Universitätsspital
Basel

Radiotherapy of Brain Metastases and Carcinomatous Meningitis

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Brain metastases

1 in 4 cancer patients develop brain metastases
In 1/3 - 1/2 of these patients brain metastasis is the direct cause of death

Risk of brain metastasis by tumor type:

SCLC	up to 80%
NSCLC	25-30%
Melanoma	up to 50%
Breast Ca	20%
Renal cell Ca	5-10%
Testicular	8-15%

Tendency:

- Rising incidence in brain metastasis due to increasing life-expectancy for cancer patients

- Modern imaging: earlier detection and intervention and, perhaps, opportunity to control CNS disease

Brain metastases

Signs and symptoms:

Usually insidious start
Sudden onset or acute worsening (often due to hemorrhage into the tumor)

- Elevated intracranial pressure:
headache (50%), nausea and vomiting, psychomotor retardation
- Focal neurological deficits
- Epileptic seizures (15-20 %)

Brain metastases

Diagnostics:

CT, MRI, stereotactic biopsy / excision + histology

Patients with new diagnosis of brain metastasis should be systematically restaged as appropriate for their primary tumor

- *Solitary:* one CNS-lesion, *no* evidence of extracranial metastases
- *Single:* one CNS-lesion *and* extracranial metastases
- *Oligo-* (3 and less)
- *Multiple (*more than 3)

Solitary metastasis: in some cases, an agressive local therapy is potentially curative
(for example, a case of an adenocarcinoma of the lung: 77.4 months survival after SRS, *Pirzkall et al, JCO 1998*)

Brain metastases

Important factors to choose treatment:

- histology
- Karnofsky index
- age
- number of brain metastases
- volume and localisation of brain metastases
- extension of extracranial disease
- reasonable systemic treatment options, if needed

Brain metastases

Favorable prognostic factors:

- Age< 65
- KI ≥ 70%
- One lesion
- Feasible surgical approach
- „Beneficiary“ localization of the metastases
- Extracranial disease is controlled
- Meninges are not affected
- CUP
- Long disease free survival
- Neurological symptoms due to local volume (edema) expansion only

Brain metastases

Gaspar et al. Int J Radiat Oncol Biol Phys. 1997 (RTOG)

Table 3. Prognostic factors

Covariate	Comparison	*p*-Value
Brain metastases	Alone vs. with other metastases	< 0.0001
KPS*	≥ 70 vs. < 70	< 0.0001
Age (yrs)	< 65 vs. ≥ 65	< 0.0001
Prior surgery	No vs. Yes	0.005
Histology	Squamous and small cell vs. others	< 0.0001
Primary lesion	Controlled vs. uncontrolled	< 0.0001
Primary site	Breast vs. lung and others	0.001
Time interval	< 2 years vs. > 2 years	0.004
Number of lesions	Single vs. multiple	0.021
Sentinal lesion side	Left and/or right vs. midline	0.038
Sentinal location	Frontal, temporal, parietal, Occipital and basal ganglia vs. cerebellum and brainstem	0.033
Neurologic function	No dysfunction vs. some dysfunction	< 0.0001
Headache	None vs. some	0.003
Total radiation dose	≥ 52 Gy vs < 52 Gy	< 0.0001
Tumor response	Complete or partial response vs. stable or progressive	0.019

