„Psychoonkologische Aspekte in der Neuroonkologie“

Jahrestagung
Österreichischen Gesellschaft für Psychoonkologie (ÖGPO)

Bad Ischl - 25. Mai 2016

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DKG KREBSGESELLSCHAFT
Zertifiziertes Neuroonkologisches Tumorzentrum

Universität Regensburg

Klinik und Poliklinik für Neurochirurgie
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Klinik und Poliklinik für Neurologie
Direktor: Prof. Dr. U. Bogdahn

Klinik und Poliklinik für Strahlentherapie und Radioonkologie
Direktor: Prof. Dr. O. Kölbl

Abteilung für Neuropathologie
Leiter: Prof. Dr. M.J. Riemenschneider

Zentrum für Hirntumoren (ZHT)
am Universitätsklinikum Regensburg

Ziele des Vortrages

- **Neuroonkologie – Was ist das?**
- **Neurologische Symptome in der Neuroonkologie**
- **Krankheitsbilder**
  - Gliome WHO I-IV
  - Hirnmetastasen und Meningeosis neoplastica
  - Hirnfunktionsstörungen und Therpienebenwirkungen
- **Zusammenfassung** Psychoonkologische Besonderheiten in der Neuroonkologie

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Neuroonkologie

Hirntumore	*Primär*	**Gliome WHO I-IV** Primäres ZNS Lymphom + PNET/Medulloblastom, … Meningeome + Hypophysentumore, Akustikus-Neurinom, …
	Sekundär	**Zerebrale Metastasen** + **Meningeosis neoplastica** Metastasen mit Infiltration und/oder Bedrängung von
Hirnfunktio		n
Therapiene		rain) odifikation
Paraneoplastische Syndrome		**ZNS** - limbische Enzephalitis, Kleinhirn-Degeneration, … **PNS** - Polyneuropathie, Lambert Eaton, …
Psychoonkologie		**Patienten-zentrierte Kommunikation + BPS Modell** Aufklärung + Begleitung, Belastungsreaktion => Entlastung Depression + Angst, Fatigue, Schlaf, Schmerz Umgang mit neurologischen Symptomen

Symptomkontrolle

Lebensqualität

Gliome

Hirntumore - Inzidenz

Jährliche Inzidenz

Primäre Hirntumoren

8-10/100.000 Einwohner/Jahr

> 65 Jahre: 18/100.000 Einwohner/Jahr

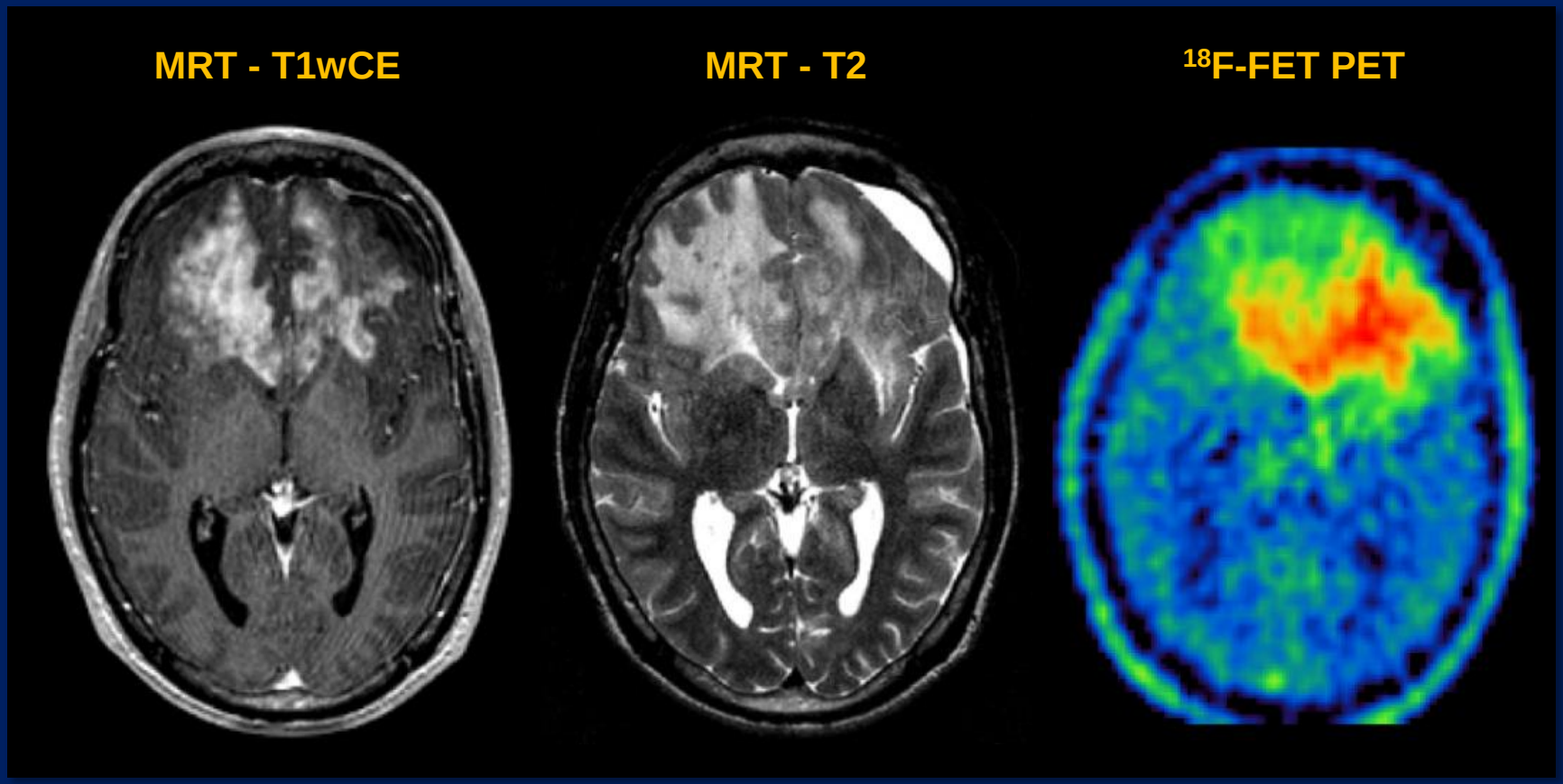
17.000 Neuerkrankungen/Jahr (USA)

13.000 Todesfälle/Jahr (USA)

Häufigkeit und Altersverteilung primärer Hirntumoren
Dolecek et al. 2012

Tumorart	Häufigkeit (in %)	medianes Alter (in Jahren)
pilozytisches Astrozytom	1,5%	13
diffuses Astrozytom	2,8%	48
anaplastisches Astrozytom	1,7%	54
Oligodendrogliom	1,3 %	43
Glioblastom	15,8%	64
Ependymom	2 %	43
Medulloblastom / PNET	1,2 %	8
Meningeome	35,5%	65
Hypophysenadenome	14,1 %	51
Neurinome	8,3 %	54
Primäres ZNS-Lymphom	2,2 %	65
Keimzelltumore	0,5 %	17

Gliome und Bildgebung



Hutterer et al., J Nuclear Medicine 2011

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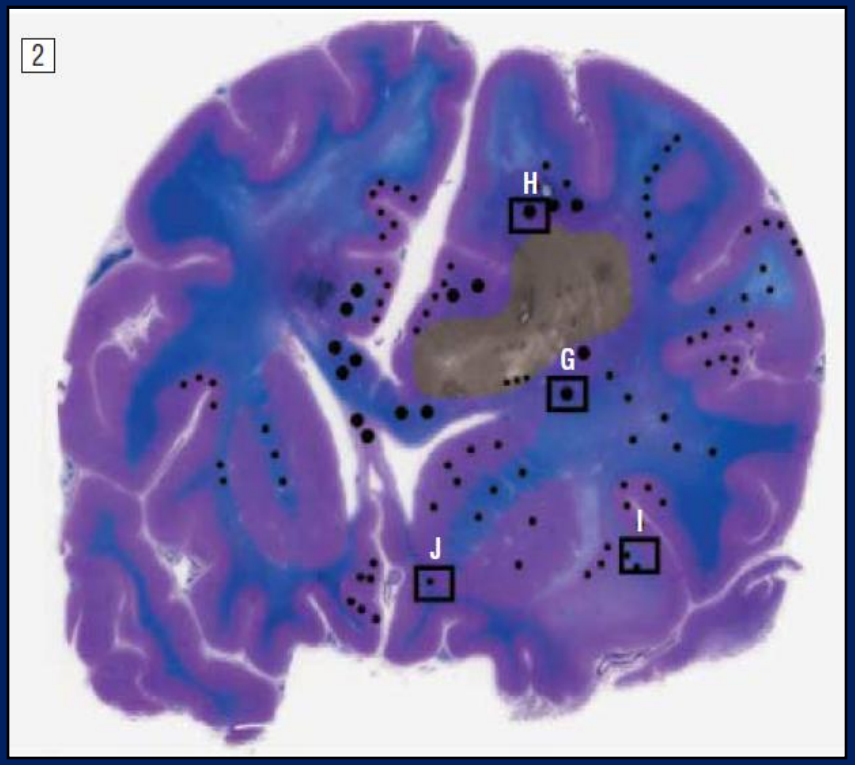
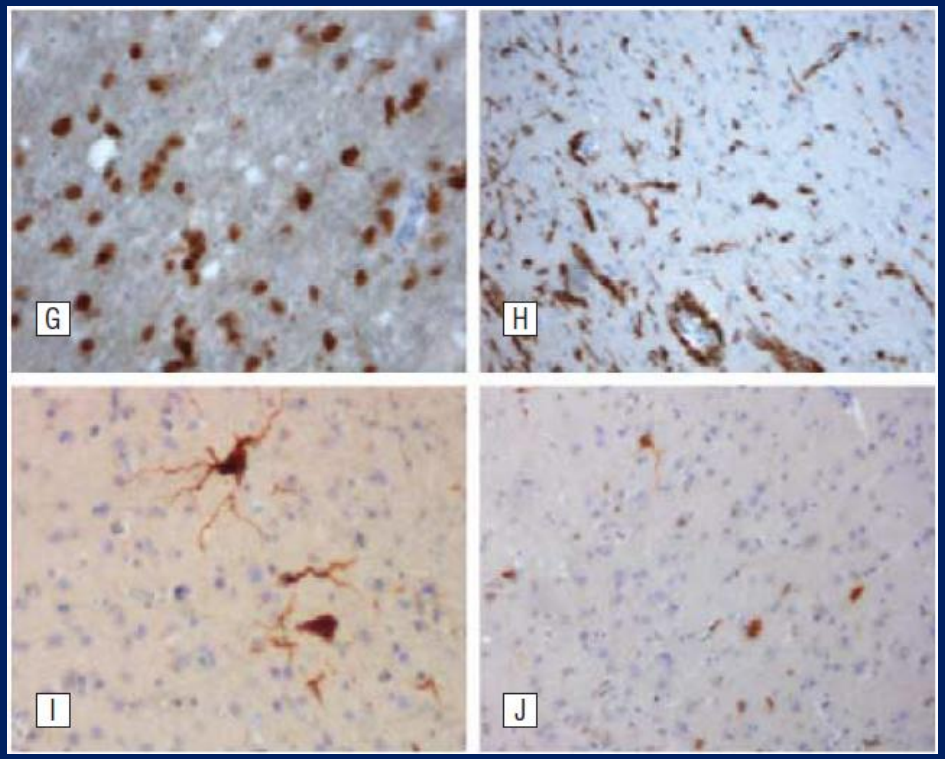
Gliome und Tumorinfiltration

Luxol fast blue / periodic acid Schiff staining
of large paraffin sections



IDH1 Immunohistochemistry
detecting infiltrating tumor cells



Sahm et al., JAMA Neurology 2011

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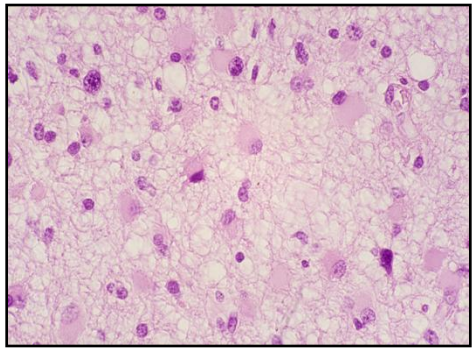
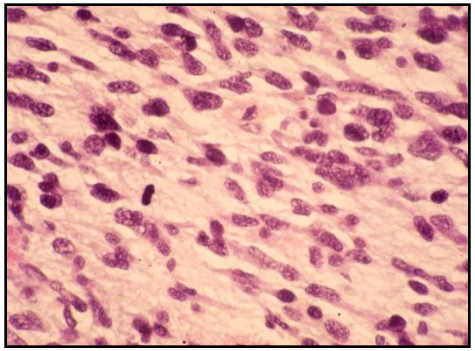
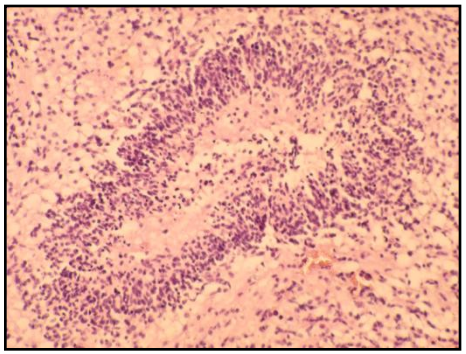
Histologie – WHO Klassifikation







	Diffuses Astrozytom WHO Grad II	Anaplastisches Astrozytom WHO Grad III	Glioblastom WHO Grad IV
Zell Dichte	gering-mittel	hoch	hoch
Zell Polymorhie	gering-mittel	stark	stark
Zellkern Polymorphie	moderat	stark	stark
Mitotische Aktivität	gering	verstärkt	hoch
Blutgefäßproliferation	keine	keine/wenige	nachweisbar
Nekrose	keine	keine	nachweisbar

Modified from **M. Riemenschneider** (Neuropathologie, Regensburg)

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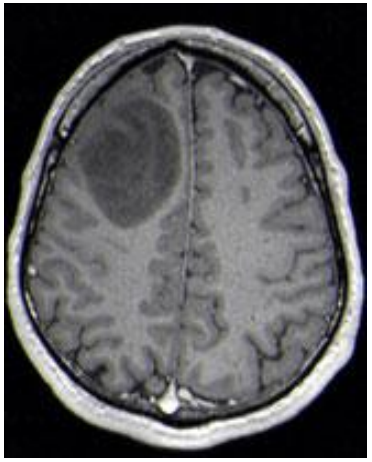
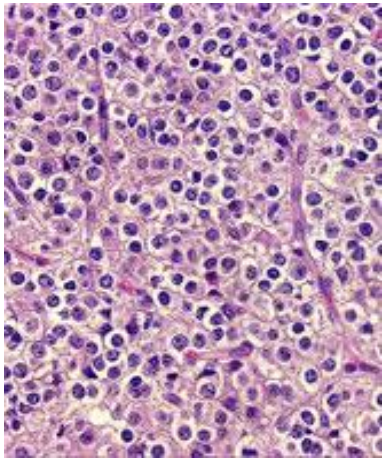
Gliome und Prognose

Astrozytom
Oligodendrogliom

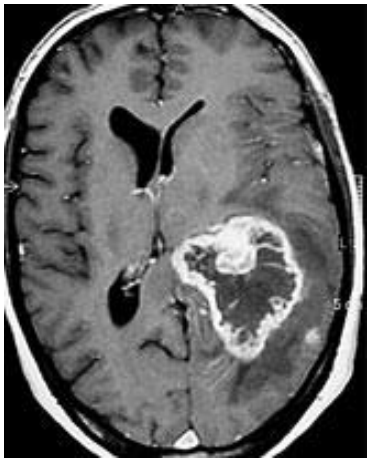


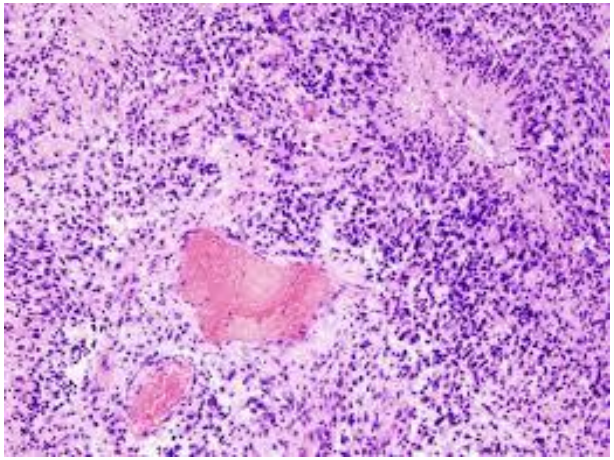
MRT



Histologie

Glioblastom





- **Histologie**
- **WHO Grad**
- **Molekulare Marker**
  (IDH1/2, MGMT, LOH1p19q)

- **Alter**
- **Karnofsky Score**

- **Ausmaß der Resektion**

- **Strahlentherapie**
- **(Chemotherapie)**

Neurologische Symptome

Erstdiagnose

Patienten-zentrierte Kommunikation

Nach der Krebsdiagnose - ist alles anders …

… ein Sturz aus der normalen Wirklichkeit

… ein kritisches Lebensereignis und Lebenskrise

Was bedeutet die Diagnose?

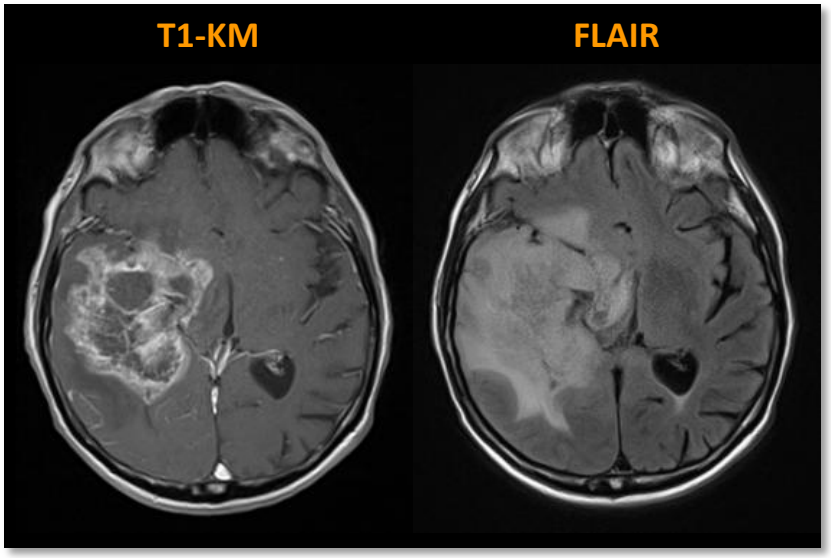
Was ist hilfreich?

Was gibt Sicherheit und Trittfestigkeit?

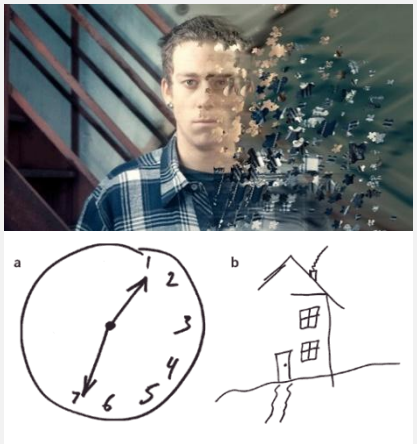
Betonung von Individualität (Autonomie) und Gemeinsamkeit

Neurologische Symptome

Glioblastoma multiforme WHO IV

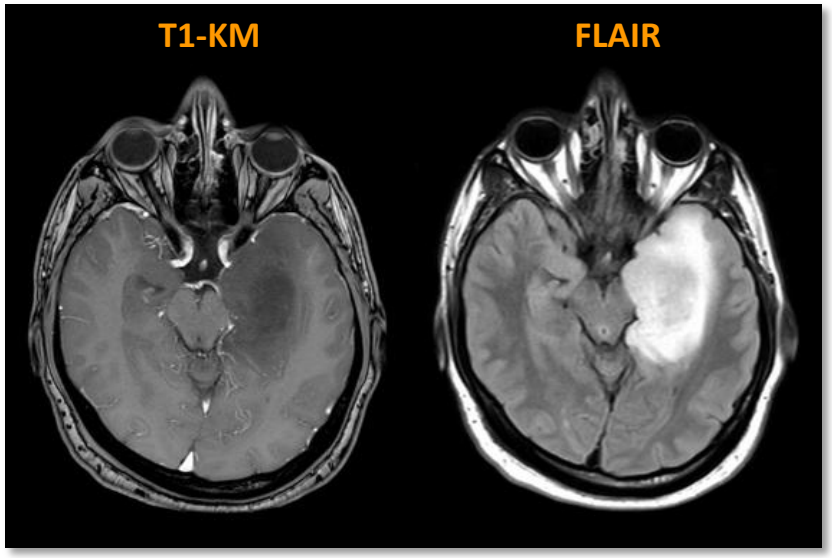


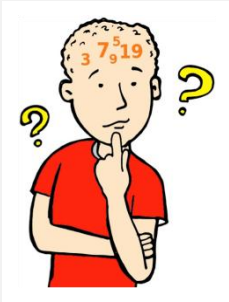
Hemiparese links



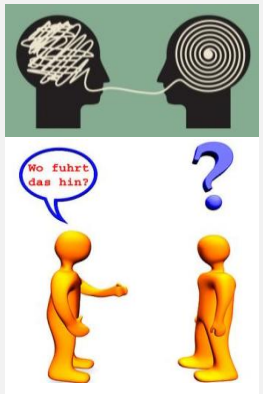
Neglect links

Diffuses Astrozytom WHO II





Gedächtnis



Sprache Kommunikation

Epileptische Anfälle

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Neurologische Symptome

Symptome	initial (%)	Diagnose (%)
Epileptische Anfälle	**38**	**54**
Kopfschmerzen	35	71
Neurokognitive Defizite (OPS)	**17**	**52**
Lähmung (Hemiparese)	**10**	**43**
Erbrechen	8	31
Sprachstörung (Aphasie)	**7**	**27**
Sehstörungen	4	18
Gefühlsstörung (Hemihypästhesie)	3	14
Sehstörung (Hemianopsie)	2	8
Hirnnervenausfall	2	1

