13. **Brain Tumours**

Introduction

In 2000, 1 009 new cases of primary brain tumours were reported to the Swedish Cancer Registry. In 1992 this number was 1 169.

The age adjusted incidence per 100 000 inhabitants in 2000 was 11.4 for men and 11.3 for women. About 70 per cent of the tumours originate in cell components that form the CNS (glioma) and 30 per cent of the tumours from the membranes surrounding the CNS (meningioma).

This overview addresses the three most common groups of primary intracranial tumours (i.e. high grade malignant glioma (grade III and IV), low grade malignant glioma (II) and meningioma.

Glioma

Modern classification of gliomas is made in accordance with the World Health Organization (WHO) scheme which was revised in 1993 [12]. Also a growing understanding of the genetics of the gliomas has developed recently [13]. Thus a distinction is now made between primary and secondary glioblastomas. Primary glioblastoma (grade IV) is formed "de novo" and is more often seen in elderly patients (median age 56 years). Secondary glioblastoma (grade IV) develops through progression from low grade (II) and anaplastic astrocytoma (III) and is more often seen in younger patients (median age 40 years). Secondary glioblastomas comprise about 10 per cent of all gliomas.

Grade I glioma in the WHO classification is a benign tumour (pilocytic astrocytoma) most often seen in children.

The main treatment modalities for patients with gliomas are surgery, radiotherapy and chemotherapy. The infiltrative growth of gliomas makes it impossible to eradicate the tumour by surgery. Radiotherapy is given postoperatively in order to prolong time to relapse and palliate the condition of the patients. Chemotherapy has proven to add very marginally to the survival of the patients.

Meningioma

Meningiomas Grade I are mostly benign tumours composed of neoplastic meningothelial cells. Grade II, atypical meningiomas tend to invade the dura and grow more aggressively. Finally, anaplastic malignant meningioma, is a grade III meningioma.

Summary of the earlier report, SBU 129/2

Conclusions

- Curative treatment is not available for patients with highly malignant glioma (grades III and IV).
- Postoperative radiotherapy for highly malignant glioma extends patients' survival, with good quality of life, by several weeks to several months. Virtually all patients die from this disease. Although the clinical benefits from radiotherapy, measured as survival, appear to be modest, it is more effective than any chemotherapy tested thus far.
- The clinical effects of radiotherapy for highly malignant glioma are improved only marginally by altering factors such as absorbed dose, fractionation, irradiated tissue volume, radiation quality, or by adding radiosensitizing substances.
- Radiotherapy alone usually provides a clear but temporary improvement in patients with highly malignant glioma, hence it clearly has a palliative benefit.
- Postoperative radiotherapy for low-grade malignant gliomas (grade I and II) may extend survival. It also reduces tumour volume. No evidence shows that radiotherapy alone or postoperatively can lead to cure.
- In patients who have undergone subtotal meningioma resection, postoperative radiotherapy substantially reduces the risk for recurrence and extends life, and is thereby indicated. Radiotherapy is not indicated following macroscopic radical meningioma surgery (WHO grade I).

SBU 129/2 also covered radiotherapy in brain metastases and some conclusions were drawn. Radiotherapy of brain metastases is not reviewed in the present report.

Discussion

The earlier report covered literature until 1994.

The classification used in these studies (Kernohan etc) was not the same as in the present report (WHO classification) This means that the distinction between grade I and II and between III and IV differs between the two time periods.

Despite of the mixture in grade and hence also prognosis the results from the previous studies [1,15,24] did show a statistically clear evidence for prolongation of survival using radiotherapy, although short in time. A randomized study with controls not having radiotherapy and stratifying for the WHO classification grades would be of great interest but due to ethical reasons difficult to perform.

Literature

The earlier report was based on 82 scientific articles, including 26 randomized studies, 13 prospective studies and 25 retrospective studies. The studies included 11 252 patients.

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients)[1)].

	1 = High	2 = Moderate	3 = Low	Total
M	–	–	–	**–**
C	17/5 344	6/1 480	3/1 106	**26/7 930**
P	10/582	3/163	–	**13/745**
R	13/1 600	5/670	7/301	**25/2 571**
O	9/6	8	1	**18/6**
Total	**49/7 532**	**22/2 313**	**11/1 407**	**82/11 252**

[1)] Studies of Brain metastases included.

Assessment of new literature

Search method and selection

Literature was searched in Medline for the period 1994 to October 2001 using the MeSH terms ”brain neoplasms” and ”glioma” in combination with ”radiotherapy” as subheading, MeSH or textword with limitation to randomized controlled studies, controlled studies and meta-analysis.

Primarily 45 articles and one abstract concerning malignant glioma and meningioma were reviewed by three referees.

After exclusion of articles not relevant for the purpose of the present presentation 19 articles and one abstract were selected for further study.