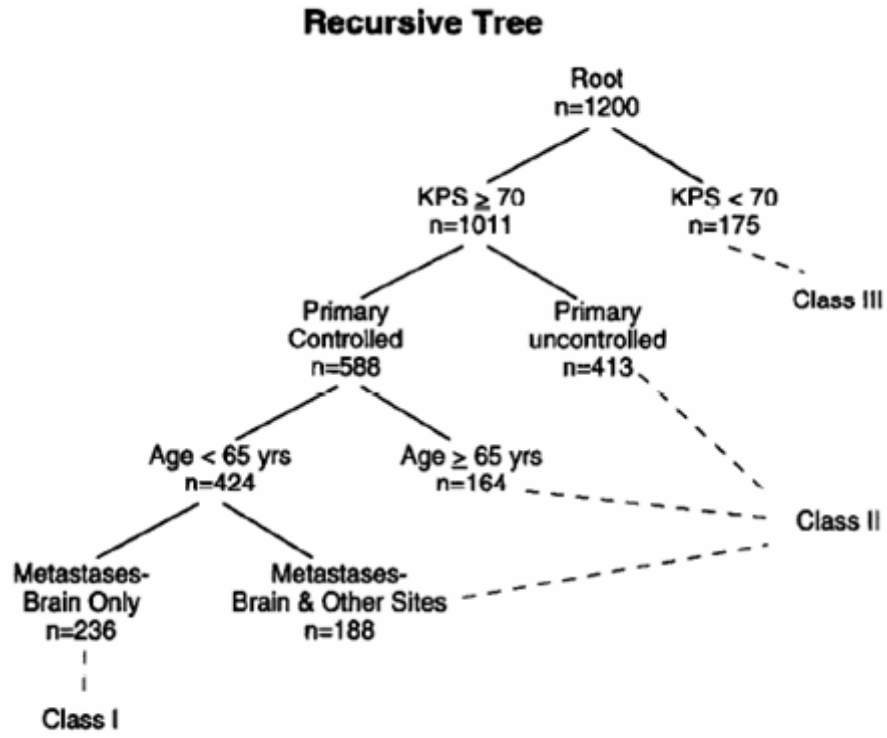


Fig. 2. Recursive tree.

Brain metastases

Prognostic **classes** of patients with brain metastases proposed from RTOG,
based on Recursive Partitioning Analysis (**RPA**)

class	characteristics	median survival, mo
I	KPS≥70, primary controlled, age<65 y, metastases to brain only	7.1
II	•KPS≥70, primary uncontrolled •KPS≥70, primary controlled, age ≥ 65 y •KPS≥70, primary controlled age<65, metastases to brain and other sites	4.2
III	KPS<70	2.3

Gaspar L et al, IJROBP 1997

Brain metastases

Prognosis & therapy

Applied therapy	*Survival (months)*
None	1-2
Steroids	2-3
WBRT+steroids	2-6
WBRT+chemotherapy	4-8
Resection+ WBRT	6->12
SRS+ WBRT	6->12

Survival is longer and the quality of life better when brain metastases are treated

Brain metastases

Treatment options:

Corticosteroids:↓perifocal edema →ameliorate many symptoms of brain metastases within some hours

Significant side effects: myopathy, hyperglycemia, edema, weight gain, avascular necrosis and psychosis

Dose tapering as soon as possible (with caution during RT, better thereafter).

Anticonvulsants (avoid aromatic antiepileptic drugs (PHT, CBZ, VPA) before and during RT). Newer anticonvulsants are preferable: levetiraceam (Keppra), gabapentin (neurontin), lamotrigine(Lamictal) and topiramate (Topamax): Prophylactic anticonvulsants have not been shown to be effective!

Brain metastases

Treatment options:

Standard:
Radiotherapy +/- radiosurgery

Neurosurgery +/- radiotherapy

Chemotherapy: in chemosensitive tumors (SCLC, germ-cell tumors, testicular cancer)

Clinical trials:
Radiotherapy + chemotherapy (Temozolomid, Talidomid, Teniposid, Gefitinib, Tegafur, CCNU)

Radiotherpy + radiosensitizers

Brain metastases

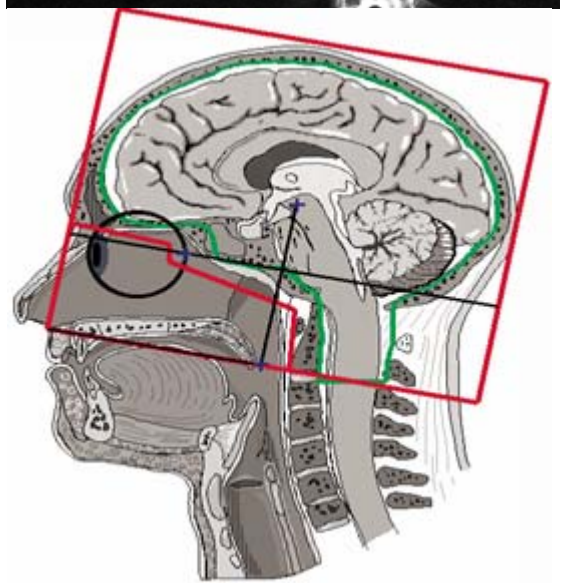
Indication for WBRT-only

- Multiple (> 3-4) metastases
- Oligometastases:
- Neither surgery nor SRS/SRT are feasible (Tu> 3,5cm or overlapping PTVs)
- Poor perfomance status (KPS <60%)
- Age >70y
- Extensive/active extracranial disease with rare or no reasonable systemic treatment options
- Estimated median survival due to extracranial disease or other comorbiditiy under 3-6 mts
- SCLC or lymphatic histology
- Breast cancer (under discussion)