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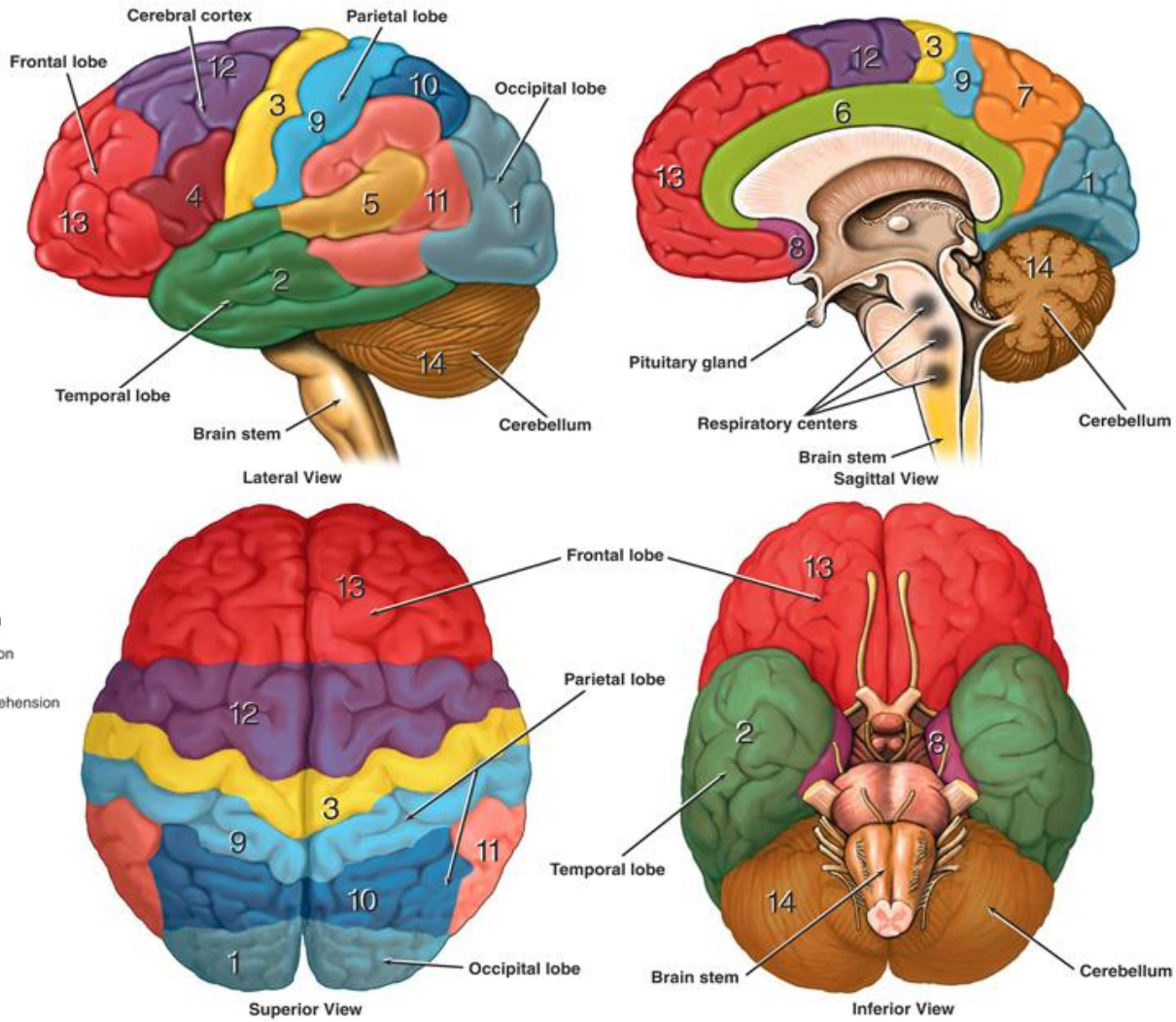
Anatomie und Funktionen

Functional Areas of the Cerebral Cortex

1. **Visual Area:** Sight, Image recognition, Image perception
2. **Association Area** Short-term memory, Equilibrium, Emotion
3. **Motor Function Area** Initiation of voluntary muscles
4. **Broca's Area** Muscles of speech
5. **Auditory Area** Hearing
6. **Emotional Area** Pain, Hunger, "Fight or flight" response
7. **Sensory Association Area**
8. **Olfactory Area** Smelling
9. **Sensory Area** Sensation from muscles and skin
10. **Somatosensory Association Area** Evaluation of weight, texture, temperature, etc. for object recognition
11. **Wernicke's Area** Written and spoken language comprehension
12. **Motor Function Area** Eye movement and orientation
13. **Higher Mental Functions** Concentration, Planning, Judgment, Emotional expression, Creativity, Inhibition

Functional Areas of the Cerebellum

14. **Motor Functions** Coordination of movement, Balance and equilibrium, Posture



Quelle: ©2014 MidBrainPower

Filmbeispiele

Neurologische Symptome

Lähmung - Parese

Quelle. www.youtube.com

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Sprachstörung - Aphasie

Quelle. www.youtube.com

Grand mal Anfall

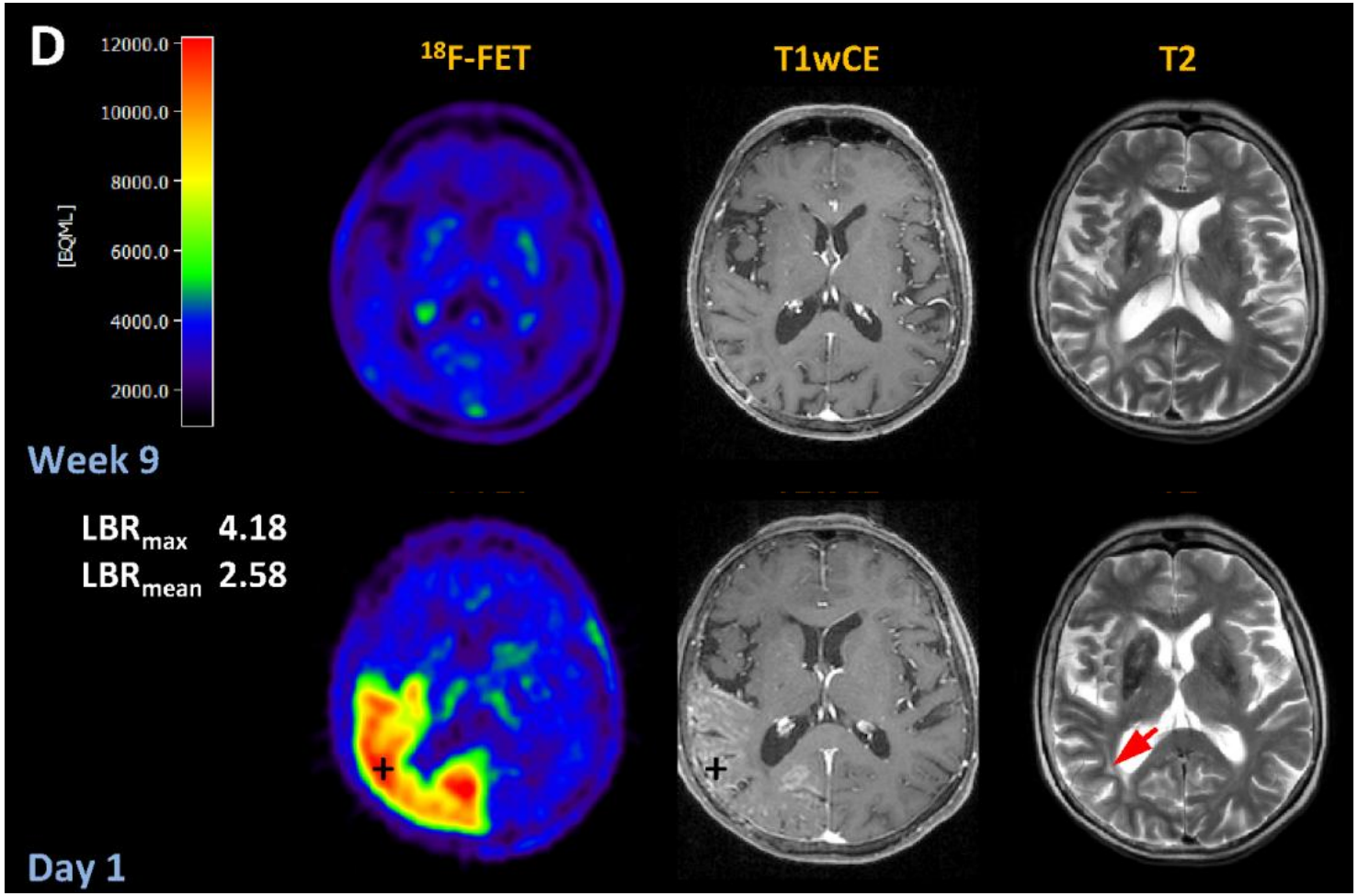
Symptomatische Epilepsie

Tumorentität	Häufigkeit
Oligodendrogliome, Gangliogliome	80%-90%
Astrozytome	70%
Anaplastische Astrozytome und Glioblastome	50%
Meningeome	50%
Hirnmetastasen	30%
Primäre ZNS-Lymphome	15%

TAKO Leitlinien Tirol - Neuroonkologie
(Stockhammer et al. 2012)

Epileptische Anfälle

Status epilepticus



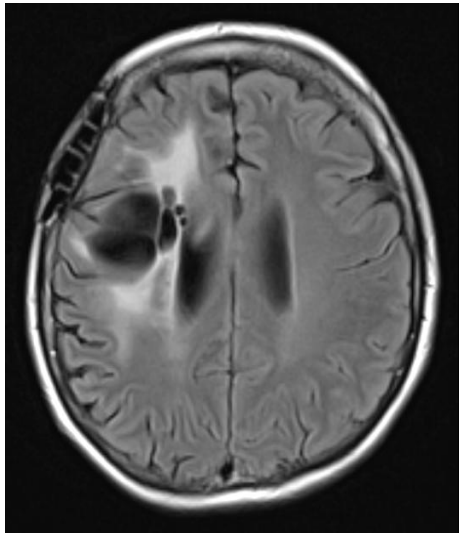
Hutterer et al., 2016, in Revision

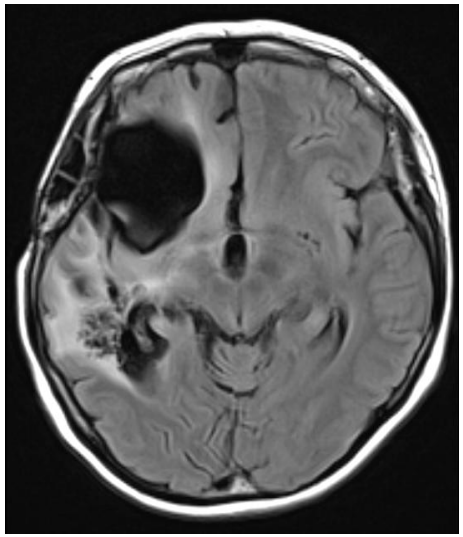
Verhaltens- und Wesensänderungen

- Antriebslosigkeit (Psychomotorik)
- Vernachlässigung vertrauter Gewohnheiten
- Störung von Konzentration und Aufmerksamkeit
- Störung der Merkfähigkeit

vor allem bei: **Frontallappentumoren**
Temporallappentumoren

Neurokognition





42 jährige Patientin - Anaplastisches Oligoastrozytom WHO III

- **Antriebslosigkeit** + **Müdigkeit** (2 x Schlaf untertags für 60 Min)
  laut Gatte: psychisch und körperlich nicht belastbar
- **Wesensveränderung**
- **Aufmerksamkeit + Konzentration** → **Gedächtnisleistungen**
  → **Orientierung**

  rasche Überforderung
  - bei komplexeren Handlungen (z.B. kochen, einkaufen)
  - bei zu vielen Reizen (mehrere Stimmen, spielende Kinder)

  Stress + Überforderung = Verstärkung der Defizite
- **Symptomatische Epilepsie**
  - *Antiepileptika* → mäßige Verträglichkeit
  - *Fahrverbot* → Mobilität, Selbstständigkeit (lebt am Land)
  - *Kind* → erlebte Grand mal Anfall mit Kopfverletzung
- **Angst** → epileptische Anfälle + Krankheit + Zukunft
- **Folgen** → **sozialer Rückzug, Überforderung (Kind), Depression**

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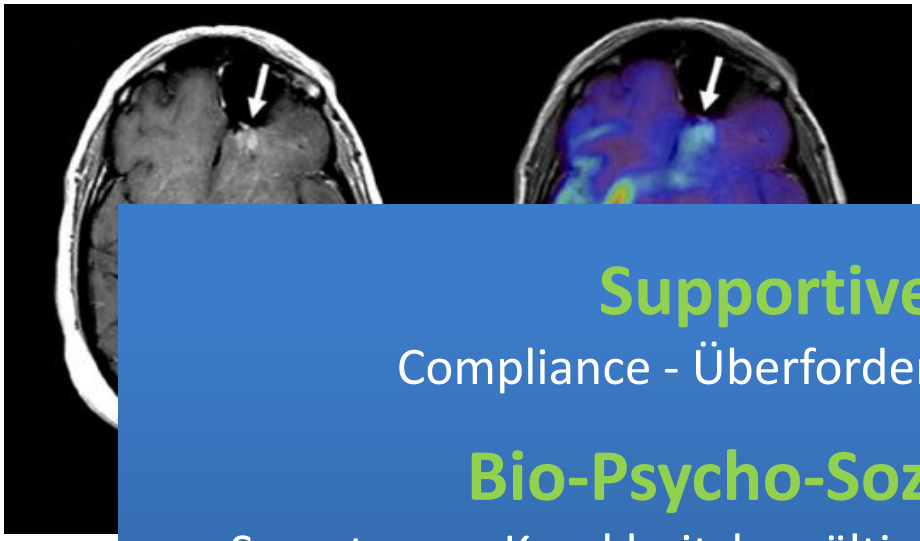
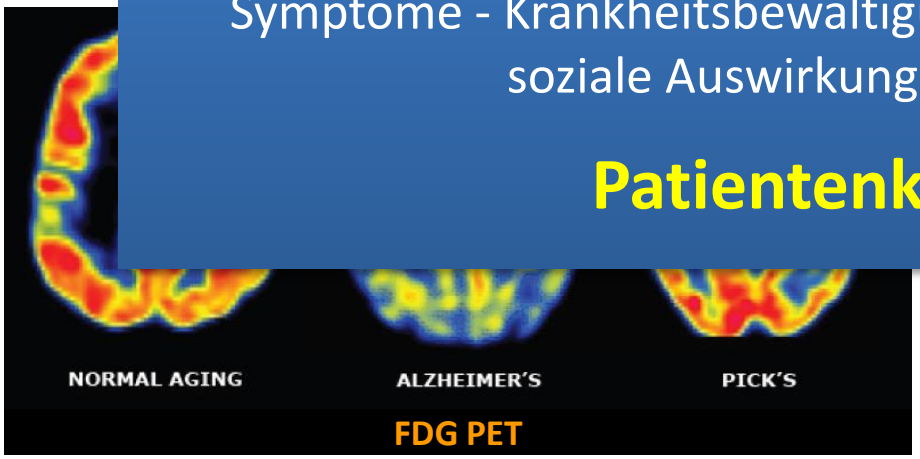
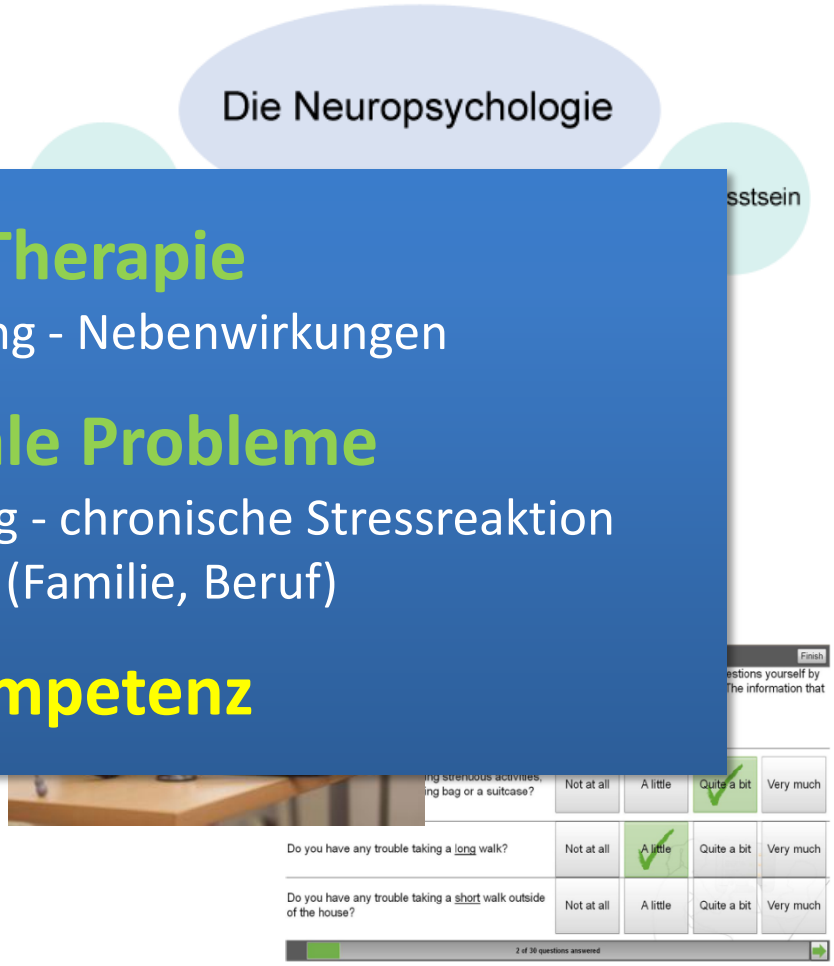
Neurokognition







Supportive Therapie

Compliance - Überforderung - Nebenwirkungen

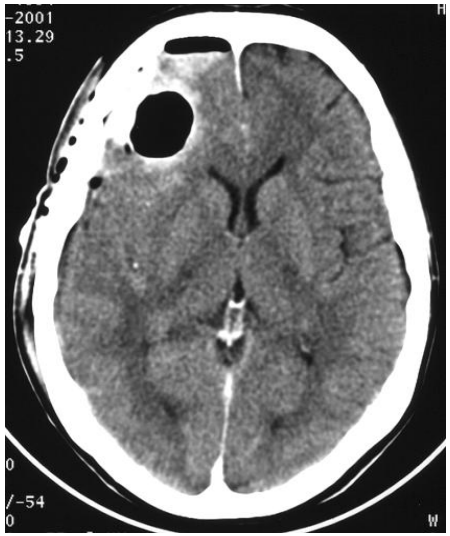
Bio-Psycho-Soziale Probleme

Symptome - Krankheitsbewältigung - chronische Stressreaktion
soziale Auswirkungen (Familie, Beruf)

Patientenkompetenz

Standardtherapie

Glioblastom WHO IV



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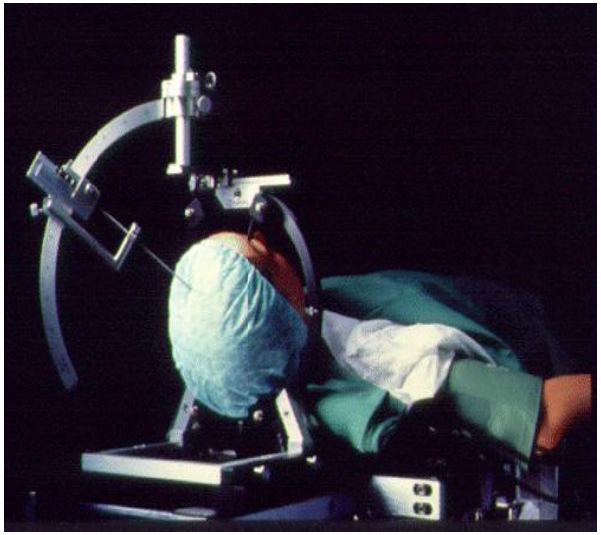

Operation

Stereotaktische Biopsie

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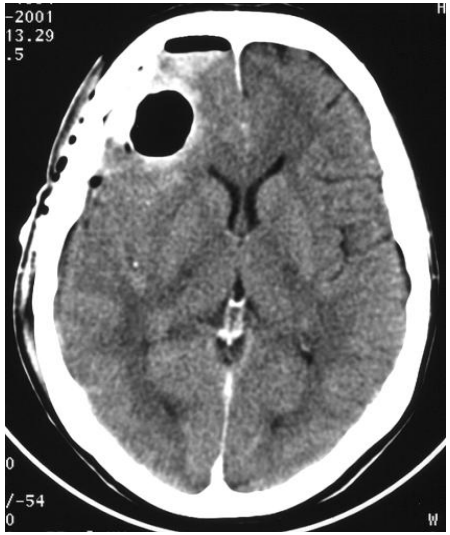
Glioblastom WHO IV



Operation

Radio- (Chemo-) Therapie

Temozolomid

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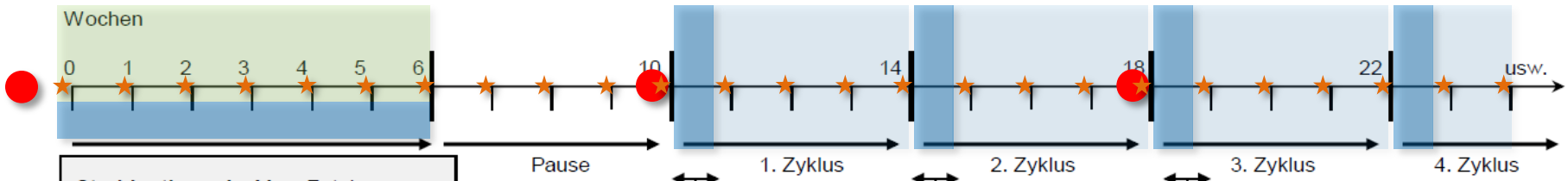
Glioblastom WHO IV

Operation => Strahlen- und Chemotherapie analog EORTC 26981 (Stupp et al., NEJM 2005)



Strahlentherapie: Mo – Fr tgl.

und

Chemotherapie:
Temodal 75 mg/qm KOF; Tag 1-ca.42

Übelkeit: Ondansetron 8 mg
60 min Pause
Chemotherapie: Temodal: ..... mg
60 min Pause
Bestrahlung

wöchentliche Kontrolle:
diff-BB, Krea, Hst, GOT, GGT, CRP

Prophylaxe gg. Lungenentzündung:
Cotrim forte Di & Do

Tag 1-5 zur Nacht:
Ondansetron 8 mg
60 min Pause
Temodal
150 mg/qm KOF:

..... mg

Tag 1-5 zur Nacht:
Ondansetron 8 mg
60 min Pause
Temodal
200 mg/qm KOF:

..... mg

Tag 1-5 zur Nacht:
Ondansetron 8 mg
60 min Pause
Temodal
200 mg/qm KOF:

..... mg

Strahlentherapie

Temozolomid Chemotherapie

Laborkontrolle

Neuroonkologie Ambulanz

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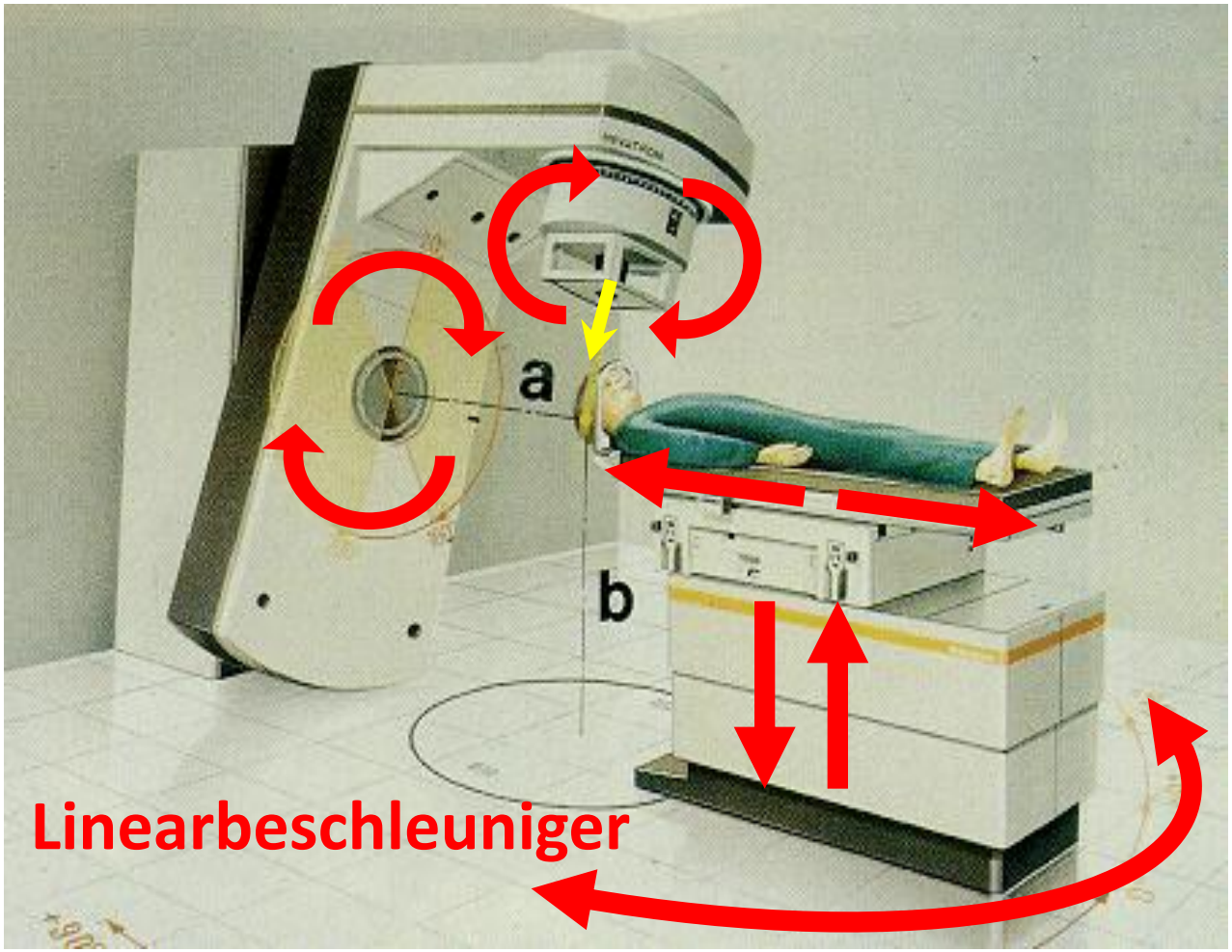
Glioblastom WHO IV



TMZ
Chemotherapie

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Glioblastom WHO IV

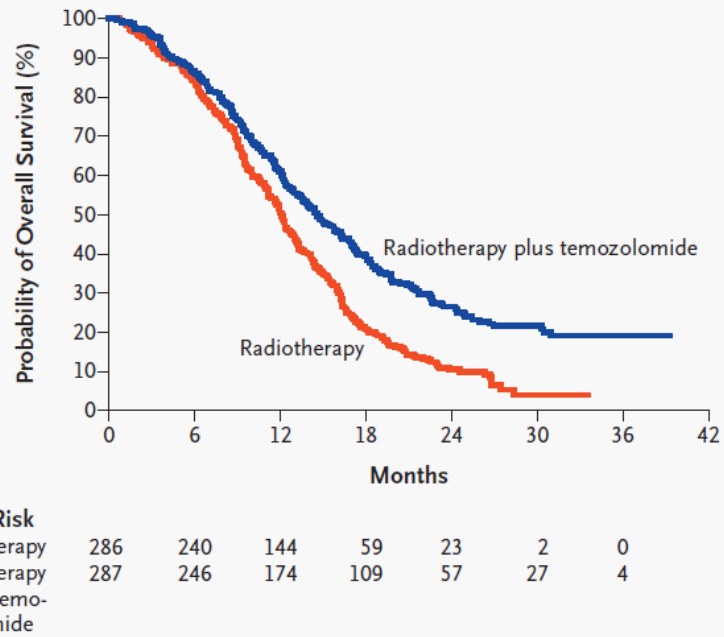


Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

Stupp et al., NEJM 2005

Glioblastom – Optune (NovoCure)

Tumor Treating Fields Are Delivered by the NovoTTF-100A System

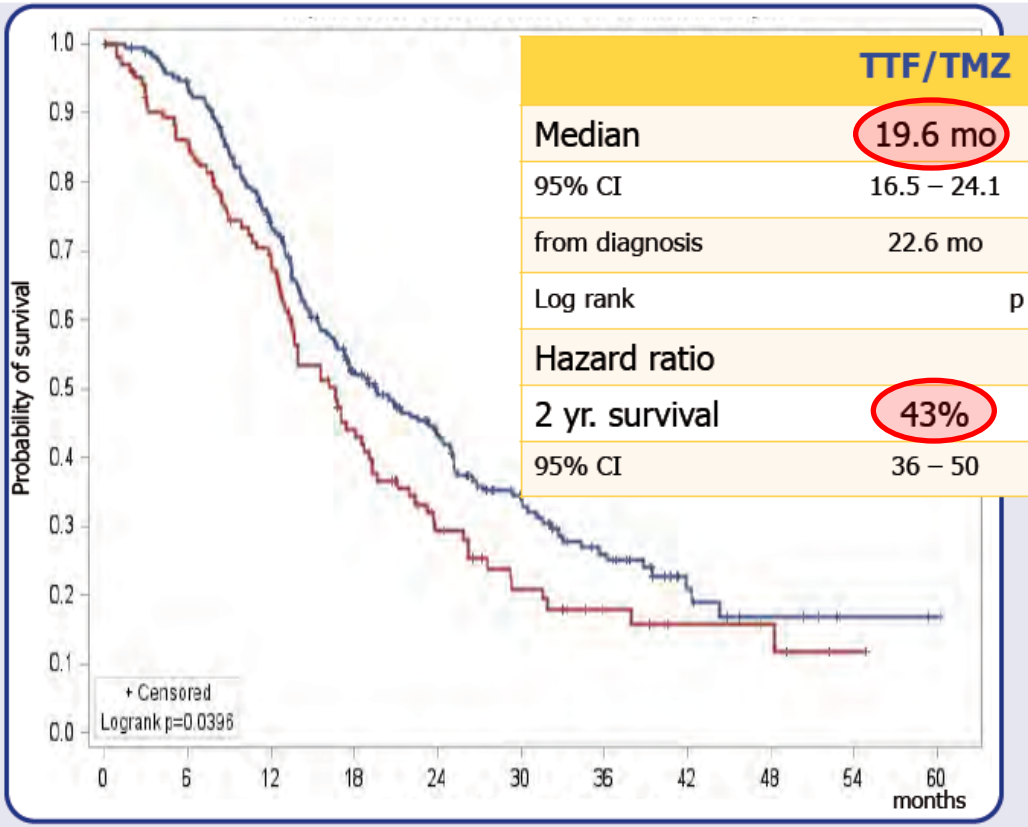
- Tumor Treating Fields (NovoTTF Therapy) uses the principles of physics and electricity to disrupt mitosis[1,2]
  - Specifically targets dividing cancer cells, not quiescent normal cells[1]
- Single-use transducer arrays deliver NovoTTF Therapy through the scalp[3]
  - Arrays deliver NovoTTF Therapy at a low intensity (1-3 V/cm) and intermediate frequency (200 kHZ)[4]

1. Kirson ED, et al. Proc Natl Acad Sci. 2007;104(24):10152-10157. 2. Gutin PH, Wong ET. ASCO Educ Book. 2012;32:126-131.
3. NovoTTF-100A Patient Information &Operation Manual. Novocure Inc. Document number QSD-QR-331. Rev. 10. Jan 22, 2014.
4. NovoTTF-100A System Instructions for Use. Novocure Inc. Document number QSD-QR-330. May 12, 2013.

novocure™

Glioblastom – Optune (NovoCure)

Overall - survival
(2° endpoint, ITT population)



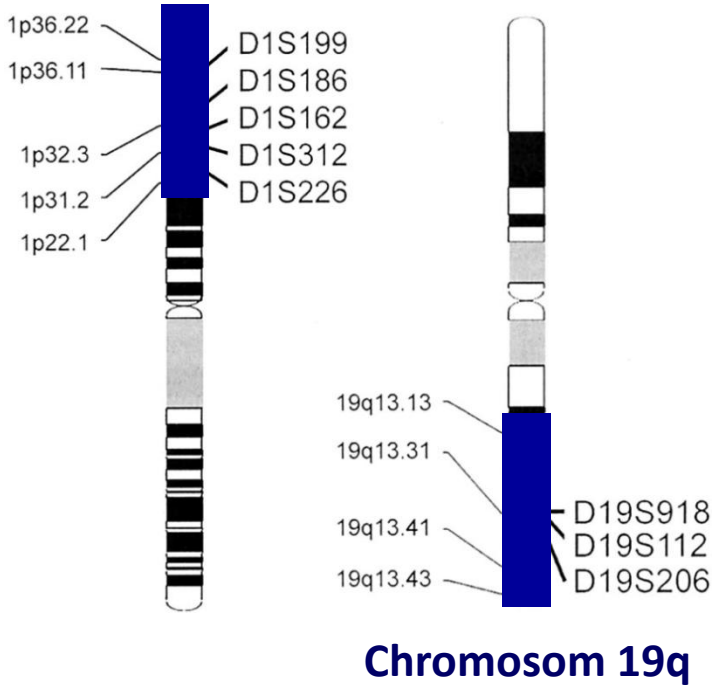
	TTF/TMZ	Adj. TMZ
Median	19.6 mo	16.6 mo
95% CI	16.5 – 24.1	13.5 – 19.1
from diagnosis	22.6 mo	19.6 mo
Log rank	p = 0.034	
Hazard ratio	0.75	
2 yr. survival	43%	29%
95% CI	36 – 50	21 – 39

Stupp et al., JAMA 2015 Dec

Oligodendrogliom – LOH1p19q

OLIGODENDROGLIOMA

Chromosom 1p



Chromosom 19q

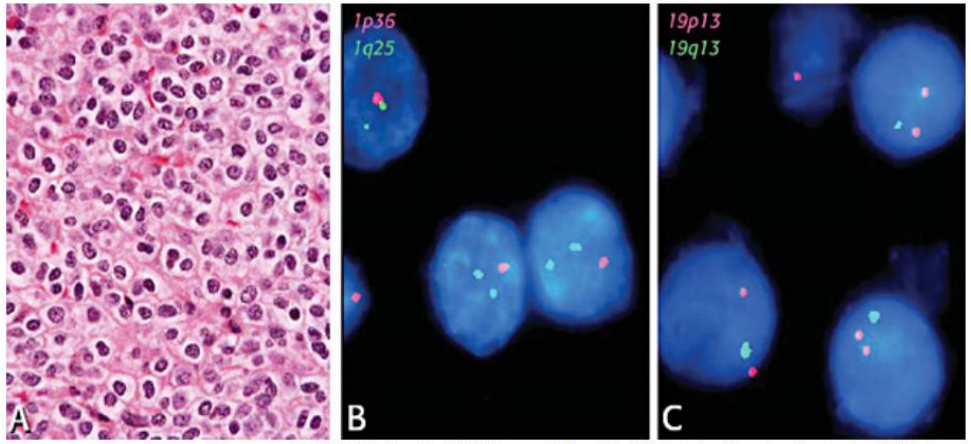
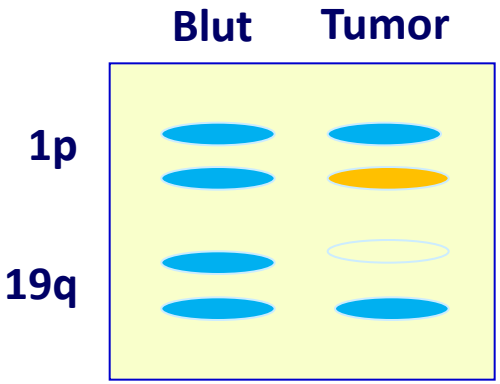


Figure 1: Oligodendroglioma grade II (WHO) with LOH 1p and 19q. *(A) H&E stain showing the typical "fried egg" appearance. (H&E stain). (B) Fluorescence In Situ Hybridization (FISH) for Chromosome 1p: The cells show 1 red signal and 2 green signals indicating a deletion of 1p36. (C) FISH for chrosome 19q: The cells show 1 green signal and 2 red signals indicating a deletion of 19q13.*



Hatanpaa et al., Lab Invest 2003

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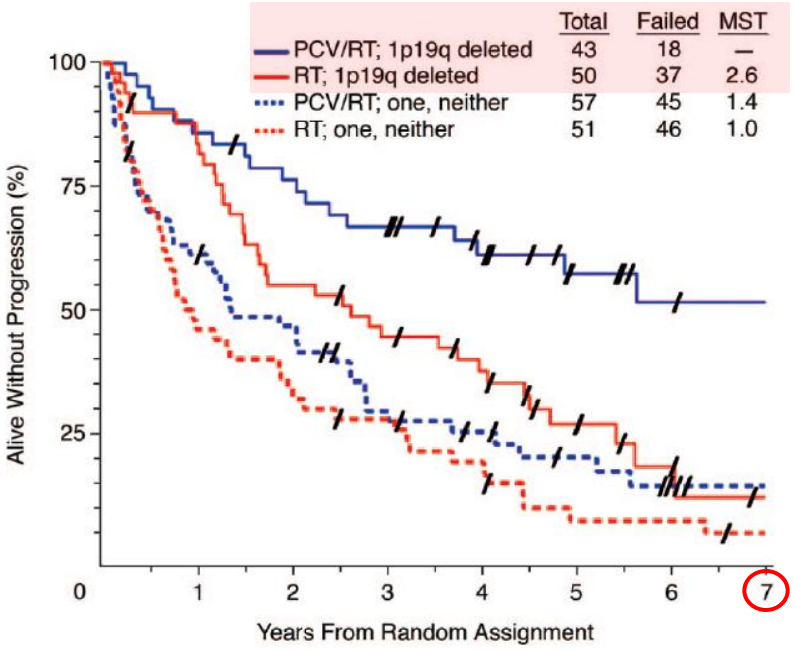
Oligodendrogliom WHO III

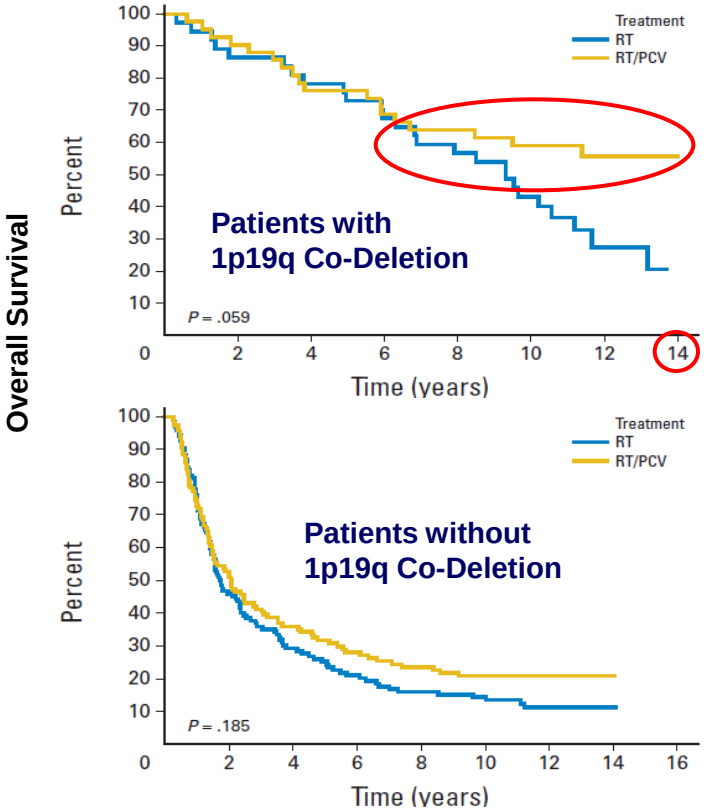
Phase III Trial of Chemotherapy Plus Radiotherapy Compared With Radiotherapy Alone for Pure and Mixed Anaplastic Oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402

Cairngross et al., JCO 2006



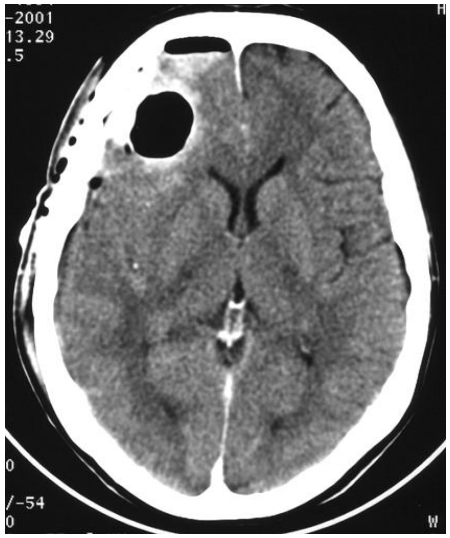
Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

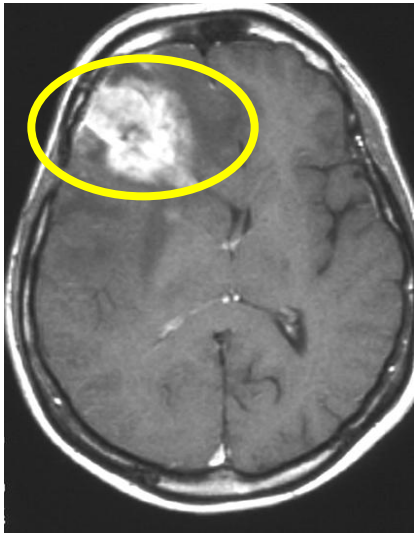
van den Bent et al., JCO 2006 and **van den Bent et al.**, JCO 2013



Rezidivtherapie

Glioblastom - Rezidiv



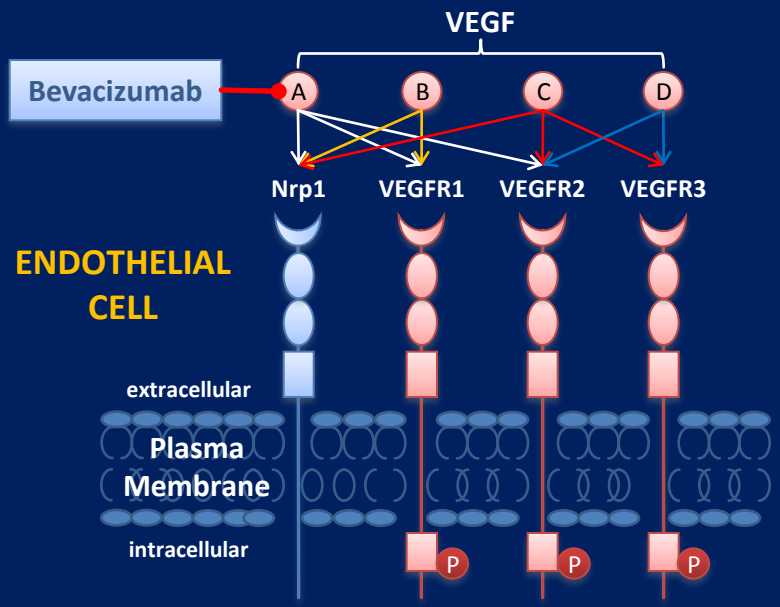


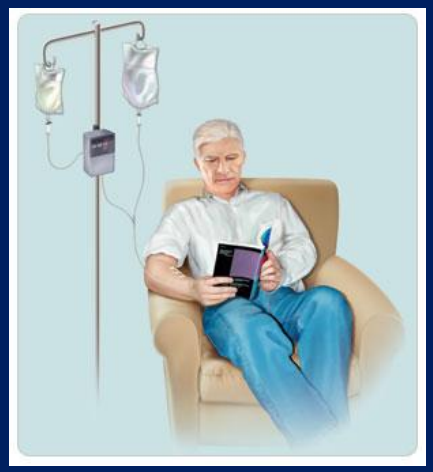
Re-Operation? Re-Bestrahlung?