Reasons for exclusion of 26 publications not selected for further analysis were:

A	2	reviews
B	7	editorials/letter/abstract
C	1	basic science
D	5	studies with low evidence
E	11	not relevant for the present presentation

Overview of new studies

High grade malignant glioma (WHO grade III–IV)

Overview 1 (after the list of references)

These tumours comprise approximately one third of the primary CNS malignancies. Patients with anaplastic astrocytoma (grade III) have a median survival of about three years compared to patients with glioblastoma multiforme where the median survival is about nine months. Radiotherapy is conventionally given after surgery. The most common radiotherapy schedule for treatment is a total radiation dose of 60 Gy given in 30 fractions over six weeks. The target for radiation is mostly the enhancing tumour as visualized on CT with a wide margin of 2–3 cm. New studies have mainly been concerned with different fractionation schemes in order to increase the total dose.

The literature shows that:

- No curative treatment is yet available for high grade malignant glioma and treatment efforts concerns prolongation of life with an optimisation of quality of life [16,21].
- A slightly better survival with radiotherapy to higher doses was seen in patients with grade IV tumours [25]. However this was not confirmed in a randomized trial (only published as abstract) [20].
- Higher radiation doses lead to more radiation induced complications [3].
- A radiotherapy boost with brachytherapy may add to prolongation of life in selected patients with glioma grade IV [17,18,22].
- Radiotherapy using hyper- and hypofractionation does not lead to better survival than conventional radiotherapy [2,7,16,25].
- Patients with grade IV glioma and poor prognosis i.e. high age may be treated with hypofractionation with similar outcome as after conventional treatment. This leads to better quality of life for the patients and is of clinical and economical importance [2,7].
- Methods for improvement of radiotherapy like sensitizers only add little to the final outcome of therapy [8].
- Experimental studies with high LET (pions) are feasible but do not improve the results [19].
- The classification used is of great importance for evaluation of the results. Oligodendroglioma component gives a better prognosis [4].
- Age is the most important prognostic factor for patients with high grade malignant glioma [5].

Future efforts to improve radiotherapy are to develop methods like stereotactic radiotherapy, BNCT (boron neutron capture therapy) and radioimmunotherapy.

Low-grade malignant glioma (Grade I–II)

Overview 2 (after the list of references)

Grade I (pilocytic astrocytoma) is a benign tumour most common in children and is curable by surgery. This tumour is not treated with radiotherapy.

Astrocytoma grade II is most common in young patients. After diagnosis the median survival time is about 10 years. Eventually the tumour will develop through grade III to IV (high grade glioma). The optimal treatment for grade II glioma has been much debated. The most important new studies is performed by EORTC (European Organization for Research and Treatment of Cancer).

The literature shows that:

- No significant evidence yet that radiotherapy prolongs life for patients with low grade glioma. [9,23]
- No dose-response found comparing 59.4 Gy during 6,5 weeks to 45 Gy during five weeks. [10]
- Higher radiation dose may give poorer quality of life without treatment benefit. [11]
- Brachytherapy is not a suitable method due to high rate of complications. [14]
- Radiotherapy can be used to treat symptoms. [23]

EORTC is performing a randomized study concerning the effect of radiotherapy in patients with low grade glioma (WHO grade II). An interim analysis indicates that early postoperative conventional RT improves time to progression but not overall survival [9]. The statistical power of the study is week and until firmer evidence is available individual decisions should be made concerning radiotherapy in low grade glioma.

Meningioma

- No new randomized studies have been found. Earlier statement that postoperative radiotherapy is indicated after subtotal resection, especially for grade II–III is therefore still valid.

Literature

The synthesis of the literature on radiotherapy for brain tumours is based on 19 scientific articles and one abstract including nine randomized and two non-randomized studies, one meta-analysis and three retrospective study. These studies involve 4 266 patients. Also four review articles have been included.

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
M	–	1/1 700	–	**1/1 700**
C	6/1 165	2/221	1/290	**9/1 676**
P	2/231	–	–	**2/231**
R	1/159	–	2/377	**3/536**
L	3/123	1	–	**4/123**
Total	**12/1 678**	**4/1 921**	**3/667**	**19/4 266**

Conclusions and comments

- The conclusion from SBU 129/2 that curative treatment is not available for patients with high grade malignant glioma (grade III and IV) is still valid. ([16]L1).
- The survival benefit from postoperative radiotherapy compared to supportive care only or chemotherapy is about 3–4 months as demonstrated in earlier randomized studies, reported before 1994 but reviewed in reference 16. ([16]L1).

Quality of life is now currently estimated and considered to be of major importance when reporting the outcome of treatment for patients with brain tumours.

- There is no scientific evidence that radiotherapy using hyperfractionation leads to longer survival for patients with high grade malignant glioma than conventional radiotherapy. There is a large documentation, but only one randomized study. ([2]P1, [7]P1, [16]L1, [25]C1).
- There is some documentation supporting that patients with grade IV glioma and poor prognosis may be treated with hypofractionation with similar outcome as after conventional fractionation. ([2]P1, [7]P1).

A shorter treatment time should be convenient for the patient.

