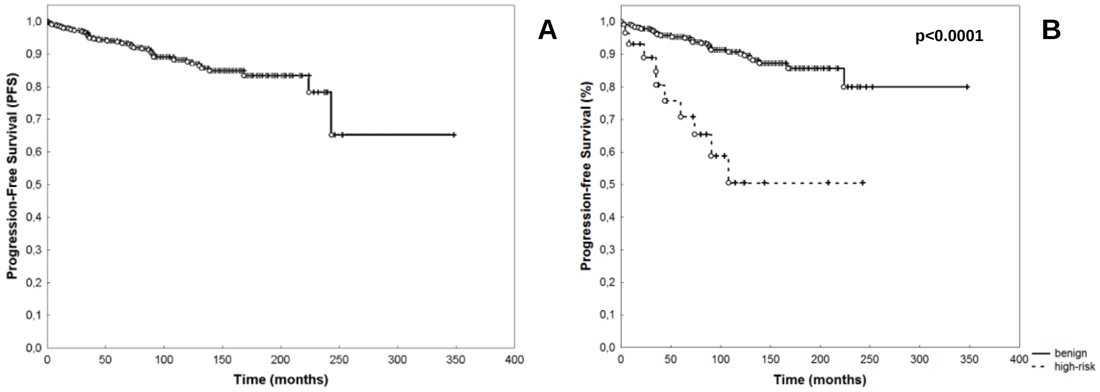
Low-Grade Meningiomas

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

- neurocognotive function and QOL preserved



Debus J et a., JCO 2001
Adeberg S, ..., Combs SE et al., IJROBP 2011
Combs SE et al., Radiother Oncol submitted

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

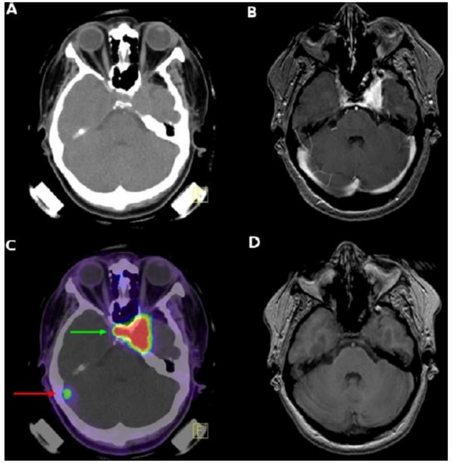
- 928 patients with skull base meningiomas
- Heidelberg (n=507)
- Freiburg (n=207)
- Munich/TUM (n=213)
- median age was 58 years
- the median follow-up time was 81 months (range 1-348 months)

Target Volume Definition:

GTV – contrast-enhancement on MRI DOTATOC-PET

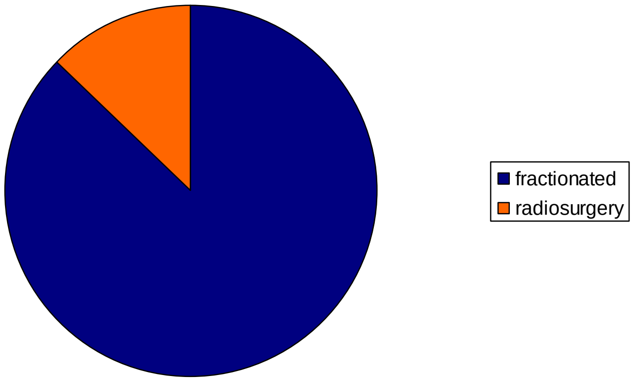
CTV – GTV plus 1-2mm for low-grade meningiomas

PTV – center and technique dependent



Afshar-Oromieh A, ..., **Combs SE**,... Haberkorn U, Eur J Med Mol Imaging 2012

Patients and Methods



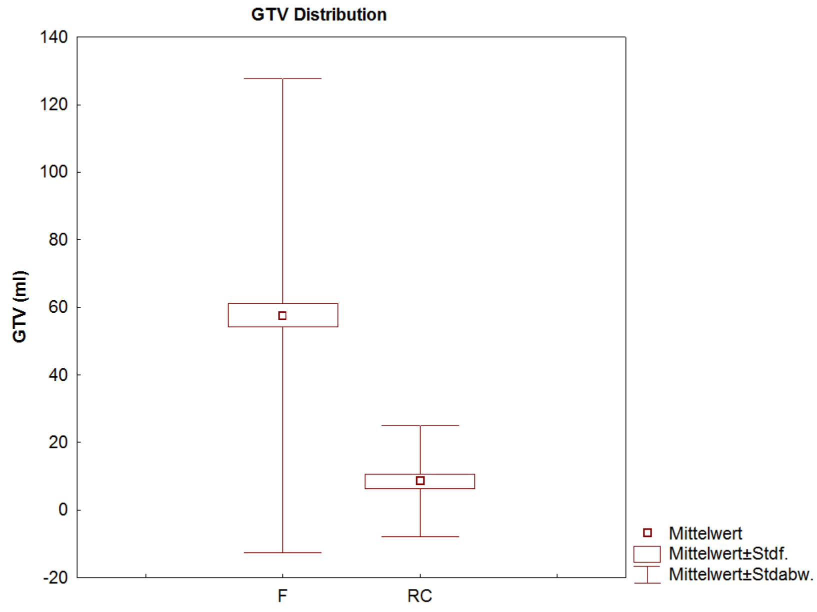
FSRT/IMRT: median total dose of 54 Gy/one center generally 57.6 Gy (HD)
median single fractions of 1.8 Gy

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.