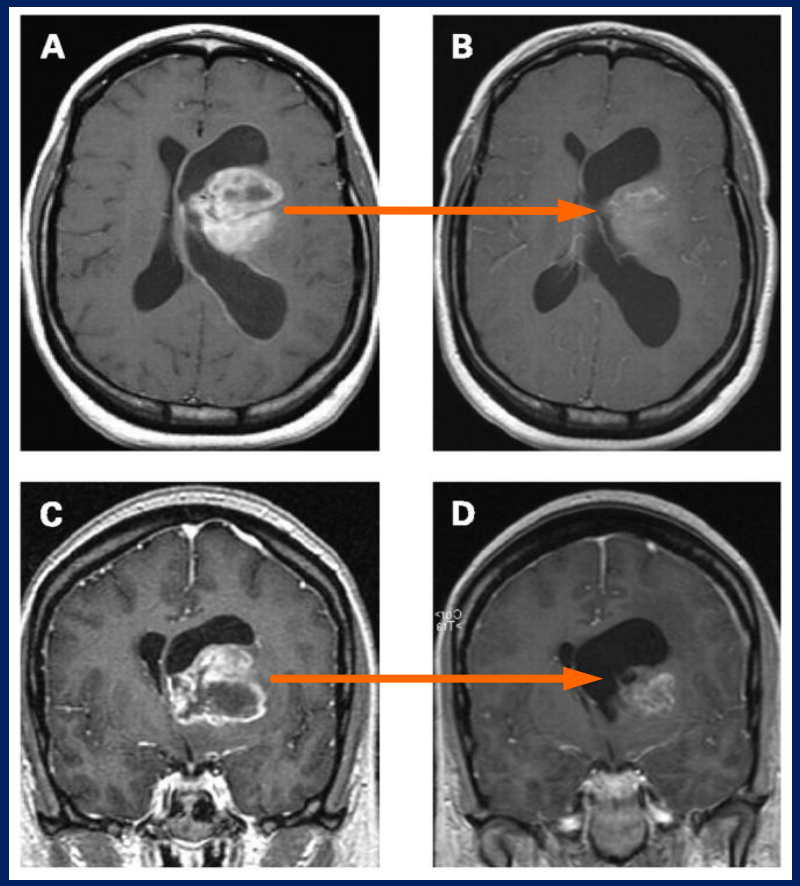
Andere Chemotherapie	z.B. TMZ, Lomustin/Procarbazin
Zielgerichtete Therapie	z.B. Bevacizumab
Experimentelle Therapie	z.B. Vakzinierungstherapie

Palliative Therapie

Antiangiogene Therapien







n = 35 patients

6-month progression-free survival	**PFS6**	**46%**
6-month overall survival	**OS6**	**77%**
Partial Response Rate	**PR**	**57%**

Vredenburgh et al, Clin Cancer Res 2007; Vredenburgh et al, JCO Oct 2007

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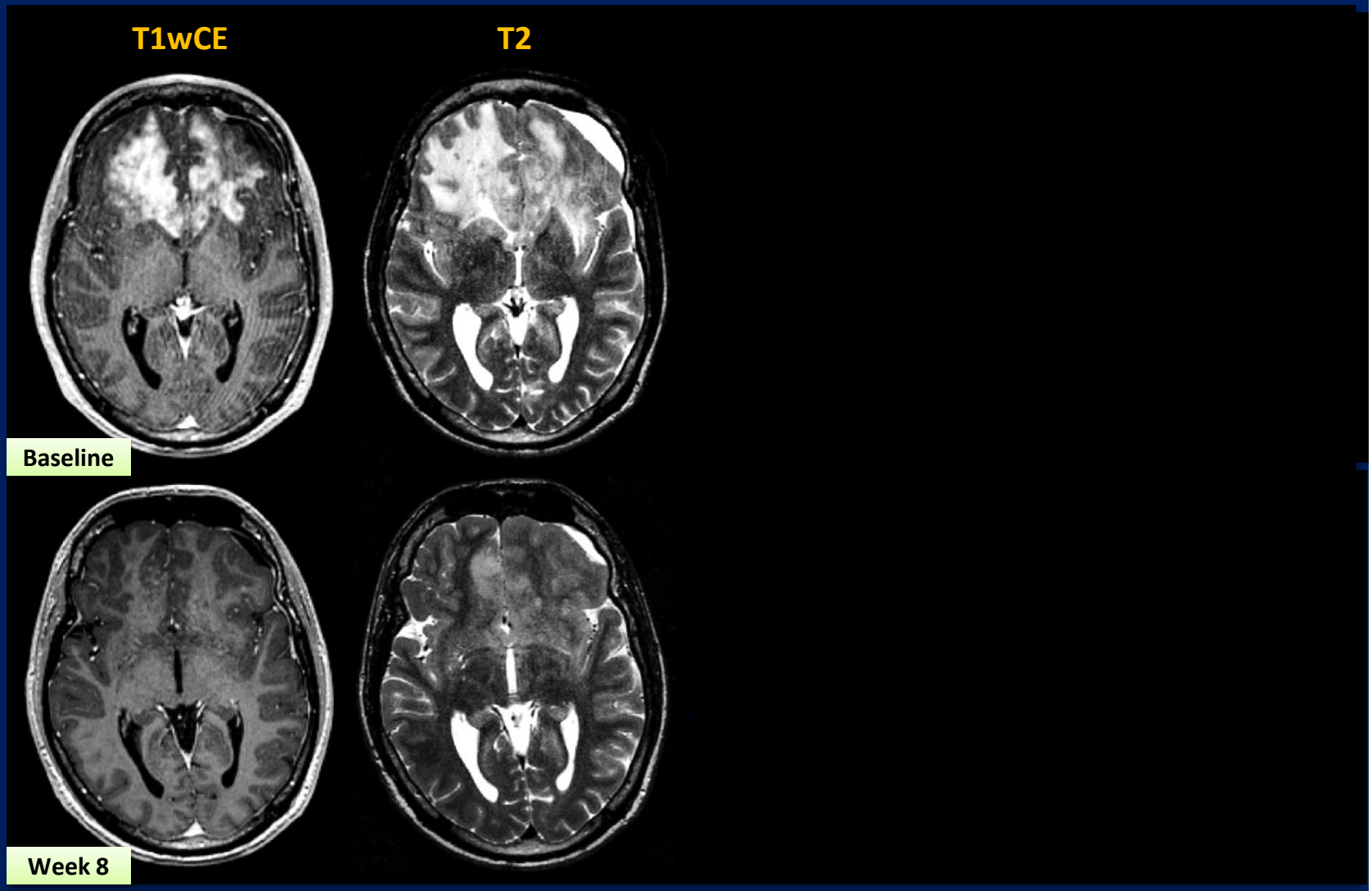
Antiangiogene Therapien

Bevacizumab + Irinotecan



Hutterer et al., J Nucl Med 2011

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Hirnmetastasen

und

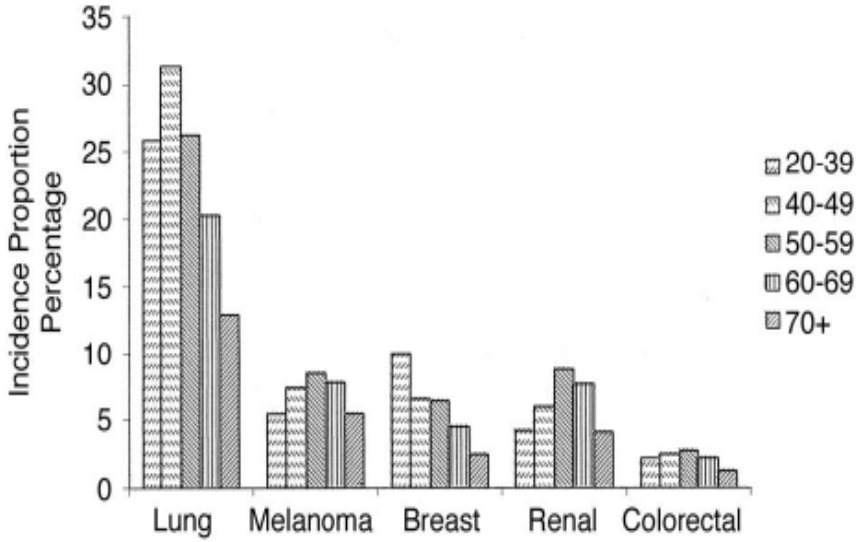
Meningeosis neoplastica

Hirnmetastasen

Hirnmetastasen
- treten in **10-30%** aller erwachsenen Tumorpatienten auf
- sind etwa **10-fach häufiger** als primäre hirneigene Tumore
- **relativ steigende Inzidenz** durch
  - effektive Systemtherapien mit verlängerten Überlebenszeiten
  - Verbesserung der bildgebender Techniken (cMRT)

Primärtumore zerebraler Metastasen

- Bronchialkarzinom (30-50%)
- Mammakarzinom (10-20%)
- Melanom (20-45%)
- Hypernephrom (Niere)
- Gastrointestinalen Tumoren

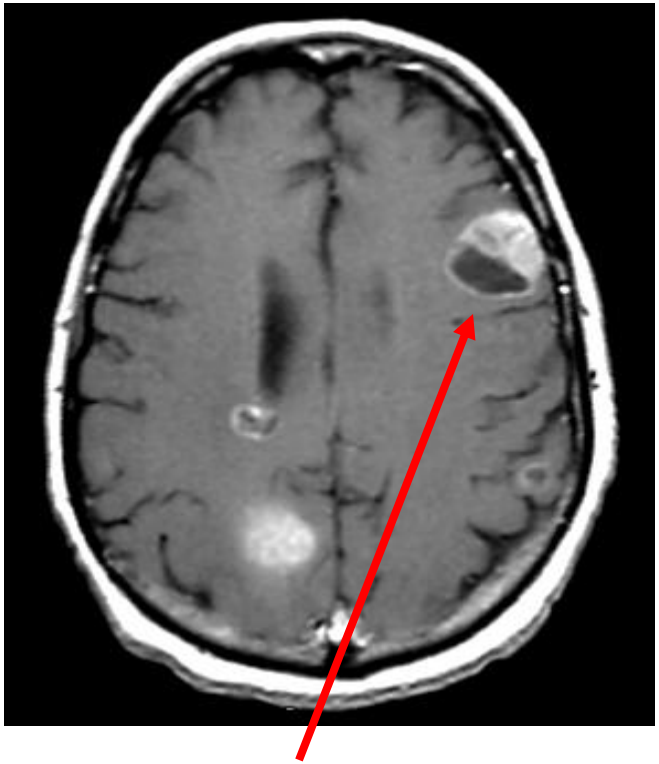


Barnholtz-Sloan et al., J Clin Oncol 2004

Hirnmetastasen

Bildgebung und Therapie

- gut abgrenzbar vom umliegenden Gewebe
- **Resektion** einzelner Metastasen möglich
  (<3 cm, maximale Anzahl)
- **Bestrahlung**
  - Ganzhirn-Bestrahlung vs.
  - stereotaktische Bestrahlung (Radiochirurgie)
- ggf. **Systemtherapie**



Lokalisation

- Rinden-Mark Grenze
- multilokulär

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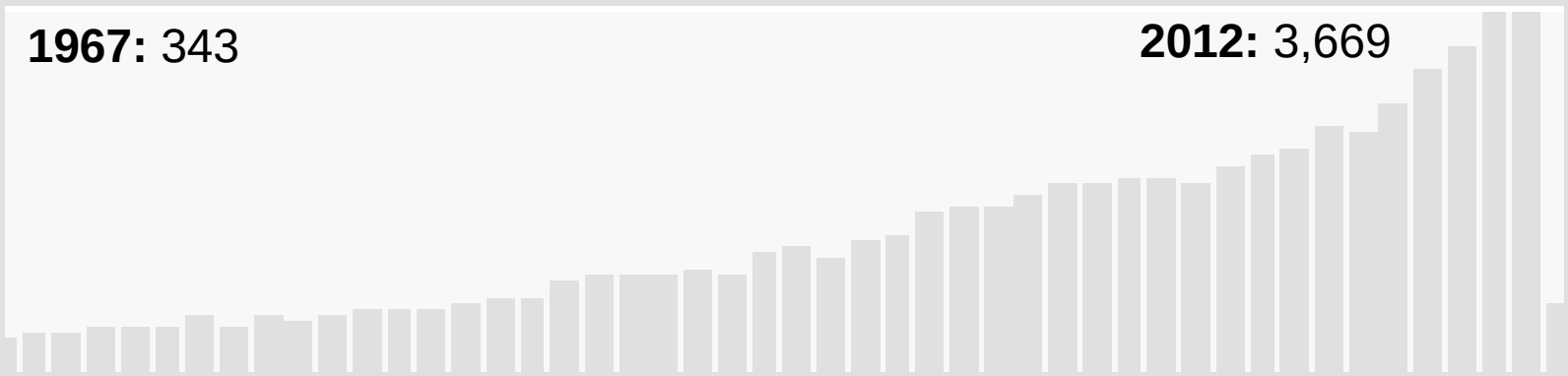
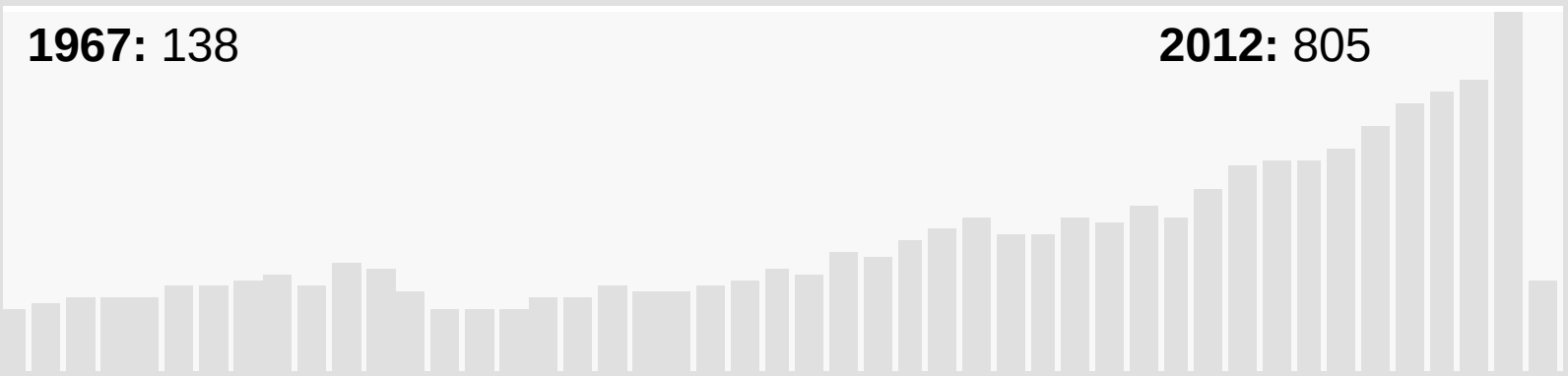
Forschung – Hirnmeta vs. Gliom



Total number of articles „**glioma**“: **61.507**



Total number of articles „**brain metastases**“: **14.104**

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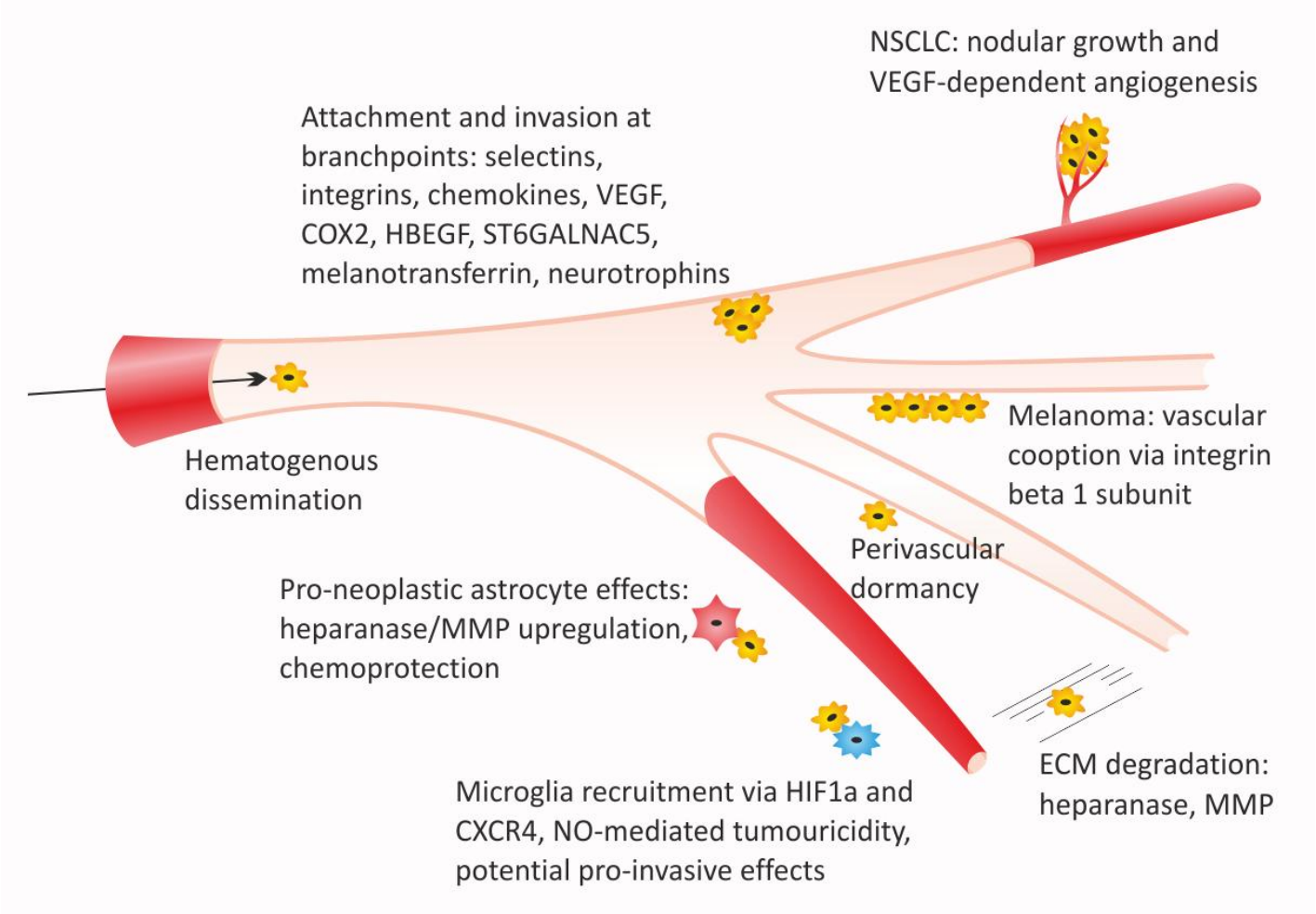
Hirnmetastasen - Pathogenese



Preusser et al., Acta Neuropath 2012

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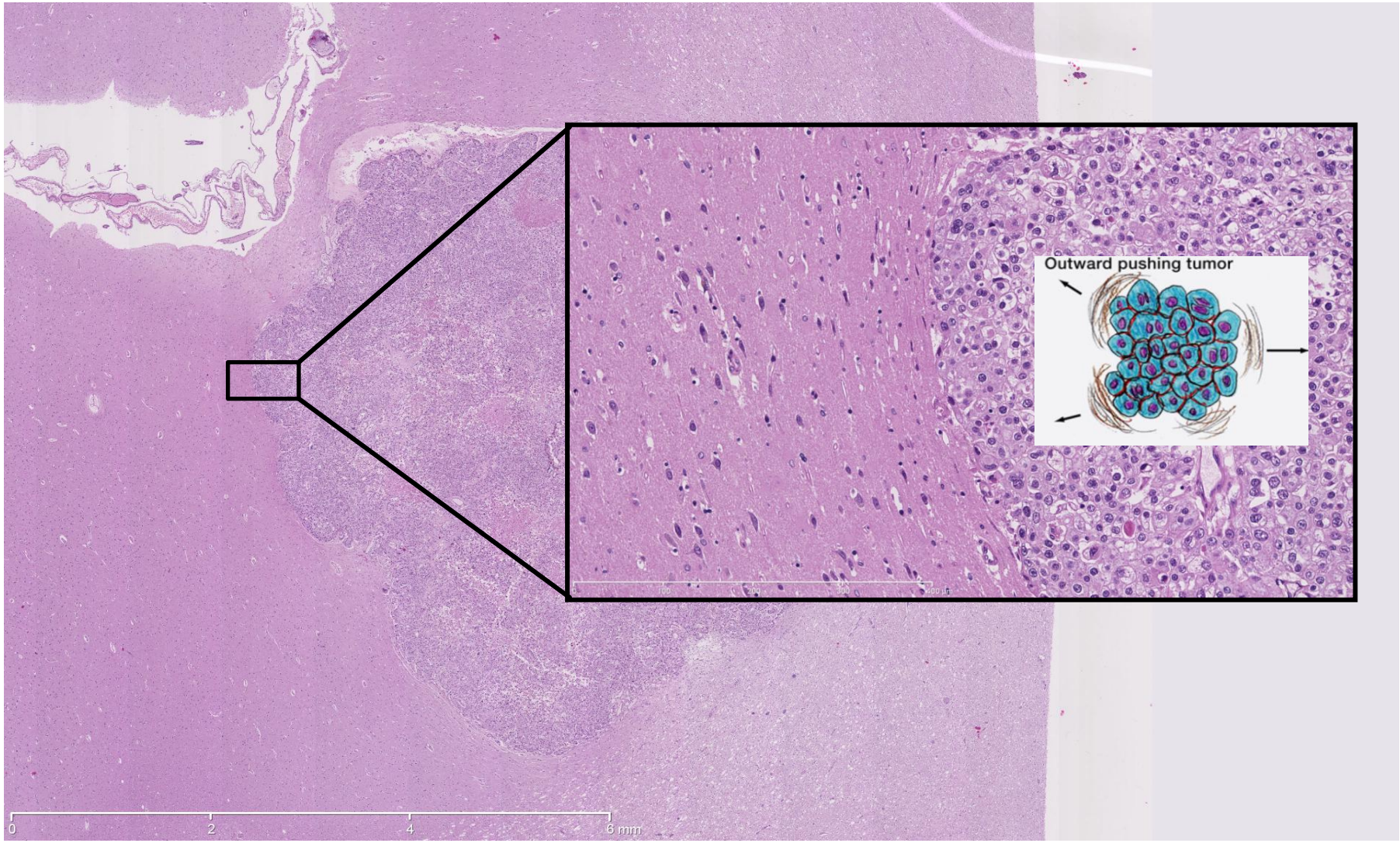
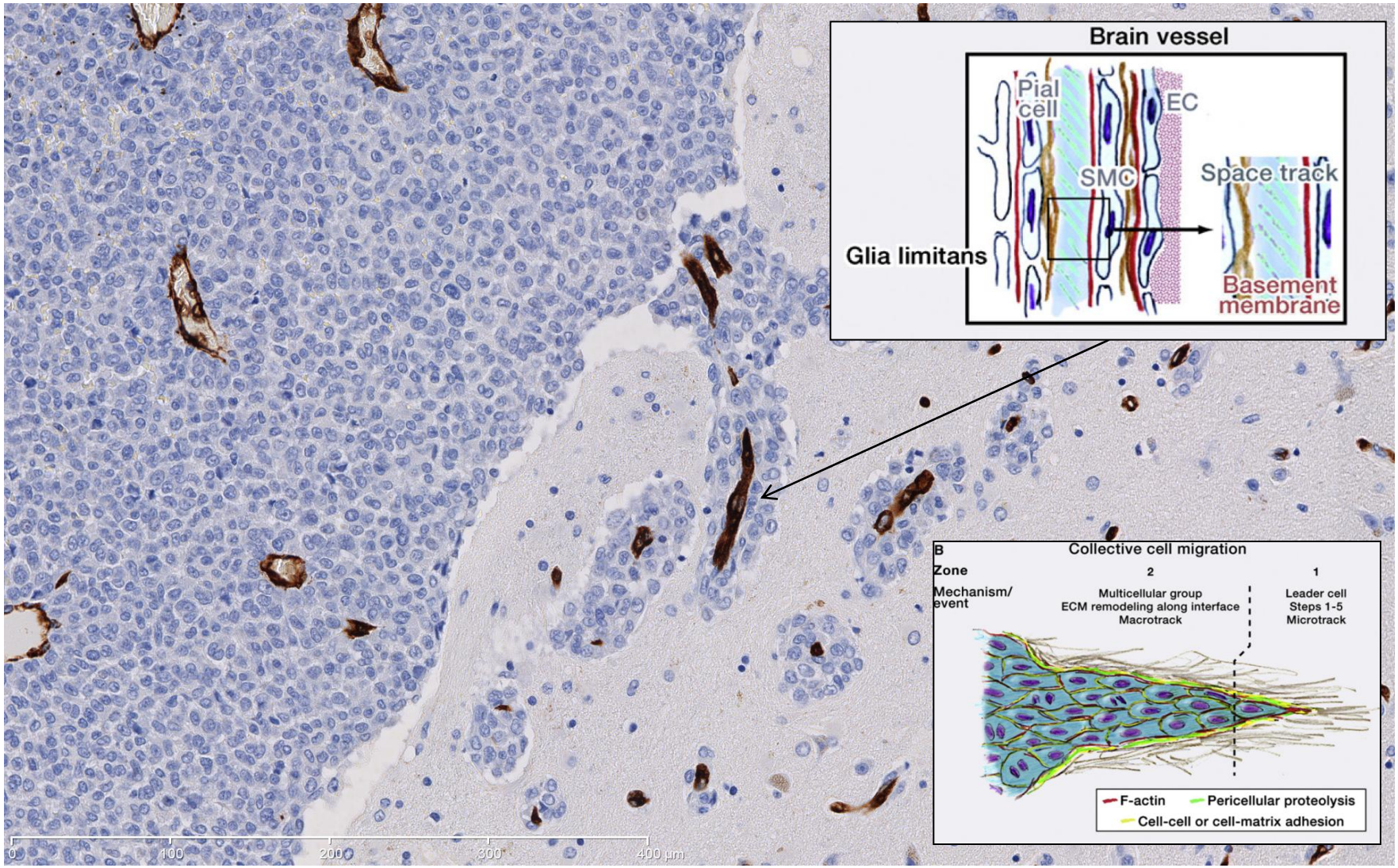
„Well-Delineated“ (51% of brain Mets)