Brain metastases *WBRT only,technique & fractionation*

2D treatment planning,
6 MV Photons,
2 opposite lateral „helmet“- fields including:
- lamina cribrosa,
- caudal part of temporal lobe,
- skull base ;

inferior boarder: 1 -2 cm below the foramen magnum
(note: provide sufficient margins in case of pontine metastases)



Brain metastases *WBRT only,technique & fractionation*

Standard: conventional fractionation
3 Gy/fx, 30 Gy total dose
In some cases boost 2 x 3 Gy

In case of relatively good risk → 2 Gy/fx, 40 Gy total dose
(Or 2,5 Gy/fx up to 35-37,5 Gy total dose)

Poor risk (RPA Stage III) and/or urgent control of neurologic deficits needed
→4 Gy/fx, 20 Gy total dose

No significant differences among various conventional fractionation schemes (30Gy in 10fr,20gy in 5 fr, 40gy in 20fr)

Larger daily fractions do not appear to prevent recurrence and may increase toxicity (↑risk to die due to brain herniation)

No benefit of altered fractionations as compared to standard (10x 3 Gy /fx, one daily fraction)

Brain metastases

Re-irradiation after WBRT:

- another WBRT is possible (if former good response to irradiation and relapse later than 6 mts after RT)

But:
- necessitate lower dose (1.8 Gy /fx to 19.8-25.2 Gy total dose)
- short-term palliation
- no long-term benefit (2-4 mts median survival)
- high toxicity rates

Therefore:
SRS /SRT or is recommended:
- effective
- good tolerability
- in some cases (even in patients with poor performance status) can yield a survival benefit: median survival of 6-10 mts for SRS is reported and 3.5-12 mts for SRT

If SRS/SRT is not feasible: consider conventional 3D planned RT with 5x5 Gy

Brain metastases

Surgery + WBRT:

- KI ≥ 70%,
- controlled primary tumor
- Age <60
- solitary/single metastasis

Surgical resection + WBRT vs WBRT alone:
→ fewer recurrences,
→ better quality of life,
→ longer survival in surgical resection group *Patchell et al , NEJM 1990*

Adjuvant WBRT with 1.8 Gy/fx to a total dose of 50.4 Gy
→ fewer cns recurrences and
→ smaller likelihood to die of neurologic causes
→ no reduction in neurologic death in surgery-only group, even with salvage WBRT. *Patchell et al , JAMA 1998*

Recommended fractionation: 20x 2 Gy, conventional fractionation

Brain metastases *Surgery + WBRT:*

Exceptions:

• Surgery is not recommended even for RPA class I patients if singular SCLC-mts, germ-cell tumor, metastatic lymphoma, leukemia, myeloma (surgery only either in case of uncertain histology or emergency)
→ initial therapy either WBRT or chemotherapy (response rates 56-92% and 30-80% correspondingly)

• Excision can be indicated even in case of more than 3 brain metastases because of emergency due to tumor volume effect

Note: In some exceptional cases after incomplete (R2) excision consider a boost additional to the WBRT 2-3 x3 Gy

Brain metastases *Stereotactic irradiation +/- WBRT*

Metastatic tumors: do not infiltrate the brain, have well- circumscribed boarders→ a good target for highly focused irradiation techniques

Radiosurgery:
- treatment of recurrent metastatic lesion
- a boost to WBRT: better OS with SRS for RPA class I, *Andrews et al, Lancet 2004*
- a sole therapy