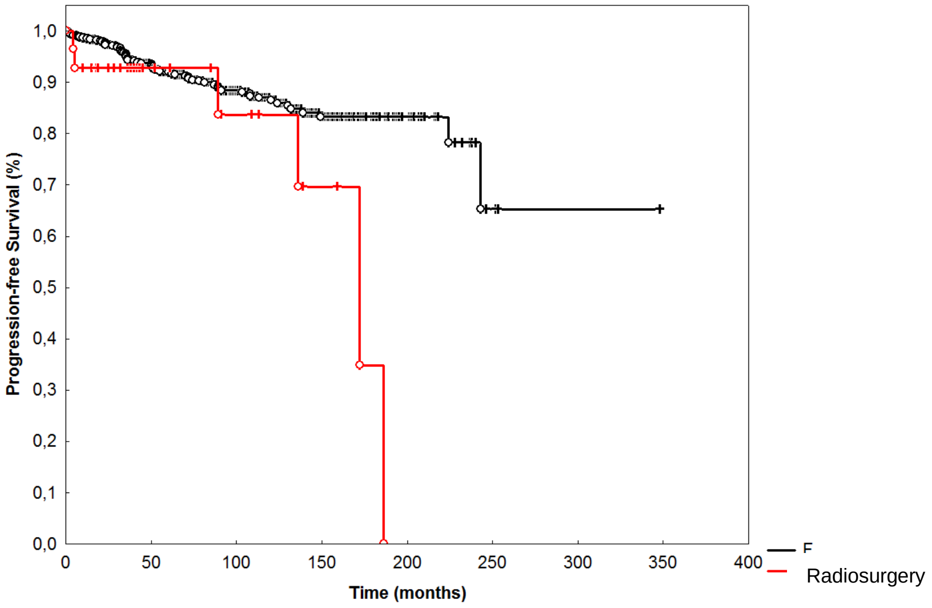


Results - II

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

Author	**Institute**	*No. of Pts.*	*Radiation Modality*	*Overall Survival*	*Local Control*	*Toxicity*
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

Combs SE et al., Semin Rad Oncol 2013

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

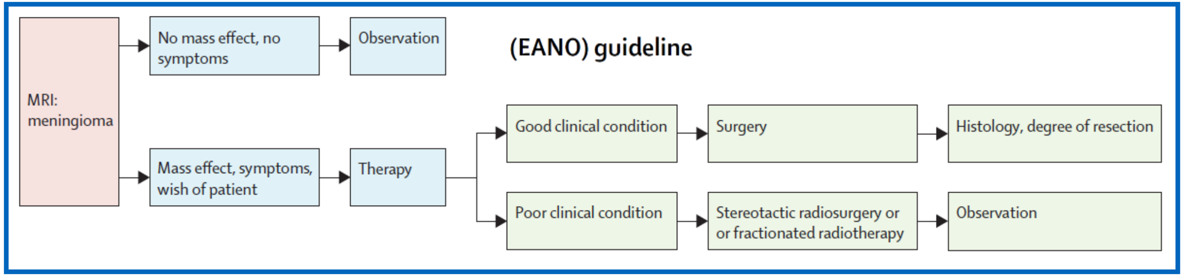
NCCN Guidelines:

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

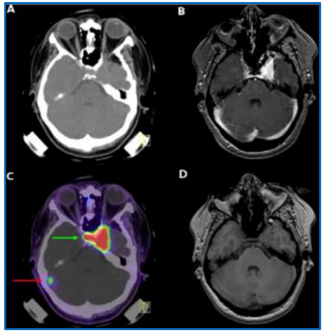
WHO grade III: should be treated as malignant tumors:
GTV (if present) + surgical bed (**CTV1**) + a margin 2–3 cm (**CTV2**) + **PTV**
receiving **59.4–60 Gy in 1.8–2.0** Gy fractions.

Meningeome – ED ohne histologische Sicherung

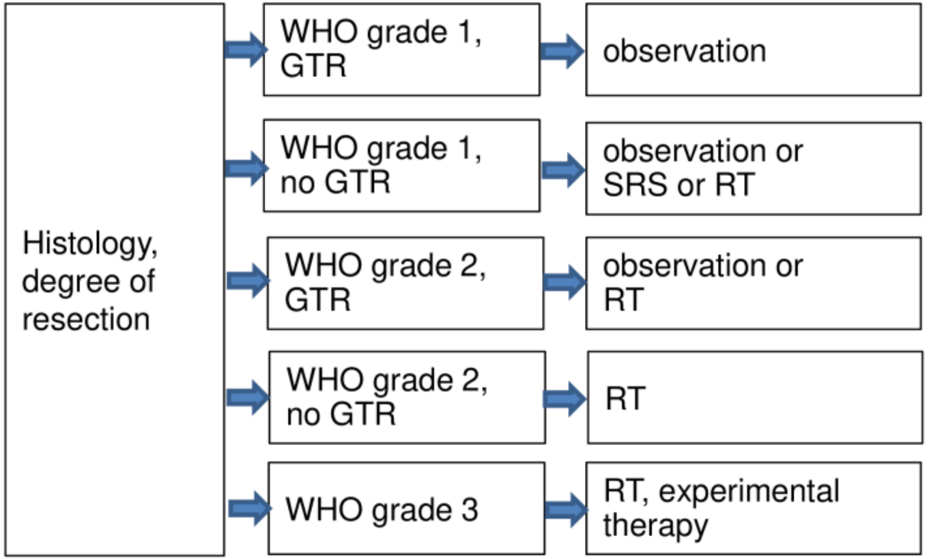


Vorgehen:

Symptomatik, Größenprogress Mass effect → **OP/ Biopsie nicht sinnvoll / Ablehnung des Patienten** → **Def. Radiotherapie Mit DOTATOC PET Planung**



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