Clear Cell Carcinoma Brain Metastasis

Universität Regensburg

„Perivascular Growth - Vascular Cooption“ (18%)



Melanoma Brain Metastasis - anti-CD34

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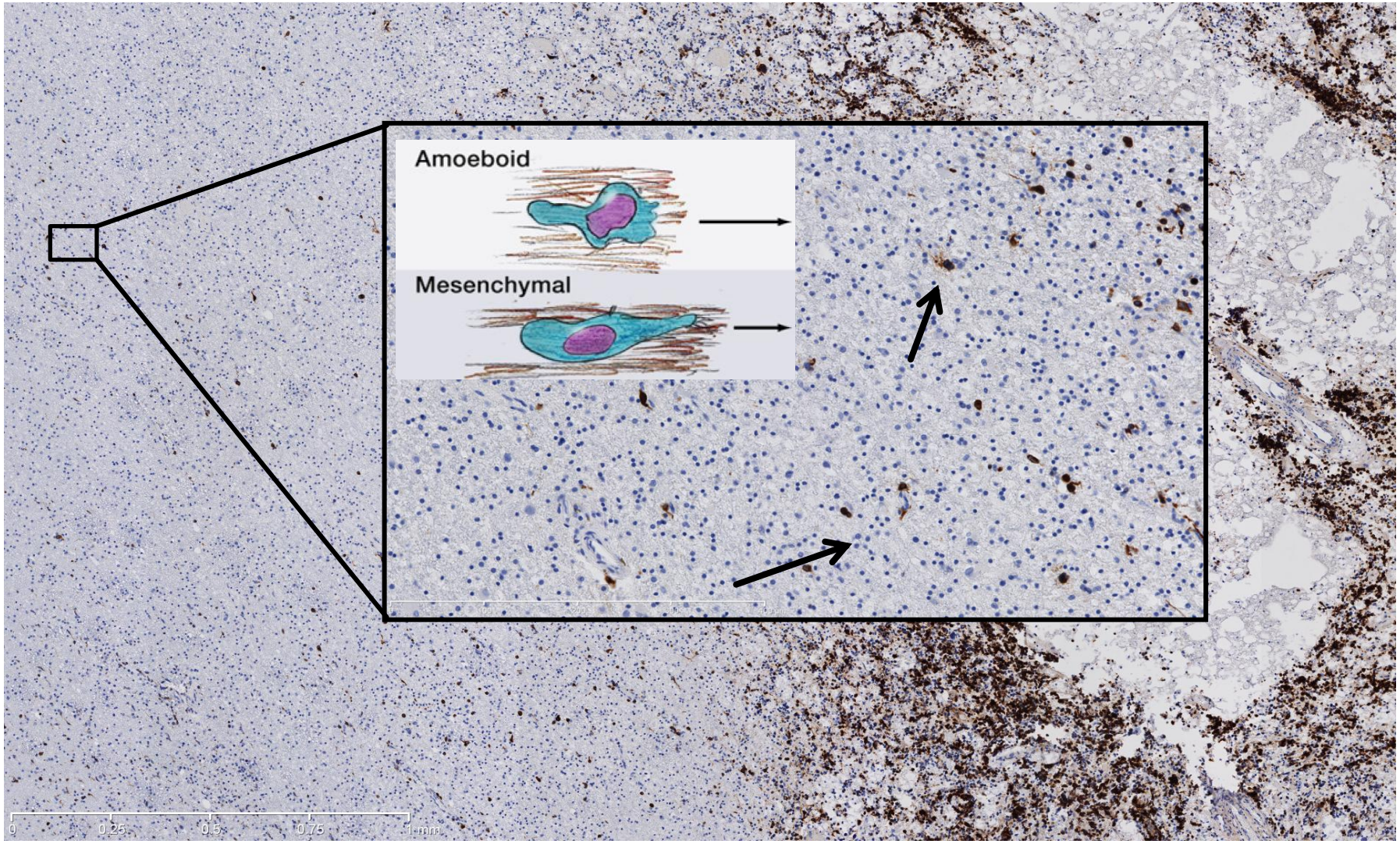
„Diffuse Glioma-like“ (32%)



Small Cell Lung Cancer Brain Metastasis - anti-CK18

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Hirnmetastasen

Oligodendrocytes

Microglia

Neurons

Astrocytes

Microenvironment

Natural Killer Cells

Macrophages

Lymphocytes

Extracellular Matrix - Integrins

Growth Factors

Growth Factor Receptors

Cytokines

Interleukins

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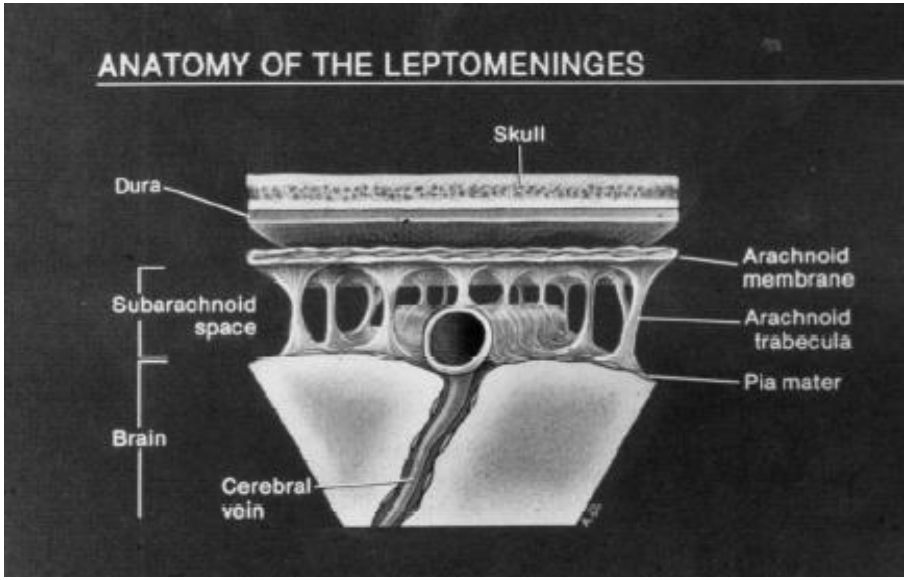
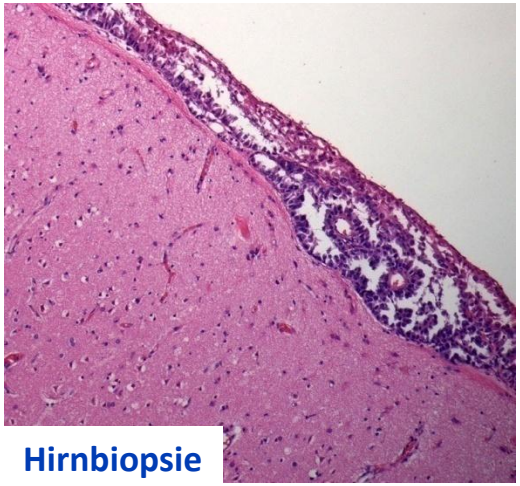
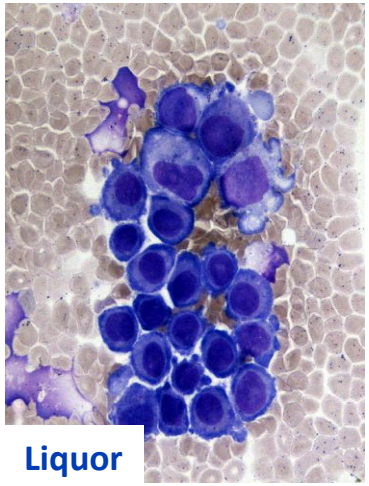
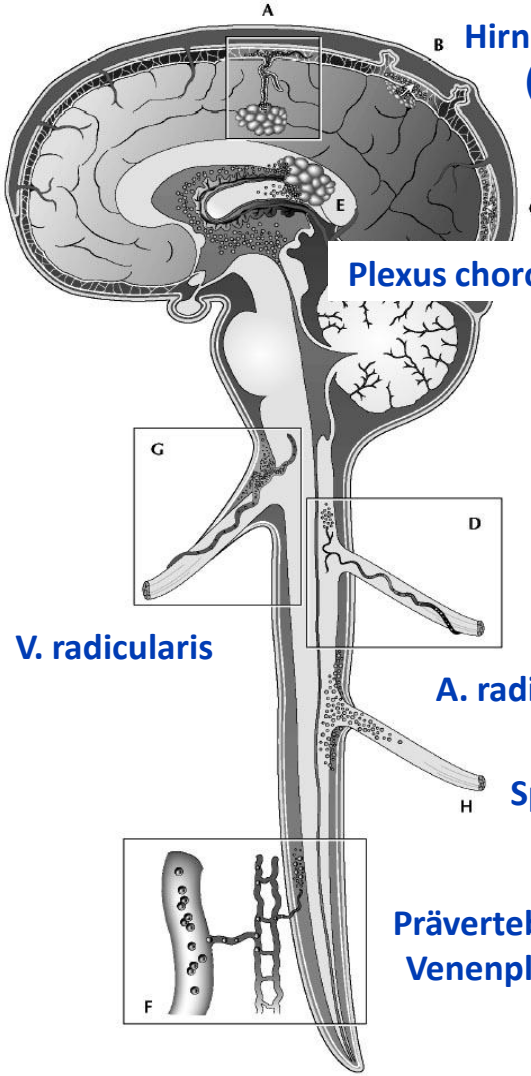




Hirnbiopsie



Liquor



Hirnparenchym (Virchow-Robin`sche Räume)

Hirnparenchym (Cortex)

Schädelkalotte

Plexus choroideus

V. radicularis

A. radicularis

Spinalwurzel

Prävertebraler Venenplexus

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Meningeosis neoplastica

Primärtumore
Prävalenz (Rate pro 100 000 Einwohner)

	Mann	Frau
Prostata-CA	**115,1**	-
Mamma-CA	-	**24,3**
Lungen-Tumore	**52,7**	**18,5**
Melanom	13,3	13,1
Gehirn-Tumore	7,3	5,2

Meningeose
nach Häufigkeit der Primärtumoren

Mamma-CA		**27-50%**
Lungen-Tumore		**22-36%**
Adeno-CA	**50-56%**	
Plattenepithel-CA	26-36%	
SCLC	13-14%	
Melanom		**10-12%**
Cancer of Unknown Primum		**1-7%**
GIT, Sarkom, Harnwege		**je 3%**

Tumorstatus

- Erstmanifestation einer systemischen Tumorerkrankung <5%
- Gute extrazerebrale Tumorkontrolle 35%
- **Disseminierte oder progrediente Tumorerkrankung 65%**
- **Simultane Hirnparenchym-Metastase(n) 30-50%**

Chamberlain, J Clin Oncol 2005

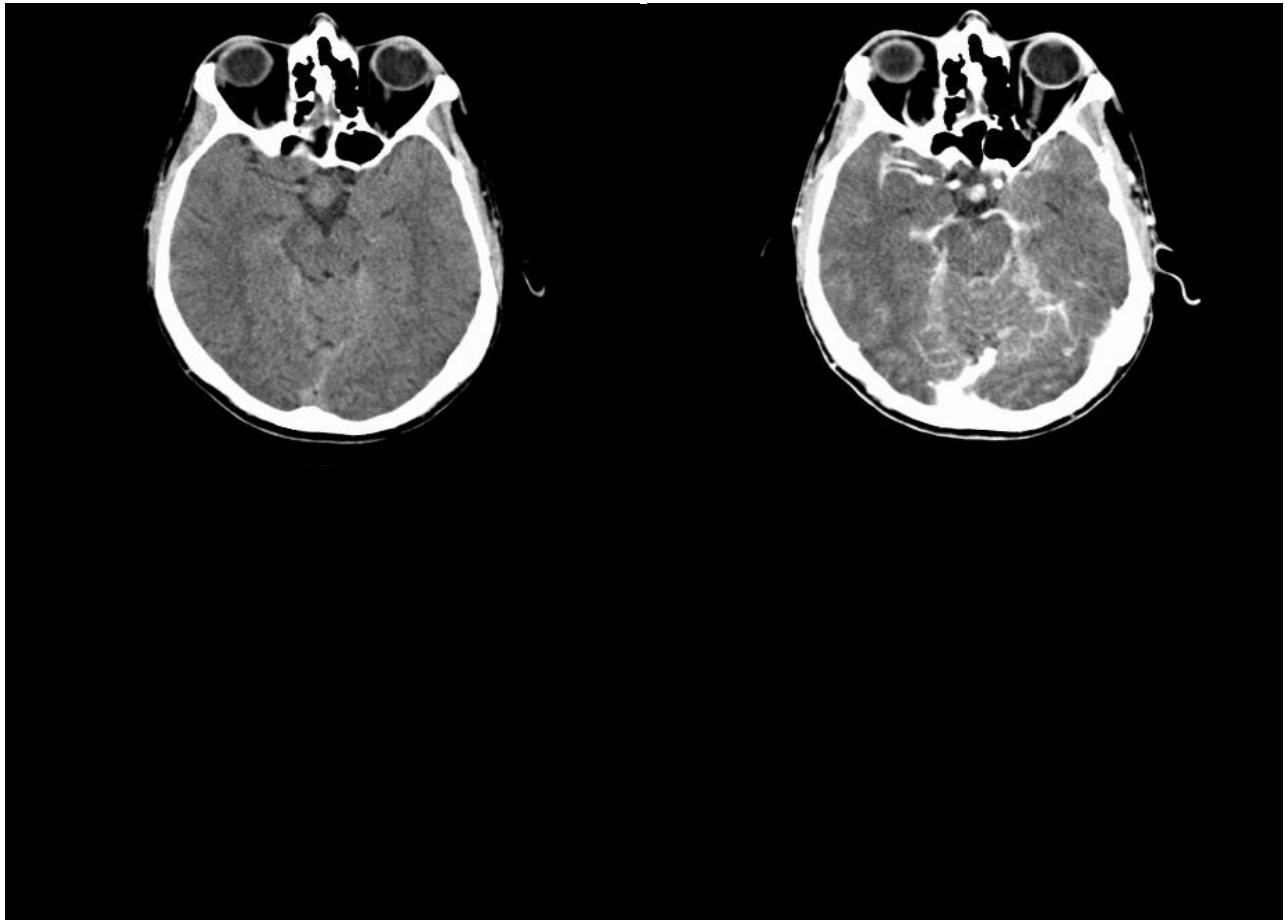
	Neurologische Befunde	Symptome
Gehirn **60%**	***Meningismus***	Kopfschmerz, Nackensteife, Licht-/Lärmempfindlich-keit, Übelkeit/Erbrechen
	Kognitive Defizite	Merkfähigkeit, Orientierung, Apraxie → **Enzephalopathie**
	Symptomatische Epilepsie	einfach fokale / einfach komplexe / Grand mal Anfälle
	Cerebelläre Symptome	Dysmetrie, Nystagmus, Stand-/Gang-Rumpf-Ataxie
Hirnnerven **40%**	*HN II, Chiasma-Syndrom*	Visusminderung, Gesichtsfeldausfall
	HN III, IV, VI	**Doppelbilder**
CAVE: BILATERAL	*HN V, VII*	Gesichtsschmerz / Sensibilität; **Gesichtslähmung**
	HN VIII	Hörminderung, Drehschwindel / Nystagmus
	HN IX, X, XI	**Dysphagie, Dysarthrie**
Myelon Conus/Cauda Radix **70%**	*Myelopathie*	**Rückenschmerzen** („**Dorsalgie**“), Par-/Dysästhesie, neuropathischer Schmerz, Parese(n) mit Reflexsteigerung (Halbseiten-/Querschnitts-Sympt.)
	Conus-Cauda-Syndrom	*Conus*: Höhe LWK1 (Dermatome S1-S5); Reithosen-Anästhesie, Störung von Miktion, Defäkation, Sexualfunktion *Cauda*: Höhe unterhalb LWK1/2; Sensibilitätsstörungen, schlaffe Parese bis Areflexie, Störung von Miktion, Defäkation, Sexualfunktion
	(Poly-) Radikulopathie	Sensibilitätsstörung, neuropathischer Schmerz, schlaffe Parese bis Areflexie
	Spinale Ataxie	**Gangstörung** („**Schwindel**“)

Hutterer, JATROS Neurologie & Psychiatrie 2010

Pat. K. F., 49a

Dez 2009 progrediente Seh- und Vigilanzstörung, Enzephalopathie

Liquor **Meningeosis carcinomatosa**, wahrscheinlich bei **Adenokarzinom**



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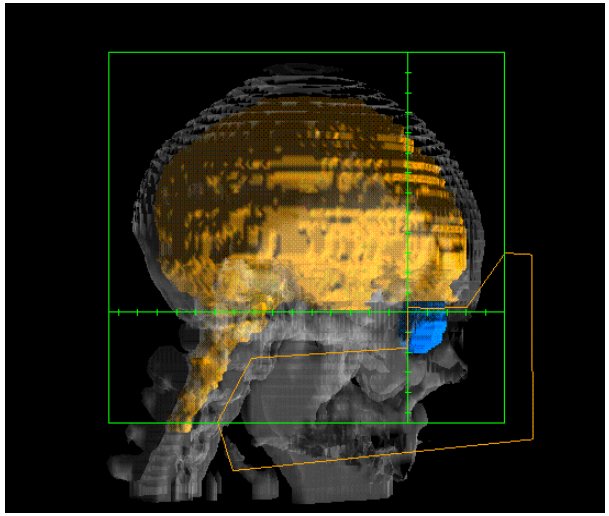
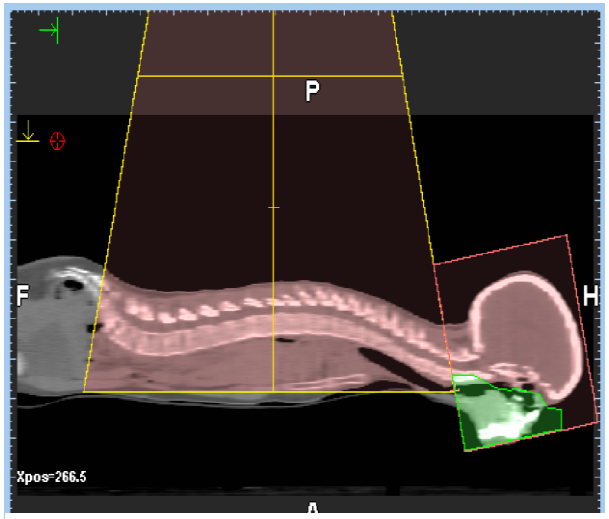
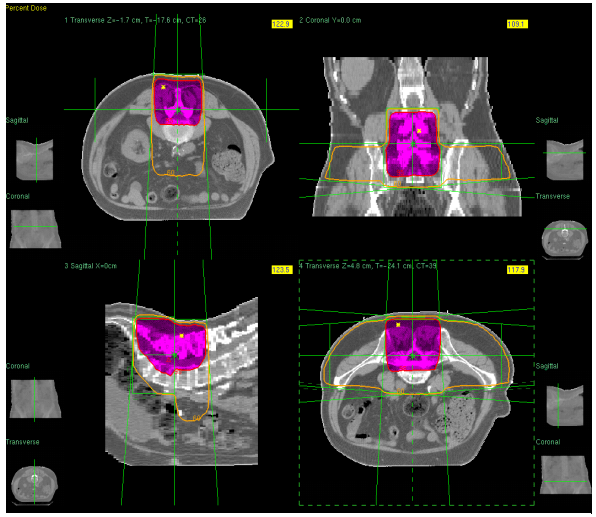
Strahlentherapie