Up to 3-4 brain metastases, < 3 cm,
KI ≥ 70%,controlled primary tumor, age <60 y

<2 cm 22- 25 Gy
2 cm 18-20 Gy

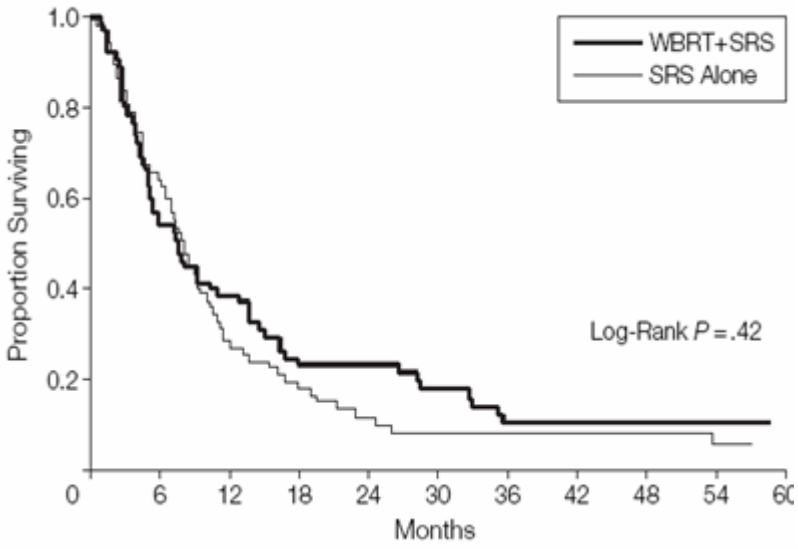
Dose prescription: 80%- isodose surrounding the GTV

If WBRT planned: 30% dose reduction for SRS + 10 x 3 Gy WBRT
Aoyama et al. JAMA, 2006

Brain metastases *Stereotactic irradiation +/- WBRT*

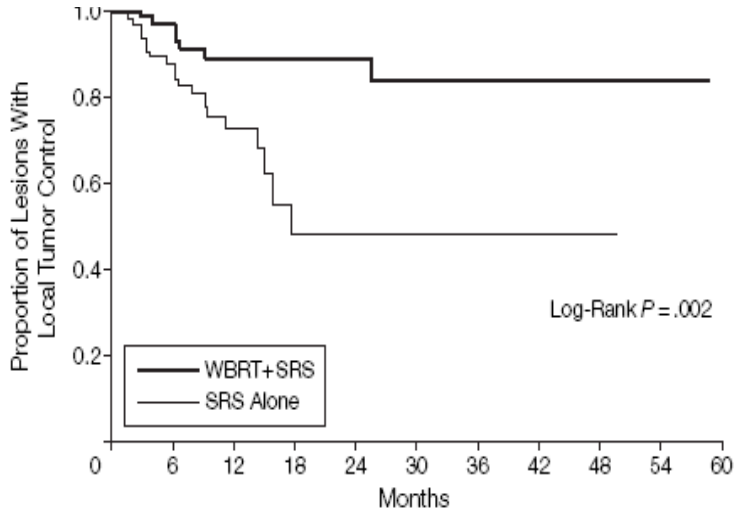
Aoyama et al. JAMA, 2006

Overall survival



No significant differences in OS (and death due to neurological relapse) identified

Local tumor control



If WBRT is omitted: more CNS relapses

Still no agreement whether WBRT after the SRS should be omitted or not

Proposed approach :
SRS only, close follow up (physical examination+ MRI every third month over 2 years), WBRT as salvage

Brain metastases *Stereotactic irradiation +/- WBRT. SRT*

Stereotactic Radiation Therapy:

Salvage-option for brain metastases either unresectable or not amenable for SRS (large lesion close to/ in brain stem or mesencephalon)

5x 6 Gy if previous or planned WBRT, otherwise 5x 7Gy
Dose prescription: commonly to a 90% isodose, which encloses the PTV (max. tumor volume MRI&CT +1-2mm)

Limiting factor:
Tolerance of the normal brain tissue, which depends on the dose-volume ratio & brain structure involved:

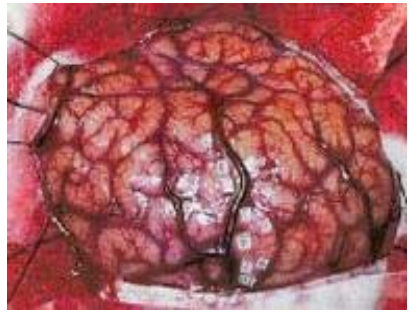
- The volume of normal tissue covered by the 10Gy isodose line is a significant variable for occurrence of radiation- induced tissue changes after single dose irradiation *J.Voges IJROBP 1996*
- Normal brain volume irradiated with >4 Gy/fx (when totally 5 fractions will be applied) should be kept under 20cc
  A.Ernst-Stecken et al, R&O 81, 2006

Brain metastases

surgery vs. radiosurgery

advantages	Allows histological diagnosis Removes mass effect Improves local control Treatment of recurrence Able to treat large lesions	Minimally invasive No hospitalisation Cost effective Treatment of recurrence Treats surgically inaccessible masses
disadvantages	Invasive Requires hospitalisation Limited to 1-3 metastases Infections	No histological diagnosis Limited to small tumors (<15ml) Limited to max 4 metastases Longer time for resolution of mass effect

Carcinomatous meningitis



Definition

Metastatic spread of cancer cells in subarachnoid space:
- solid leptomeningeal metastases,
- diffuse spread of non-adherent cells into the subarachnoid space
- both of these patterns of spread

Malignances that can lead to carcinomatous meningitis:
- breast ca
- lung ca
- melanoma
- lymphoma und leukemia
- primary brain malignancies (germinoma, medulloblastoma und PNET, ependymoma, seldom- malignant glioma)

Incidence in malignant disease is about 10%

In half of the cases there are additional solid brain metastases present
Most of patients (two thirds) exhibit extracranial spread of primary disease

Carcinomatous meningitis

***Symptoms**:*
- Elevated ICP: nausea, vomiting, headache
- Meningeal signs: neck stiffness, pain on straight leg raising
- Brain invasion: focal deficits or diffuse complains (confusion, generalized seizures)
- Cranial nerves palsy (for example, n.abducens affection→ “double vision”)
- Spinal nerve root involvement: neurologic deficits and radicular pain

Most common complaints: pain, radicular discomfort, headache, mental status abnormalities and weakness

Prognosis: poor
- without treatment ***6-8 weeks*** (exception- lymphatic malignancy- somewhat better)
- with treatment ***2-8 months***

1 year survival is still possible in *5-25%* (breast ca, lymphatic malignancy)
Most of the treated patients die due to systemic tumor progression

Carcinomatous meningitis

	Median survival, months
Without treatment	1.0
Treatment resistant	2.0

Histology	
Melanoma	4.0
NSCLC	6.0
AIDS-associated Lymphomas	6.0
Breast Ca	7.5
Not- AIDS-associated Lymphomas	10.0

Carcinomatous meningitis

- most treatment proposals are not based on prospective randomized trials
- treatment is palliative

The aim of therapy:
- prolongation of life expectancy
- relief of pain and neurologic symptoms caused by localized CM

Treatment choice: according to prognosis, spread pattern and tumor load in CNS (MRI, CSF)

Poor: poor perfomance status (KI≤60); type of metastases: multiple, in a region of critical vital structures, pronounced neurologic deficits; „bulky“ CNS lesions; massive extracranial spread with rare or no reasonable treatment options left, carcinomatous encephalitis (extensive brain infiltration)

Good: good perfomance status (KI>60); minor neurologic deficits; low extracranial tumor load; several reasonable treatment options left against systemic disease

„Poor“- symptoms palliation only
„Good“- „agressive“ approach

Carcinomatous meningitis

....Therapy choice

2. *Spread pattern according to MRI und craniospinal fluid findings*
   - solid nodal versus diffuse und non-adherent- superficial growth prevails, free cells and cell clumps in CSF

Often combined presentation of nodular/solid and diffus/non-adherent tumor spread. Thus, combined therapy methods are needed ;

intrathecal chemotherapy
+/- RT to sites of obstruction, small RT- volume
+ RT to lesions >1mm

Carcinomatous meningitis

<u>Treatment options</u> :

- Corticosteroids (↑ICP, pain/ headache, neurologic deficits)
- Anticonvulsants: only for patients with seizures
- Chemotherapy: intrathekal vs. high dose systemic administration
  MTX, DepoCyt (liposomales Cytarabine), Thiotepa