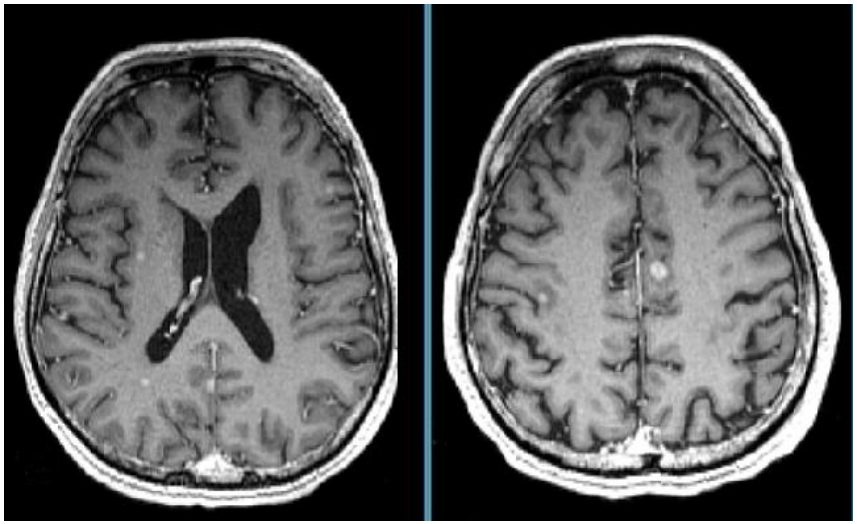
Ganzhirn-Bestrahlung

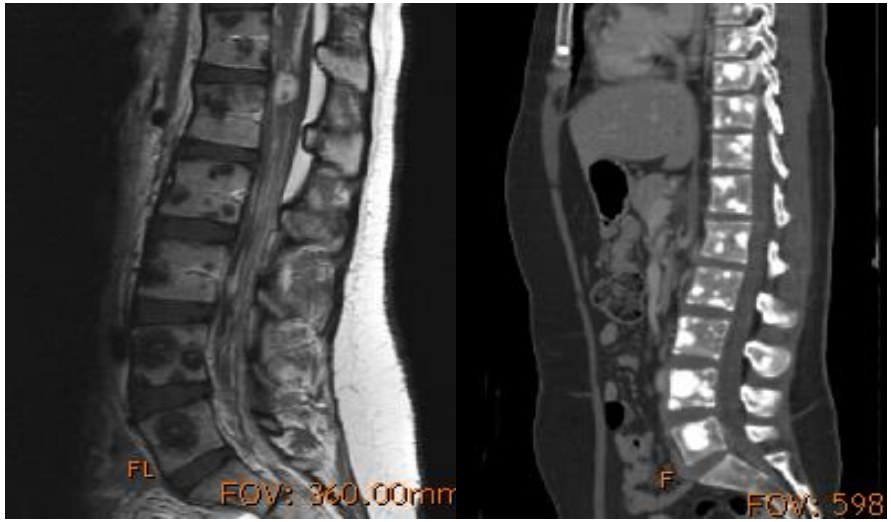


Neuroachsen-Bestrahlung



Spinale Herd-Bestrahlung





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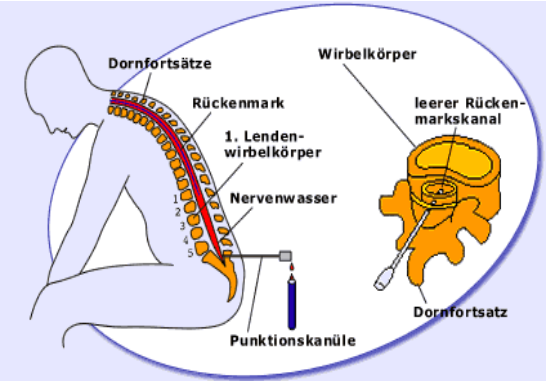
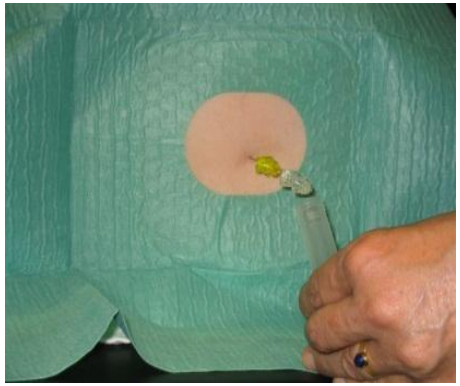
Intrathekale Chemotherapie

Lumbalpunktion → intrathekal





Vorteile

- einfach und jederzeit durchführbar

Nachteile

- schmerzhaft
- postpunktionelles Syndrom
- Thrombozyten > 50.000
- sub-/epidurale Applikation (bis 10%)
- variable Verteilung im Liquorraum

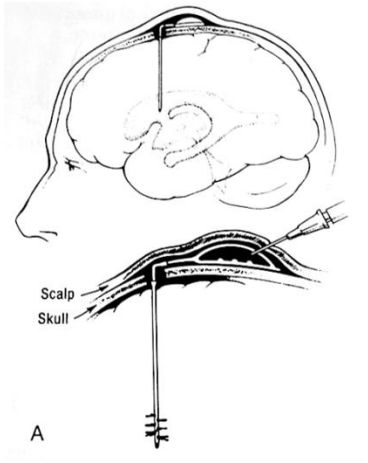
Ommaya- oder Rickham-Reservoir → intraventrikulär

Vorteile

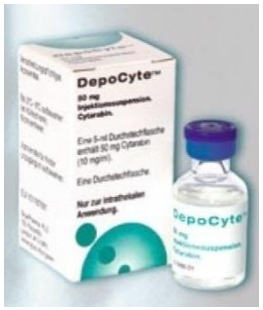
- physiologischere Verteilung im Liquorraum
- höhere Wirkspiegel intraventrikulär
- schmerzlose Punktion - kein „Abliegen“
- Punktion bei Thrombozyten < 20.000

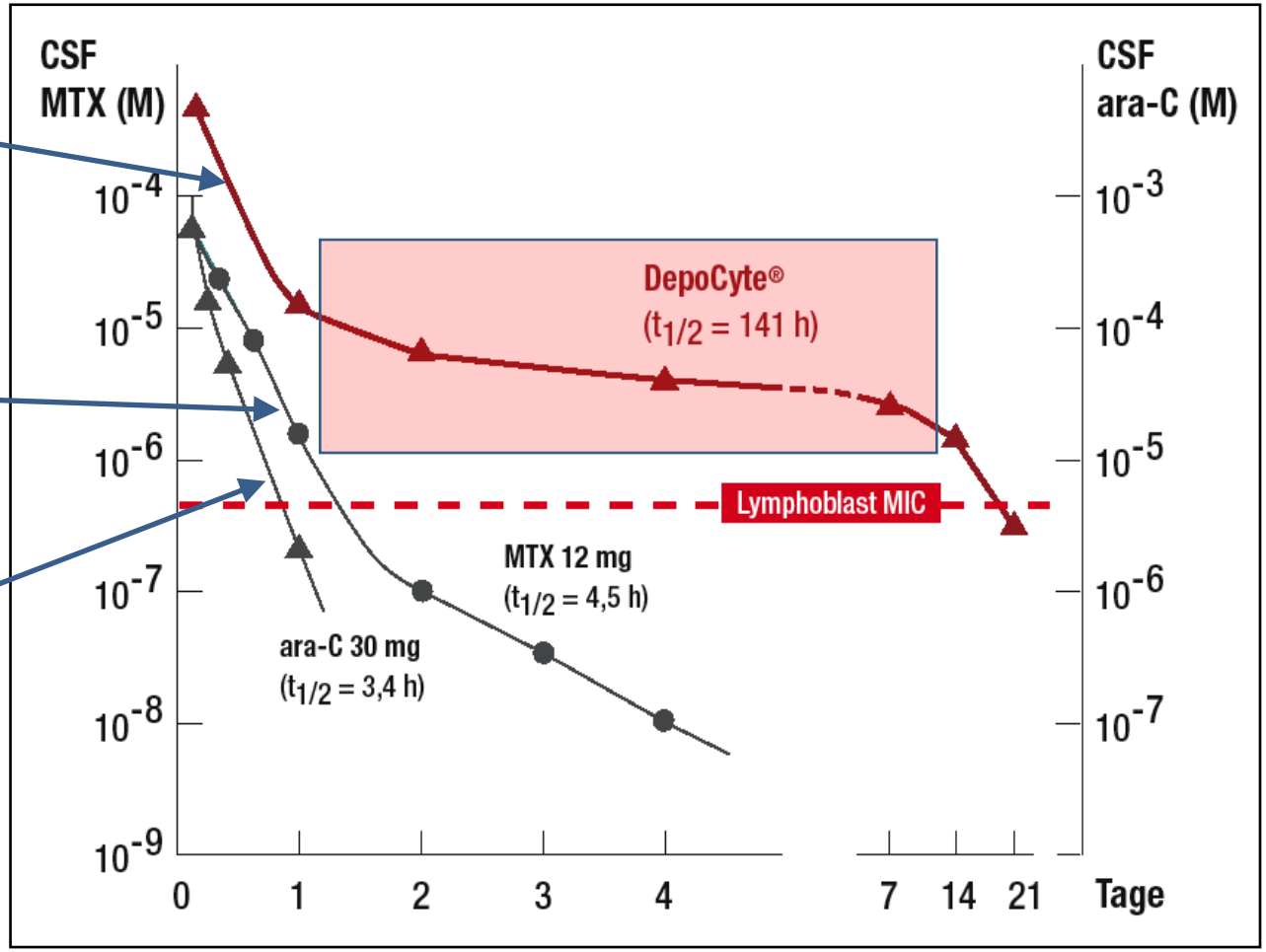
Nachteile

- OP-/Blutungs-/Infektionsrisiko (2-10%)
- Katheterdislokation /-obstruktion



Intrathekale Chemotherapie





Bleyer et al., Clin Cancer Res 1999

Neurotoxizität

und

Hirnfunktionsstörungen

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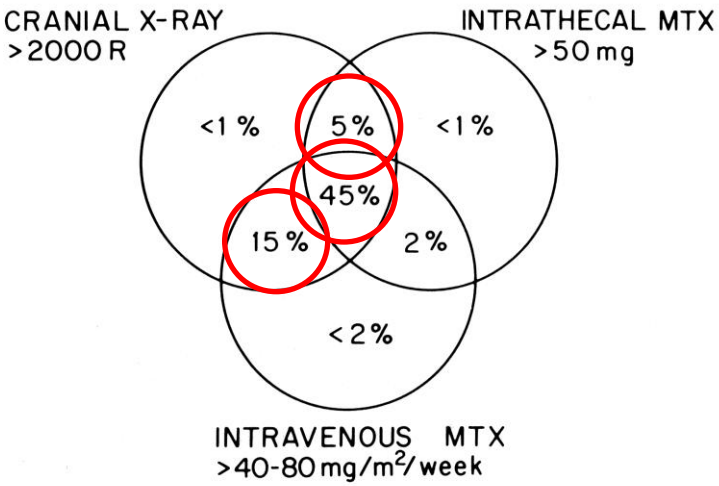
Neurotoxizität - Chemotherapie

Akute Nebenwirkungen

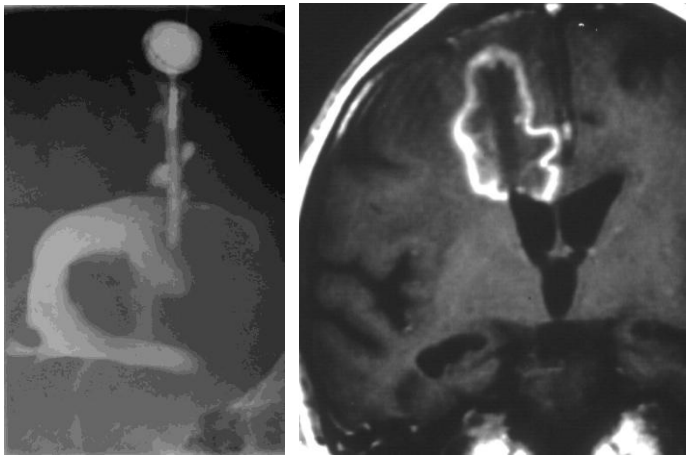
- Akute Arachnoiditis (aseptische Meningitis)
- Nekrose, Radikulitis
- Hirnödem

Chronische Nebenwirkungen

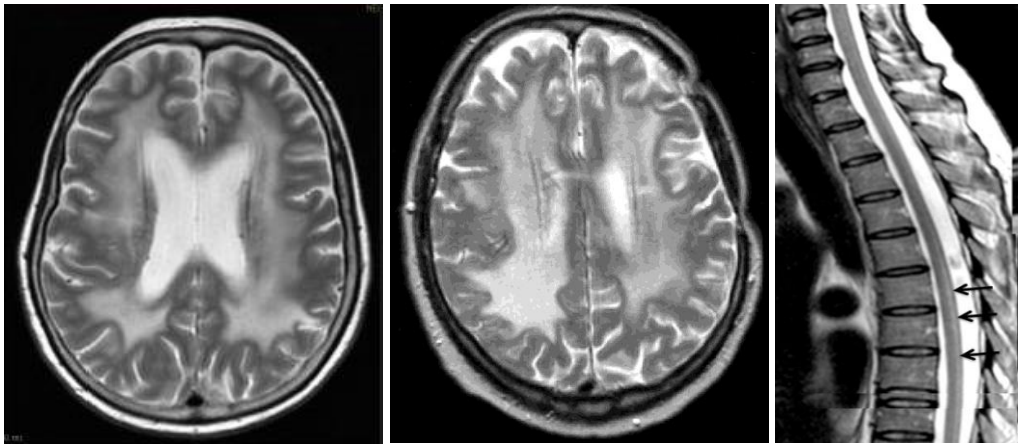
- Leukenzephalopathie + Myelopathie
- (Poly-) Radikulopathie
- Hirnnervenausfälle



Methotrexat Nekrose



Leukenzephaolopatie - Myelopathie



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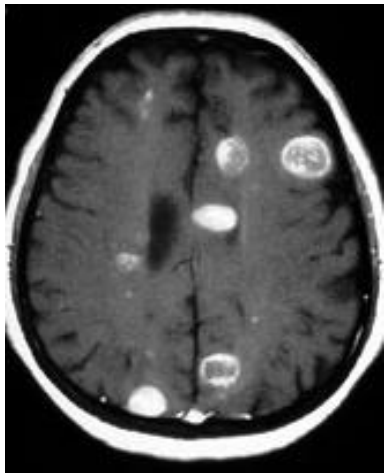
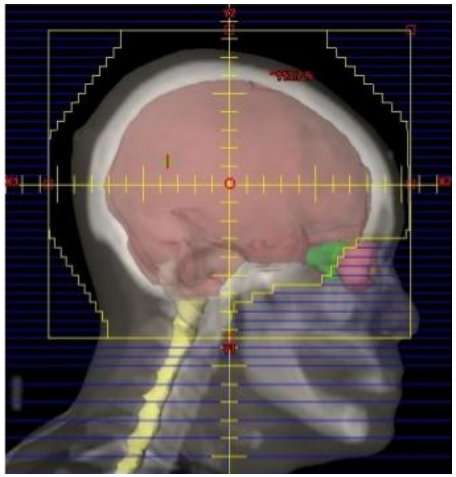
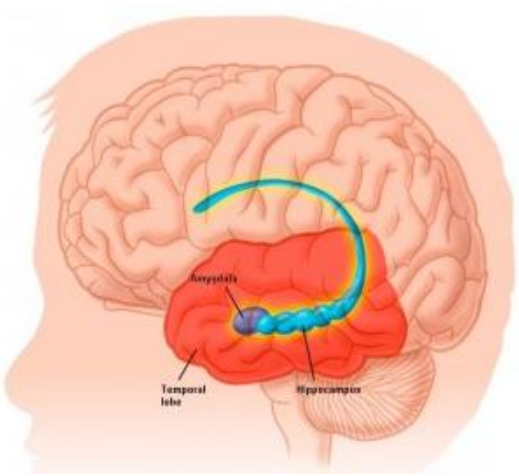
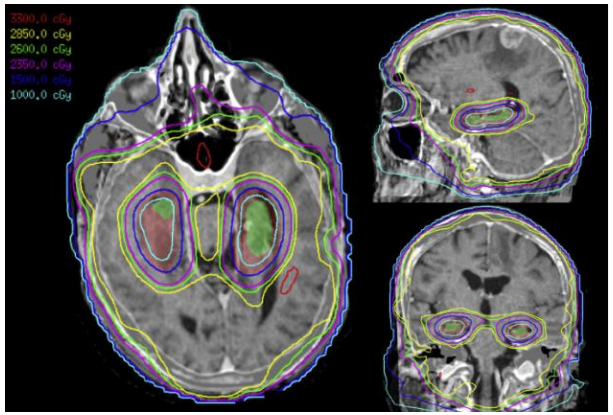
Neurotoxizität - Strahlentherapie









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Neurotoxizität - Strahlentherapie

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits

Thomas E. Merchant, Heather M. Conklin, Shengjie Wu, Robert H. Lustig, and Xiaoping Xiong

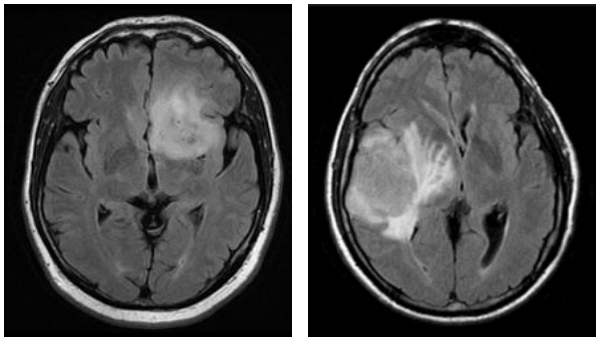

Table 1. Models of Cognitive Effects After CRT for Pediatric Low-Grade Glioma

Evaluation	No. of Patients Who Had at Least Two Measures	Score*			
		Baseline	Change per Month	Month 60	*P*†
IQ	55	98.9642	−0.0591	95.4182	
Math	55	96.9703	−0.0435	94.3603	
Reading	56	98.9448	−0.0989	93.0108	.0039
Spelling	56	98.2341	−0.1434	89.6301	.0014
Memory	53	47.5523	0.0164	48.5363	
Behavior problems‡	55	49.2340	−0.0556	45.8980	.0641
Externalizing‡	58	43.9829	−0.0099	43.3889	
Internalizing‡	58	51.5753	−0.0550	48.2753	.0248
Activities	55	43.2365	0.0031	43.4225	
School	53	41.8430	−0.0515	38.7530	.0479
Socialization	56	44.5348	−0.0084	44.0308	
Communication	57	94.6115	−0.1308	86.7635	.0041
Composite	57	94.4170	−0.1026	88.2610	.0433
Daily living	57	94.0500	−0.0635	90.2400	
Socialization	57	98.7889	−0.0559	95.4349	
Visual auditory learning	30	92.2834	0.1768	102.8914	< .0001

Neurotoxizität - Strahlentherapie

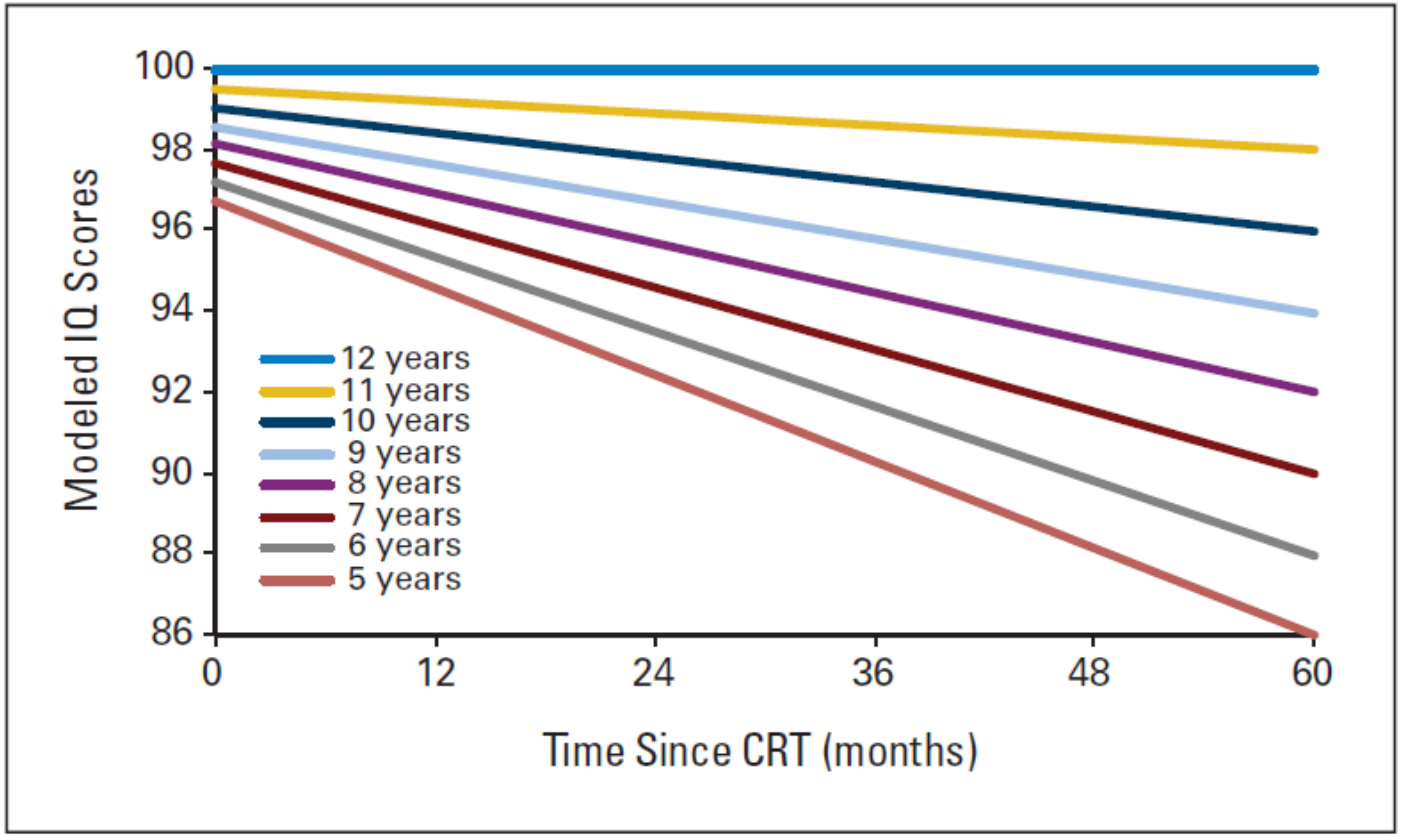

Fig 1. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age for pediatric low-grade glioma. Age is measured in years, and time is measured in months after the start of CRT.

Merchant et al., J Clin Oncol 2009

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Neurotoxizität - Strahlentherapie

VOLUME 29 · NUMBER 33 · NOVEMBER 20 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Compromised Health-Related Quality of Life in Patients With Low-Grade Glioma

Neil K. Aaronson, Martin J.B. Taphoorn, Jan J. Heimans, Tjeerd J. Postma, Chad M. Gundy, Guus N. Beute, Ben J. Slotman, and Martin Klein

Table 3. Self-Reported Cognitive Symptoms (MOS-CF scale) of the Sample With LGG (n = 195)

Symptom	Prevalence (%)*
Problem solving	18.5
Concentration	25.8
Confusion	10.7
Forgetfulness	27.4
Sustained attention	19.7
Slowed reaction	14.3
MOS-CF scale score	
Mean	71.2
SD	19.4

Abbreviations: LGG, low-grade glioma; MOS-CF, Medical Outcomes Study self-reported cognitive functioning; SD, standard deviation.

*Response categories "a good bit of the time," "most of the time," and "all of the time" were combined.

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Table 5. Results of Linear Regression Analyses on the SF-36 PCS and MCS, MOS-CF Scale, and EORTC QLQ-BN20

	Age		Sex		Education		Tumor Lateralization		Surgical Intervention		Radiotherapy		Epilepsy Burden		No. of Tests < 2 SDs		
	P	R^2 Change	*P*	R^2 Change	*P*	R^2 Change	*P*	R^2 Change	*P*	R^2 Change	*P*	R^2 Change	*P*	R^2 Change	*P*	R^2 Change	Total R^2
SF-36 PCS	.057	0.087	**.008**	0.042	.179	0.018	.531	0.000	.923	0.002	.364	0.002	**.001**	0.082	.022	0.031	0.263
SF-36 MCS	.518	0.003	**.001**	0.074	.466	0.000	.627	0.007	.083	0.020	.029	0.036	**.003**	0.074	**.010**	0.040	0.254
MOS-CF scale	.967	0.031	**.002**	0.058	.839	0.002	.882	0.005	.402	0.008	.975	0.000	.153	0.034	**< .001**	0.116	0.255
QLQ-BN20																	
Future uncertainty	.863	0.024	.278	0.005	.317	0.013	.495	0.010	.020	0.041	.544	0.006	**.001**	0.093	.068	0.021	0.213
Visual disorder	**.039**	0.068	**.002**	0.058	.560	0.000	.346	0.011	.967	0.001	.673	0.000	.019	0.045	.158	0.012	0.196
Motor dysfunction	.812	0.024	**.006**	0.042	.936	0.003	.848	0.003	.452	0.009	.985	0.000	**.002**	0.090	**< .001**	0.077	0.247
Communication deficit	.867	0.016	.088	0.011	.718	0.001	**.001**	0.096	.962	0.000	.103	0.019	**.007**	0.070	**.001**	0.065	0.277
Headaches	.933	0.009	**.001**	0.077	.884	0.001	.605	0.000	.228	0.017	.383	0.003	.046	0.035	.214	0.010	0.153
Seizures	.920	0.037	.178	0.004	.385	0.000	.699	0.007	.348	0.011	.730	0.006	**< .001**	0.303	**.002**	0.043	0.412
Drowsiness	.351	0.002	.142	0.013	.586	0.000	.243	0.021	.091	0.023	.346	0.008	.033	0.049	.012	0.042	0.156
Hair loss	.505	0.005	.740	0.001	.828	0.000	.785	0.000	.519	0.005	.598	0.001	.452	0.003	.637	0.002	0.018
Itching skin	.419	0.018	.458	0.005	.533	0.006	.645	0.004	.270	0.008	.541	0.002	.493	0.001	.157	0.015	0.059
Weakness of legs	.666	0.012	.028	0.029	.114	0.027	.933	0.003	.917	0.003	.097	0.014	.021	0.052	.031	0.030	0.170

NOTE: *P* values ≤ .01 are highlighted in bold.
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; MOS-CF, Medical Outcomes Study self-reported cognitive functioning; MCS, mental component score; PCS, physical component score; R^2 change, change in variance explained by introduction of the variable; SD, standard deviation; SF-36, Short Form-36; Total R^2, total amount of variance explained by the set of independent variables; QLQ-BN20, brain cancer quality-of-life module.

Symptomatische Epilepsie

- Angst vor Anfällen → sozialer Rückzug
- Nebenwirkungen durch Antiepileptika
- Immobilität (Fahrverbot)

Aaronson et al., J Clin Oncol 2011

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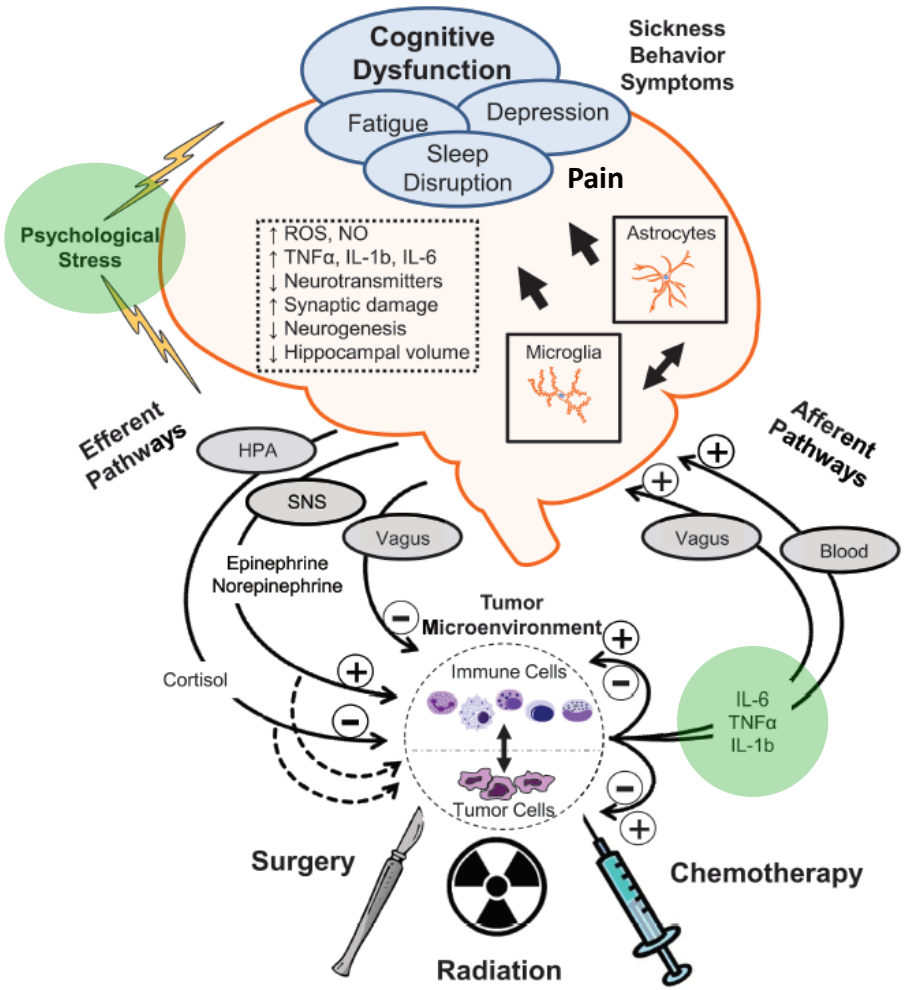
Cancer-Related Cognitive Impairment



- **vor - während - nach einer Tumorbehandlung … „ChemoBrain“?**
- 174 postmenopausale MammaCA Patientinnen => Entzündungsmarker im Blut bei Diagnosestellung

  sTNF-RII↑ … Gedächtnisleistungen↓

  IL-1ra↑ … Gedächtnisleistungen↓
- **Alter, Ausbildung, Fatigue, Angst, Komorbiditäten** (z.B. Diabetes, Bluthochdruck) wurden berücksichtigt

Patel et al., J Natl Cancer Inst 2015; **Low et al.**, J Natl Cancer Inst 2015

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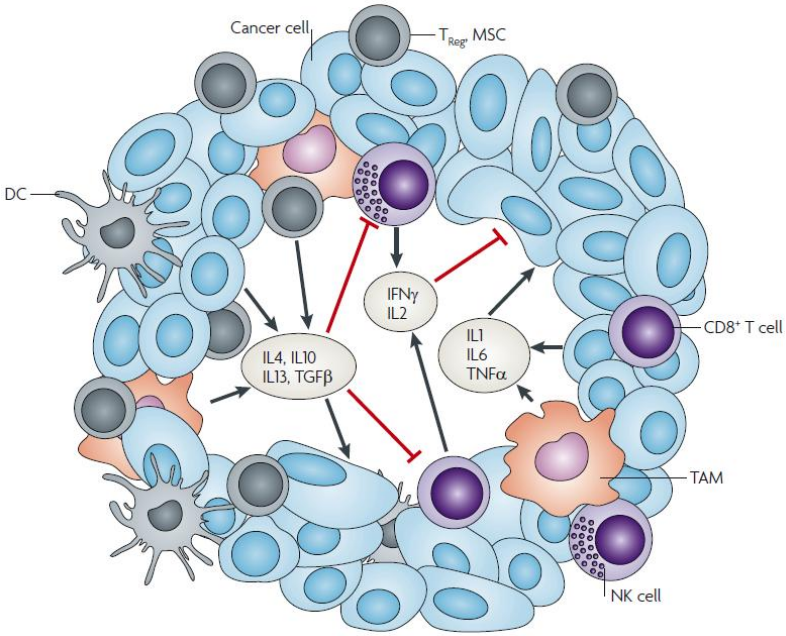
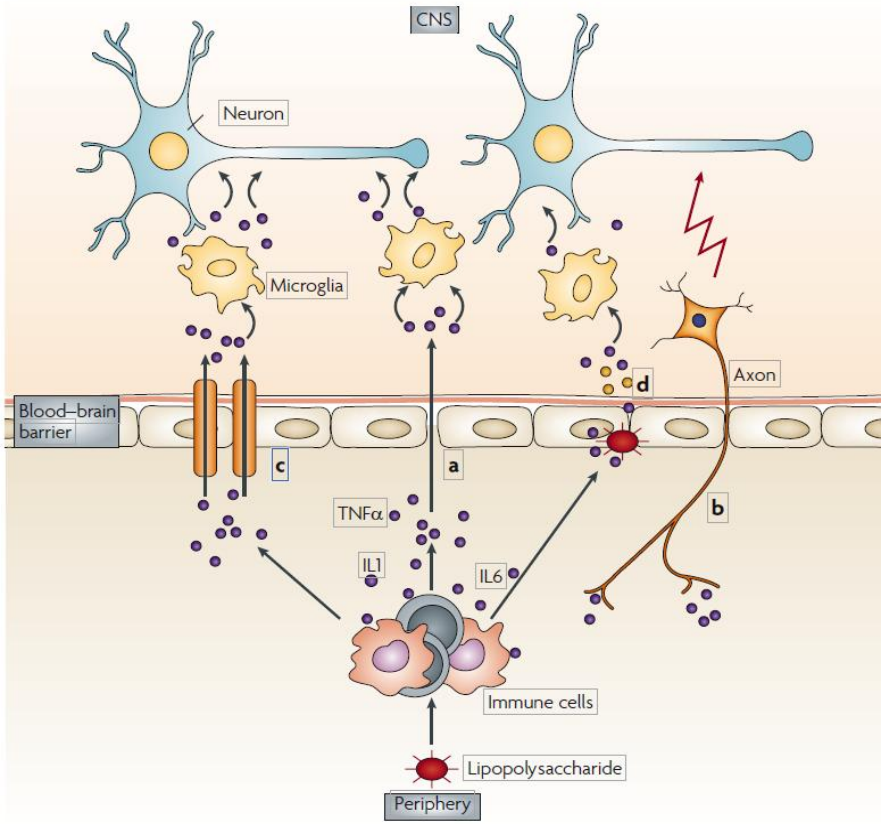
Cancer-Related Cognitive Impairment





Role of major cytokines in the tumour microenvironment

TAM, tumour-associated macrophages; TReg, T- regulatory cells; DCs = dendritic cells; MSCs, myeloid suppressor cells; TNFα, tumour necrosis factor-α

Pathways of communication between periphery and the central nervous system (CNS)

Seruga et al., Nature Reviews Cancer 2008

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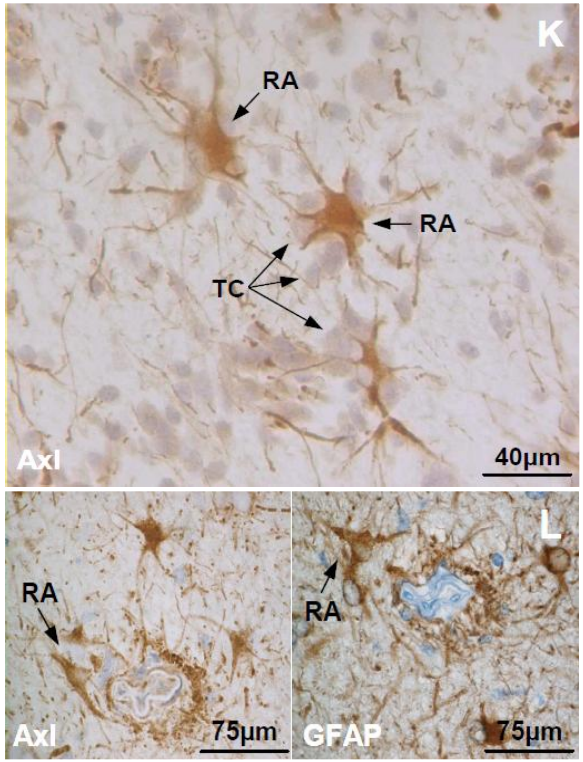
Cancer-Related Cognitive Impairment

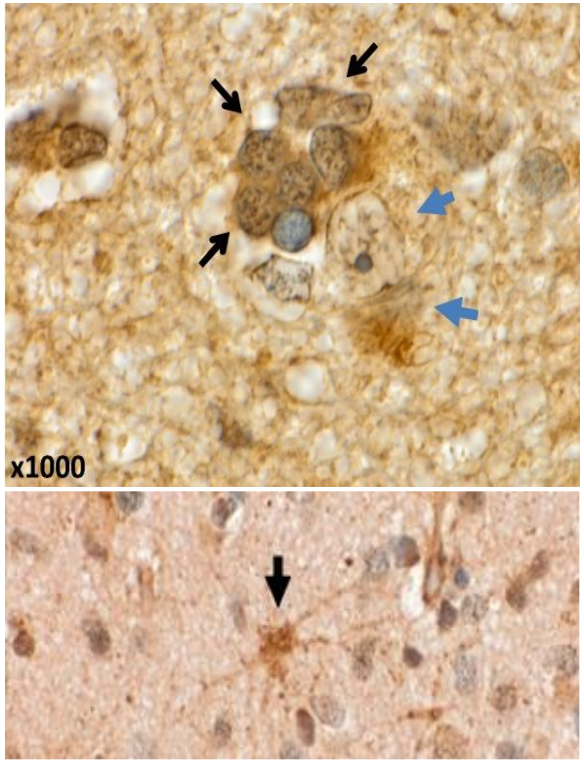
Glioma Infiltrating Zone

Axl/Gas6 Expression



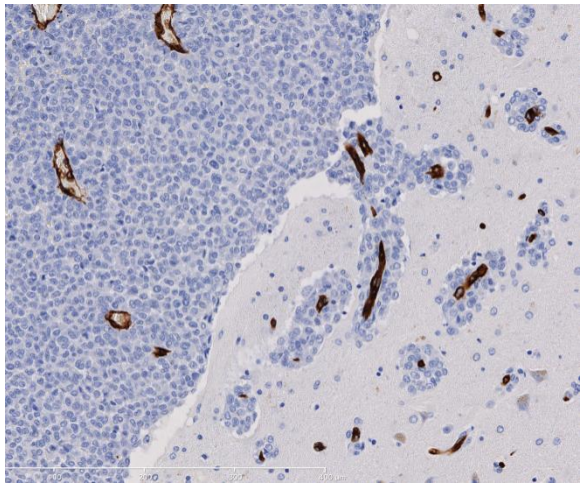
Glioma and Epileptic Seizures

LAT2 Expression



Melanoma Brain Metasasis

CD31 Expression



Hutterer et al., Clin Can Res, 2008; **Hutterer et al.**, in Revision 2016

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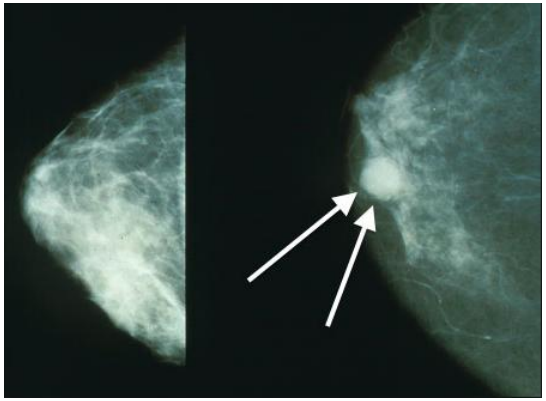
Stress-Related Cognitive Impairment

ARTICLE

Elucidating Pretreatment Cognitive Impairment in Breast Cancer Patients: The Impact of Cancer-related Post-traumatic Stress

Kerstin Hermelink, Varinka Voigt, Judith Kaste, Franziska Neufeld, Rachel Wuerstlein, Markus Bühner, Karin Münzel, Dorothea Rjosk-Dendorfer, Susanne Grandl, Michael Braun, Franz Edler von Koch, Kristin Härtl, Stephan Hasmüller, Ingo Bauerfeind, Gerlinde Debus, Peter Herschbach, Nadia Harbeck

JNCI J Natl Cancer Inst (2015) 107(7): djv099



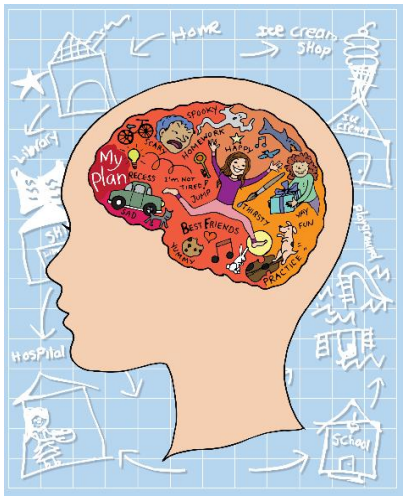
Women aged 65 years or younger with

diagnosis of breast cancer (case patients, n = 166) and
negative routine breast imaging (control patients, n = 60)

underwent

- traditional and computerized neuropsychological testing
- clinician-administered diagnostic assessment of stress disorders
- self-report assessments of cognitive function and depression

prior to any local or systemic treatment



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Stress-Related Cognitive Impairment

Domain/ cognitive index	Control patients n	Control patients Z score or PR Mean (SD)	Control patients P vs test norms*	Individually matched case patients n	Individually matched case patients Z score or PR Mean (SD)	Individually matched case patients P vs test norms*	All case patients n	All case patients Z score or PR Mean (SD)	All case patients P vs test norms*
Attention									
Alertness, RT condition 1†	60	-0.65 (0.83)	<.001	60	-0.58 (0.84)	<.001	165	-0.56 (0.79)	<.001
Alertness, RT condition 2†	60	-1.03 (0.72)	<.001	60	-0.77 (0.84)	<.001	165	-0.81 (0.75)	<.001
Alertness, SD of RT, condition 1†	60	0.17 (1.13)	.46	60	0.08 (1.22)	.75	165	0.17 (1.14)	.11
Alertness, SD of RT, condition 2†	60	0.03 (0.88)	.95	60	0.27 (1.07)	.08	165	0.21 (0.94)	.02
Alertness, index phasic alertness†	60	-0.68 (0.94)	<.001	60	-0.37 (0.77)	.001	165	-0.40 (0.79)	<.001
Go/Nogo, RT†	60	-0.09 (0.95)	.49	58	0.07 (0.95)	.63	164	-0.14 (0.93)	.05
Go/Nogo, SD of RT†	60	0.07 (0.87)	.57	58	-0.12 (0.85)	.31	164	-0.15 (0.86)	.03
Trail Making Test A (TMT-A)‡	60	52.75 (28.10)	.44	59	56.95 (28.54)	.08	165	52.42 (28.83)	.31
Memory									
Digit Span Forward†	60	0.08 (0.98)	.52	60	0.08 (1.10)	.48	166	-0.04 (1.11)	.59
Digit Span Backward†	60	-0.02 (1.05)	.72	59	0.02 (1.07)	.48	165	-0.08 (1.09)	.02
VLMT learning efficiency†	60	0.76 (0.76)	<.001	58	0.84 (0.97)	<.001	164	0.74 (0.99)	<.001
VLMT free recall†	60	0.49 (1.02)	<.001	59	0.48 (1.01)	<.001	165	0.45 (0.95)	<.001
VLMT consolidation†	60	-0.01 (1.19)	.76	58	0.09 (0.99)	.51	164	0.06 (0.96)	.31
Executive function									
Trail Making Test B (TMT-B)‡	60	51.17 (29.66)	.81	59	51.61 (33.18)	.71	164	50.06 (31.85)	.88
RWT lexical search‡	60	31.70 (22.40)	<.001	60	34.50 (24.43)	<.001	165	32.42 (25.23)	<.001
RWT semantic search‡	60	34.83 (22.64)	<.001	59	39.85 (29.05)	.011	164	37.82 (30.29)	<.001

* Two-sided Wilcoxon Signed Rank Test was used for all comparisons. PR = percent rank; RT = reaction time; RWT = Regensburg Word Fluency Test; SD = standard deviation; VLMT = Verbal Learning and Memory Test.
†Z scores are given; mean = 0, SD = 1.
‡Percent ranks are given; mean = 50, range = 1 to 100.

Conclusion: Prior to any treatment, breast cancer patients may show **limited cognitive impairment** that is apparently largely caused by **cancer-related post-traumatic stress**.