Intrathecal chemotherapy: in 70% of patients liquor circulation is obstructed → ↑neurotoxicity at one site and less effectiveness at another → small volume RT at the site of obstruction

High dose systemic chemotherapy → ↑systemic side effects

- Radiotherapy: alone or in combination with chemotherapy (RT preferably after the chemotherapy administration, never concomitantly)

Carcinomatous meningitis

Investigational chemotherapeutic agents for systemic administration:

- Capecitabine (Xeloda)
- Gefitinib in EGFR pos. NSCLC
- Trastuzumab (Herceptin) systemic/ intrathekal in HER2 pos. breast ca
- Lapatinib for HER2 pos., Herceptin- resistant breast ca

Investigational intrathecal therapies:

- Mafosfamide (pediatric malignancies)
- Etoposide
- Dacarbazine
- Nitrosoureas
- Busulfan
- Trimetrexate
- Melphalane
- Topotecan
- IL-2 (melanoma)
- Rituximab (lymphomas)

Carcinomatous meningitis

Treatment proposals according to risk group:

1. Poor risk: poor perfomance status (KI≤60) and poor prognose (fast progressive extracranial metastasing with rare or no reasonable treatment options left):

Steroids, analgetics, RT against lesions causing major complaints / deficits

Fractionation: decision on individual basis (symptoms, site and volume of the metastatic lesion): 10x 3 Gy, 4x 5 Gy, 5x 5 Gy...

In exceptional cases of extensive spread of relevant neurologic deficiency: primary craniospinal irradiation: 1.6 Gy/ fx up to 24 Gy total dose followed by a boost on bulky lesions up to 35.2 Gy cumulative dose

Carcinomatous meningitis

2. Good risk 1: good perfomance status (KI>60) und discreet leptomeningial spead (few cell clumps in CSF, minor radiologic lesions):

Upfront intrathecal chemotherapy.
Small volume RT only in case of obstruction (10x 3 Gy) before or after chemotherapy
After the chemotherapy: only in case of persistant cranial nerve affections: WBRT „helmet“ and C2 inclusive, 2-3 Gy/fx up to 30-36 Gy total dose

3. Good risk 2: good perfomance status (KI≥70), age<65 y, controlled extracranial tumor or several reasonable systemic treatment options left
BUT: pronounced leptomeningeal lesions

Initially intrathecal chemotherapy and RT thereafter :
WBRT „helmet“ , incl. C2 inclusive and bulky- sites 2-3 Gy/fx up to 30-36 Gy total dose
In case if chemotherapy is not feasible/inefficient but stable performance status: craniospinal irradiation 1.6 Gy/fx up to 24 Gy total dose, boost to bulky lesions up to 35,2 Gy cumulative dose.

Carcinomatous meningitis

RT techniques

1. *WBRT / Intracranial liquor spaces*
Mainly 2D treatment planning

„*Helmet*“ : brain, lamina cribrosa, optical nerves up to retina, skull base, cervical vertebras 1&2.
2 Gy/fx, 30- 36 Gy total dose
(poor prognosis → 3 Gy/fx, up to 30 Gy total dose)

2. *Focal spinal lesions*:
Additional vertebra cranial and caudal the last affected level for the safety margins. Whether 2 Gy or 3 Gy/fx → decision on an individual basis (prognosis, tumor radiosensitivity, tumor load, treatment volume), up to 30-36 Gy total dose

Carcinomatous meningitis

RT techniques

3. *Total irradiation of the CSF-space*

3D treatment planning

- Positioning: prone, head inclination, ventral gantry rotation 3-5°
- In pediatric patients: supine positioning is possible
- *Helmet"* (brain, lamina cribrosa, optical nerves up to retina,caudal part of temporal lobe, skull base, cervical vertebras 3&4) → → S4