Hermelink et al., J Natl Cancer Inst 2015

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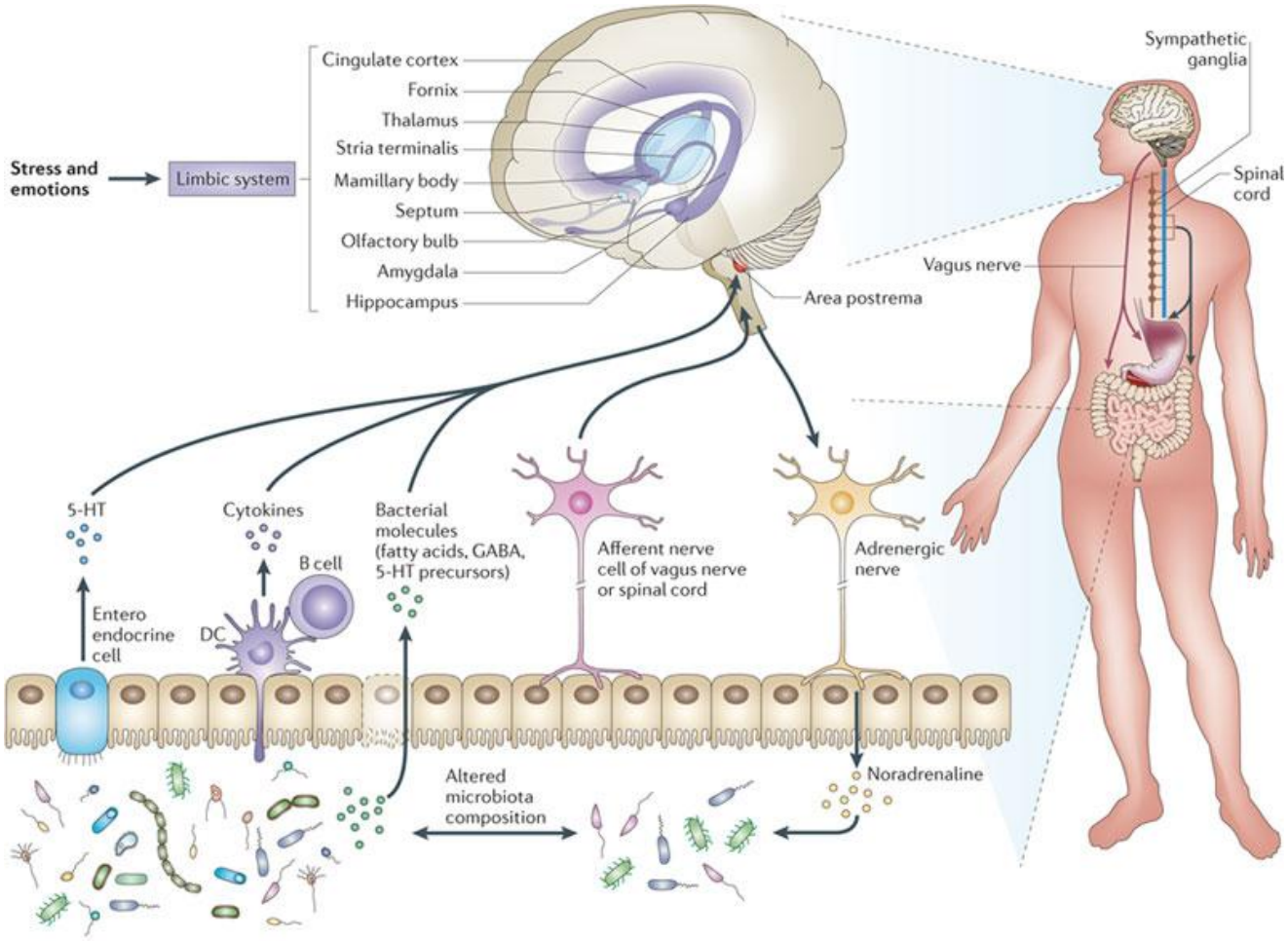
Mikrobiom-Darm-Hirn Achse



Diseases

- **Inflammatory bowel disease**
- **Atherosclerosis**, Cardio-Vascular diseases
- Obesity, Metabolic syndrome, Insulin-resistance (**Diabetes**)

Immune system

- Immune system development (interaction with thymus)
- Autoimmune arthritis
- Hepatobiliary-Pancreatic autoimmune disease
- Experimental multiple sclerosis

Brain function

- Emotion (Anxiety, Depression)
- Cognition (Learning, Memory)
- Appetite
- Stress susceptibility
- Autism, Pain (nociception)

CANCER?

- Distress? Nutrition?
- Drugs (Antibiotics, Probiotics)?
- Gut infection and inflammation?

Neuronal Message
Endocrine Message
Immune Message

Neuroendocrine Systems
Neuroimmunological Systems
Autonomic and Enteric Nervous Systems

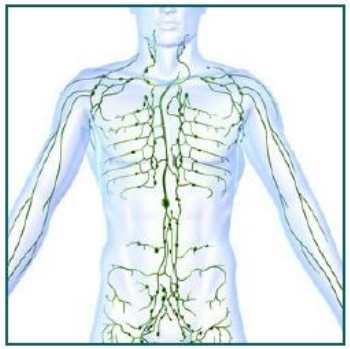
Collins et al., Nature Reviews Microbiology 2012

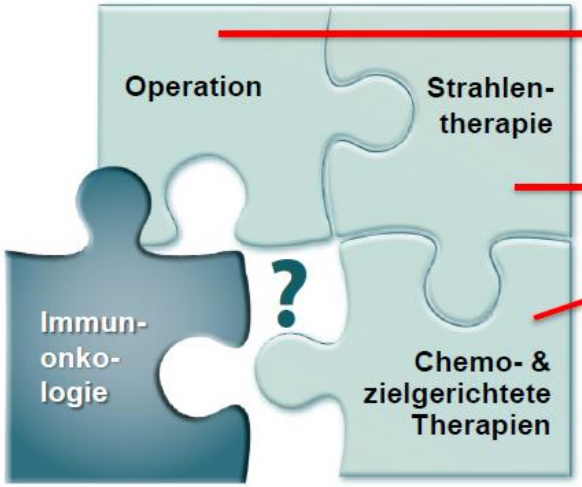
Immunonkologie

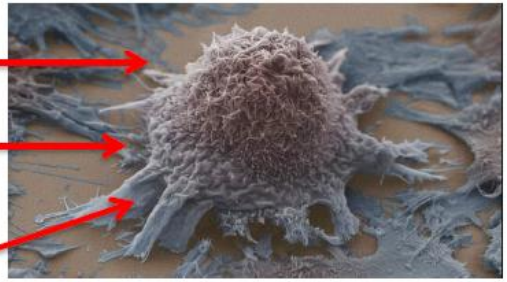
Checkpoint Inhibitors

Ipilimumab - Nivolumab - Pembrolizumab

- Die konventionellen onkologischen Ansätze sind direkt gegen den Tumor gerichtet.[2]
- Bei der Immunonkologie wird die natürliche Fähigkeit des eigenen Immunsystems genutzt, um den Krebs zu bekämpfen.[2]







DeVita and Rosenberg, NEJM 2012; **Borghaei et al.**, Eur J Pharmacol 2009

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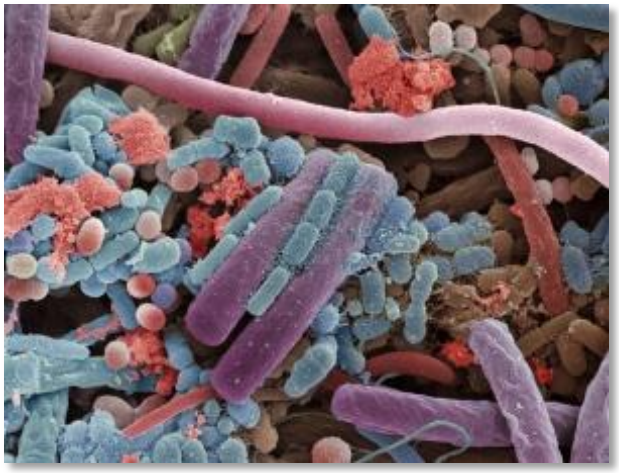
Mikrobiom - Immuntherapien

Science AAAS

REPORT

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti –PD-L1 efficacy

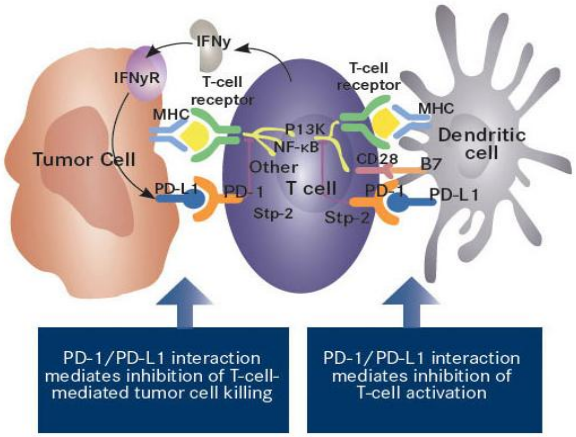
Ayelet Sivan[1,*], Leticia Corrales[1,*], Nathaniel Hubert[2], Jason B. Williams[1], Keston Aquino-Michaels[3], Zachary M. Earley[2], Franco W. Benyamin[1], Yuk Man Lei[2], Bana Jabri[2], Maria-Luisa Alegre[2], Eugene B. Chang[2], Thomas F. Gajewski[1,2,†]



REPORT

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou[1,2,3], Jonathan M. Pitt[1,2,3], Romain Daillère[1,2,3], Patricia Lepage[4], Nadine Waldschmitt[5], Caroline Flament[1,2,6], Sylvie Rusakiewicz[1,2,6], Bertrand Routy[1,2,3,6], Maria P. Roberti[1,2,6], Connie P. M. Duong[1,2,6], Vichnou Poirier-Colame[1,2,6], Antoine Roux[1,2,7], Sonia Becharef[1,2,6], Silvia Formenti[8], Encouse Golden[8], Sascha Cording[9], Gerard Eberl[9], Andreas Schlitzer[10], Florent Ginhoux[10], Sridhar Mani[11], Takahiro Yamazaki[1,2,6], Nicolas Jacquelot[1,2,3], David P. Enot[1,7,12], Marion Bérard[13], Jérôme Nigou[14,15], Paule Opolon[1], Alexander Eggermont[1,2,16], Paul-Louis Woerther[17], Elisabeth Chachaty[17], Nathalie Chaput[1,18], Caroline Robert[1,16,19], Christina Mateus[1,16], Guido Kroemer[7,12,20,21,22], Didier Raoult[23], Ivo Gomperts Boneca[24,25,*], Franck Carbonnel[3,26,*], Mathias Chamaillard[5,*], Laurence Zitvogel[1,2,3,6,†]



Sivan et al., Science Nov 2015; **Vetizou et al.**, Science Nov 2015; **Yong**, Nature 2012

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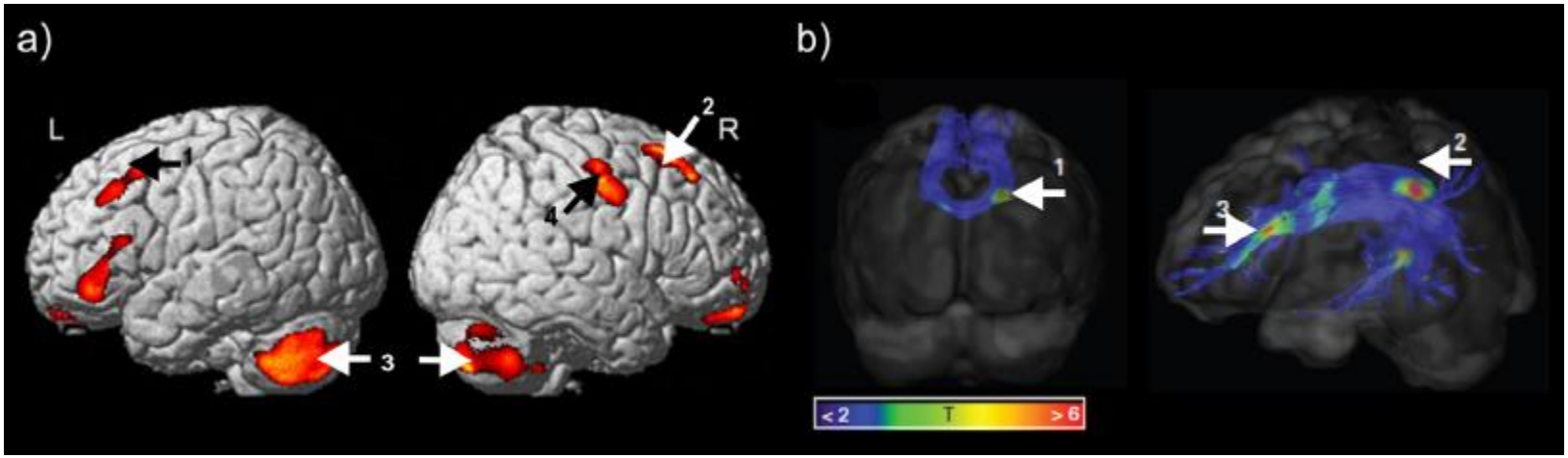
ChemoBrain – does it exist?



Memory	Working	The ability to actively monitor, temporarily store, and manipulate information or behaviors
	Episodic	The memory of autobiographical events that can be explicitly stated
	Remote	The ability to recall events that happened years ago
	Verbal	The ability to retain linguistic information for a designated time period and typically presented orally
	Visual	The ability to create an eidetic image of past visual experiences
Executive function		Cognitive abilities that control and regulate other abilities and behaviors
Processing speed		The ability to automatically and fluently perform relatively easy or overlearned cognitive tasks
Visual-spatial ability		The ability to generate, retain, retrieve, and transform well-structured visual images
Attention		The ability to selectively concentrate on one aspect of the environment, while ignoring other things
Concentration		The ability to concentrate mental powers on an object
Reaction time		The ability to react and/or make decisions quickly in response to simple stimuli
Motor speed		The ability to perform body motor movements (movement of limbs) with precision, coordination, or strength

McDonald et al., J Clin Oncol 2012; **Argyriou et al.**, J Pain Sympt Management

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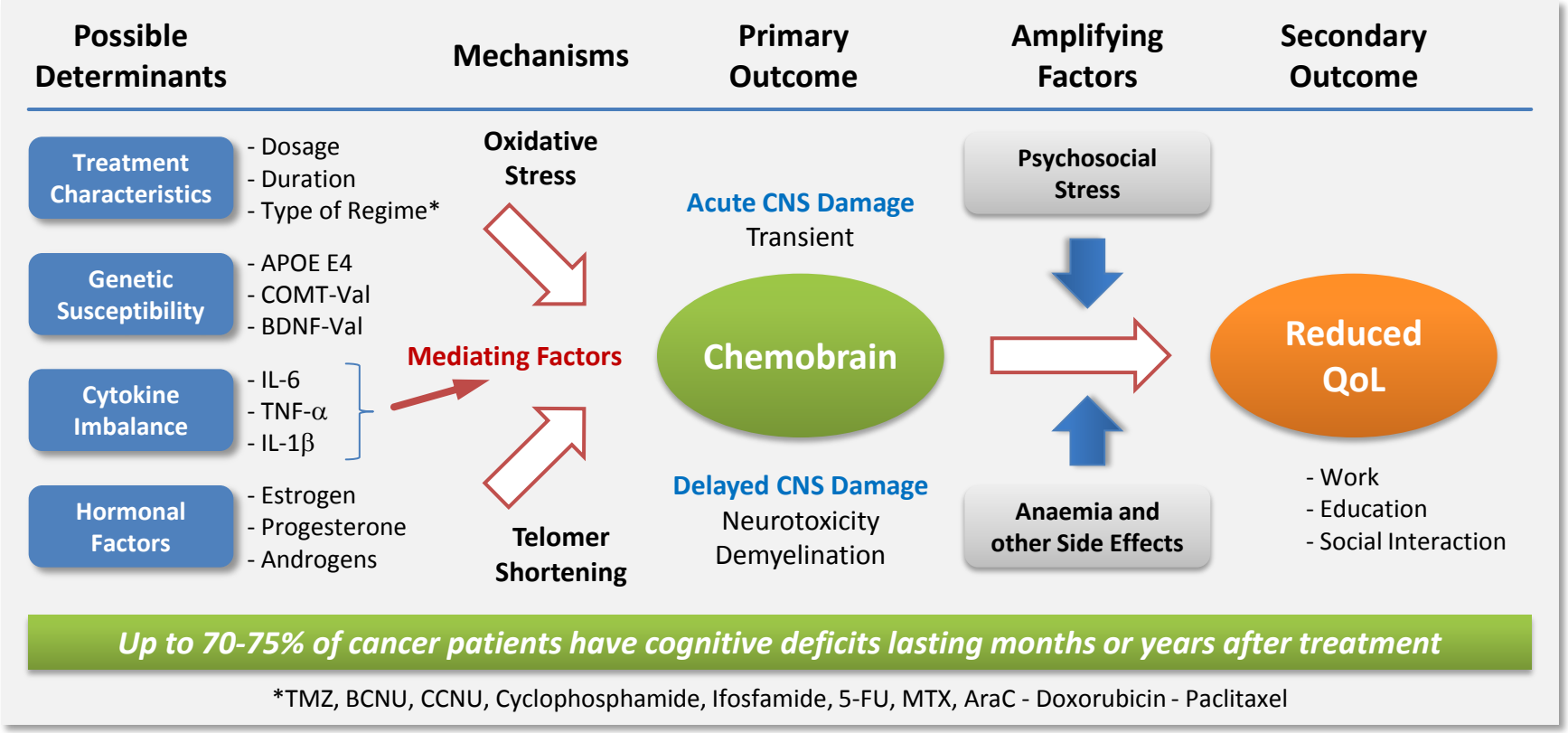
ChemoBrain – does it exist?



Genetic predisposition

- *Neuronal (DNA) repair mechanisms*
  - APOE E4, BDNF
- *Neurotransmission*
  - COMT (catecholamine metabolism, dopamine)
- *Blood-brain-barrier*
  - Altered drug transporter (enhanced influx)
  - Less-efficient efflux pumps (P-glycoprotein)

Neurotoxicity

- neurons and axons (demyelination), progenitor and stem cells
- astrocytes, oligodendroglia, microglia

Risk factors

- poor education, reduced cognitive stimulation, older age
- comorbidities (diabetes, arterial hypertension, dementia)
- psychosocial stress

Kok-Ho Ho, AMSJ 2015

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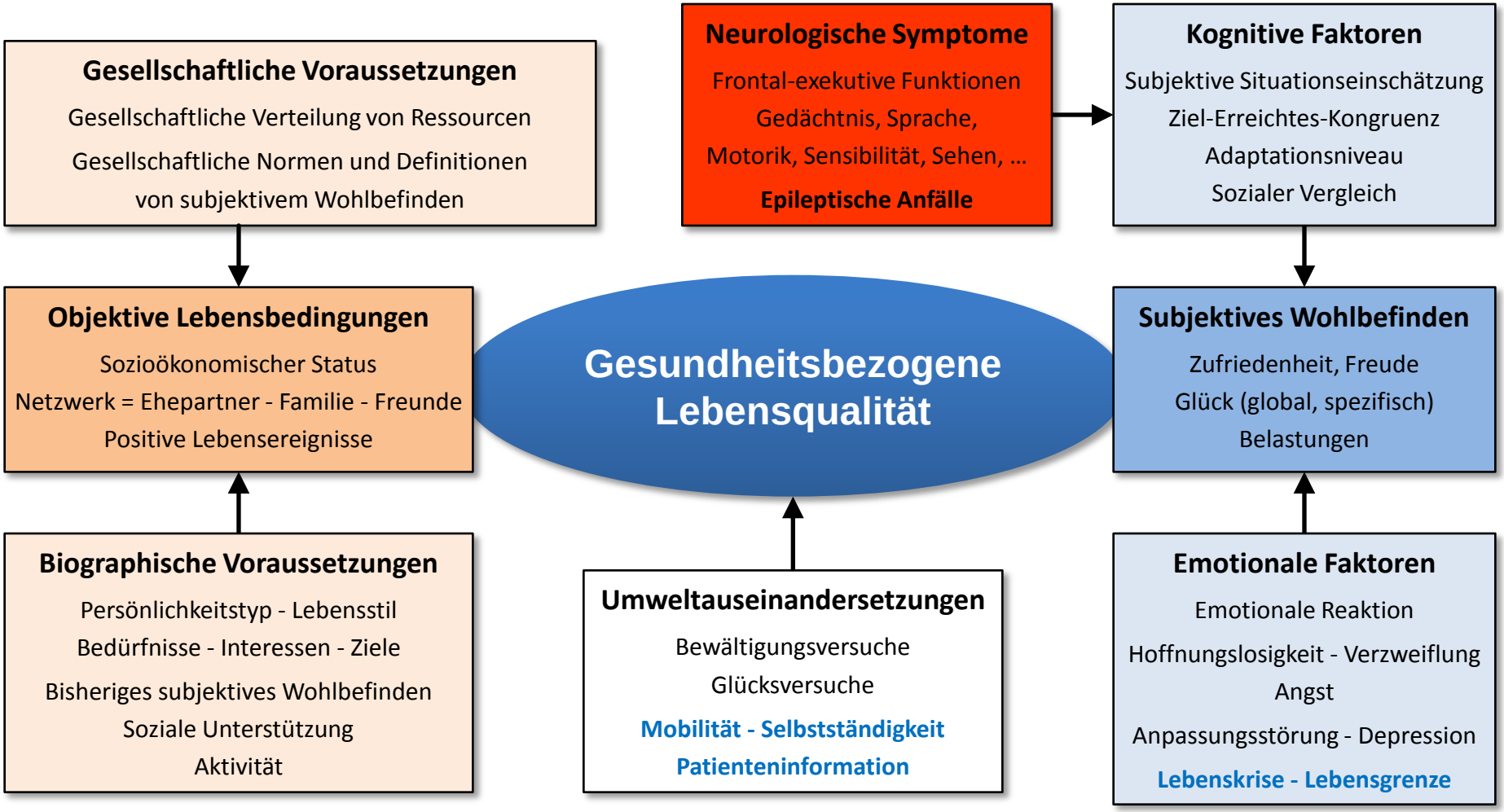
Zusammenfassung



Faktoren zur Beurteilung der Lebensqualität

nach Phillip Mayring, "Psychologie des Glücks", Kohlhammer, Stuttgart, 1991, eigene Bearbeitung

Zusammenfassung

Psychoonkologische Besonderheiten in der Neuroonkologie

- **Krankheitsverarbeitung** und **Krankheitsbewältigung**
- **Umgang mit den neurologischen Symptomen**
  - Verhaltens- und Wesensänderung, Psychomotorik und Antrieb
  - Neurokognitive Defizite — Aufmerksamkeit, Konzentration, Lern- und Merkfähigkeit Reaktionsschnelligkeit, exekutive Funktionen
  - Epileptische Anfälle => Antiepileptika (NW), Immobilität, Stigmatisierung
  - Sprachstörung => Kommunikationsfähigkeit
  - Lähmung => Mobilität, Selbstständigkeit, Selbstwert
- **Belastungsreaktion – Depression - Angst**
  - Angst vor epileptischen Anfällen
  - Angst vor Wesensveränderung
  - Angst vor Kontroll- und Autonomieverlust und Einsamkeit
  - Angst vor der Krankheit und der schlechten Prognose
  - Angst vor Zukunft und Tod

=> **körperliche und seelische Überforderung** => **chronischer psychosozialer Stress**

=> sozialer Rückzug, fehlende Tagesstruktur, schlechte Lebensqualität

Vielen Dank!