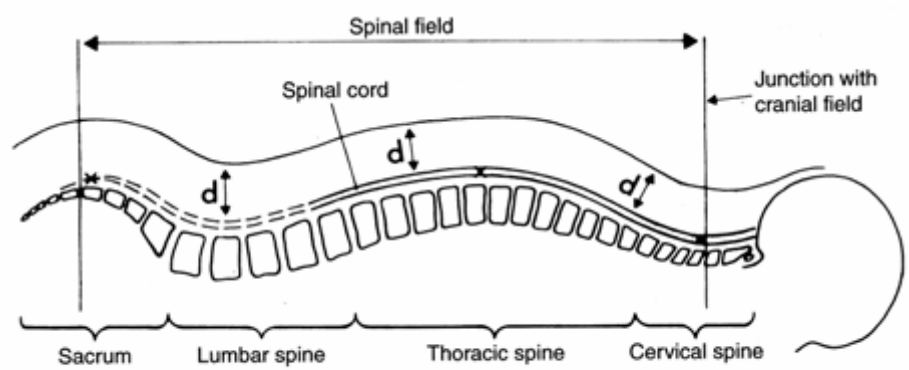
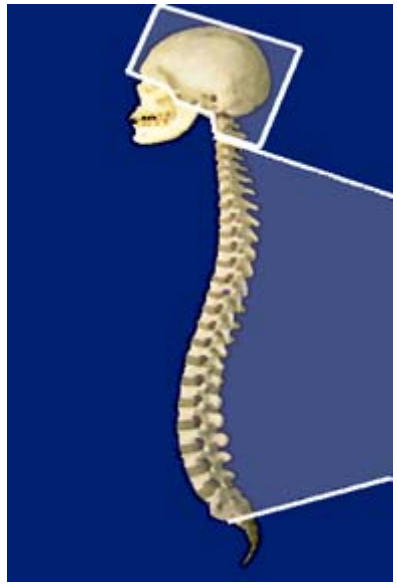


Fig 21.6 Diagram of simulator film showing patient in the prone position for CNS axis irradiation. d = depth for gap calculation.

J.Dobbs Practical treatment planning, 1999

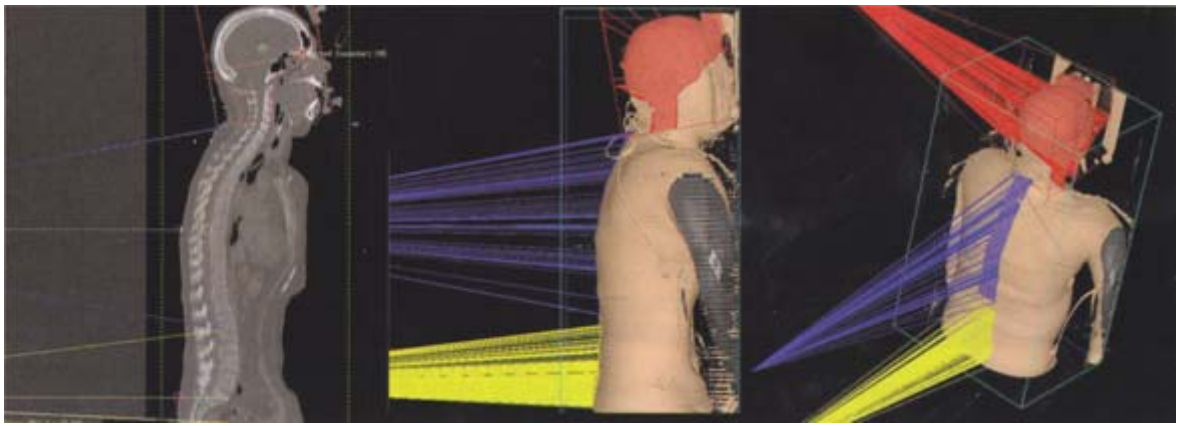


Carcinomatous meningitis

RT techniques

3. …*Total irradiation of the CSF-space*
- Adults: vertebral arch roots +1cm
- Pediatric patients: the entire vertebras
- Middle spinal volume at least up to L1/L2 with steady beam irradiated (field junction under the conus)
- Junction switch: daily or weekly (after 5 fractions)

Entire neuroaxis: 1.6 Gy/fx, 24 Gy total dose, boost up to 35.2 Gy cumulative dose



Technical Basis of Radiation Therapy . Practical clinical application 4th edition S.H.Levitt et al.

Other RT-treatment techniques: spinal IMRT, tomotherapy, proton-RT (pediatric patients)