- The documentation of the benefit of a radiotherapy boost with brachytherapy is limited and no conclusion can be drawn. ([17]C2, [18]R3, [22]L1).
- There is no scientific evidence that radiotherapy prolongs life for patients with low grade glioma. ([9]C3, [23]L1).
- There is some data supporting that radiotherapy can be used to treat symptoms in low grade glioma. As no controlled studies are reported no firm conclusion can be drawn. ([23]L1).

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Overview 1 *Brain tumours. High grade malignant glioma, different approaches in radiotherapy.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Werner-Wasik RTOG 1996 [25] C, phase I/II	RT dose/schedule 1. 1.2 Gy/fr, 2 fr/d, to **A:** 64.8 Gy **B:** 72.0 Gy **C:** 76.8 Gy **D:** 81.6 Gy 2. 1.6 Gy/fr, 2 fr/d, to **A:** 48 Gy **B:** 54.4 Gy CHT (BCNU) to all	1983–89 81% GBM, 19% AA 747/786 pts, eligible 1. A 78 pts B 158 pts C 86 pts D 120 pts 2. A 168 pts B 137 pts
Scott, RTOG 1997 [21] C, phase I/II	Dose effect on Q-time (Q-time=quality adjusted survival taking account of neurological signs and symptoms)	Same 786 patients with high grade malignant glioma as ref 25 above.
Scott, RTOG 1998 [20] ASCO abstract 1548	RT dose schedule **A:** 1.2 Gy/fr, 2 fr/d, to 72 Gy **B:** 2 Gy/fr, 1fr/d, to 6O Gy CHT (BCNU) to all	1990–1994 712 pts
Corn, RTOG 1994 [3] C, phase I/II	Toxicity Study of white matter changes (CT, MRT) Tox grade 0–6 (Fazekas) **A:** RT dose: 48.0/54.4 Gy **B:** RT dose: 64.8/72.0 Gy **C:** RT dose: 76.8/81.6 Gy	Long time survivors from RTOG study ref 25 177 pts A 60 pts B 66 pts C 51 pts
Brada 1995 [2] P matched controls	Hyperfractionation **A:** RT 1.53–1.72 Gy/fr, 2 fr/d (min 6 h interval) to 55 Gy/3 w **B:** 2.0 Gy/fr to 60 Gy/ 6 w	1988–1993 Grade III–IV 101/116 study pts eligible A 101 pts B 101 pts (controls)
Hulshof 2000 [7] P	Hypofractionation **A:** RT 2 Gy/fr to 66 Gy/6.6 w **B:** RT 5 Gy/fr, 3 fr/w to 40 Gy/17 d **C:** RT 7 Gy/fr, 2 fr/w to 28 Gy/8–11 d	1988–98 Glioblastoma (WHO) Unfav prog% A 66 pts 27 B 41 pts 78 C 48 pts 87

AA: anaplastic astrocytoma; BRT: brachytherapy; CHT: chemotherapy; d: day(s); GBM: glioblastoma multiforme; fr: fraction(s); LET: linear energy transfer; m: month(s); MST: median survival time; NR: not reported; ns: no significant; OS: overall survival; pts: patient(s); QoL: quality of life; RT: radiotherapy; Unfav prog: unfavorable prognosis; w: week(s)

Results	Conclusion/Comments
Median survival time, m 1. A = 11.4 B = 12.7 C = 12.0 D = 11.7 2. A = 11.9 B = 10.8 ns 5-year survival no sign difference	No significant survival advantage observed for any treatment arm. However, patients with AA appeared to respond differently than GBM and it is concluded that they should be studied separately. Groups 1 A and 1C was closed during the study which explains different number of patients in groups. **C1**
Group 1 B (72 Gy) showed both good survival and moderate loss in QoL.	Emphasis the importance of taking account of quality in survival in studies concerning brain tumour patients **C1**
MST: numbers NR No survival advantage from hyperfractionation	A full manuscript has not been published to date. Abstract.
Toxicity % grade: 3 6 A 8.3 1.6 B 21.2 6.1 C 29.4 17.7 Median time to tox grade ≥2 14.5 m	Severe white matter changes continued to increase significantly with escalating total doses. To be considered together with ref 21 and 25. **C1**
OS% 1 y 2 y A 33 13 B 39 13 ns No difference in toxicity between groups	Kernohan classification. Reducing duration of treatment is feasible. **P1**
Median survival time, m A 7 B 5.6 C 6.6 ns	An extreme hypofractionation (gr C) is well tolerated and provides equal palliation to a lower cost than conventional RT (grA). Grade of late toxicity not known in these poor prognosis patients. **P1**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Halperin 1995 [6] L	Cost-benefit discussion	Glioblastoma poor prognosis pts
Glinski 1998 [5] R	RT dose/schedule **A:** 2 Gy/fr to 50 Gy/5 w **B:** same as A + CHT **C:** 2 Gy/fr to 60 Gy/10 w, with 2 splits, 2 w each **D:** 2.65 Gy/fr, 2 fr/d, to 53 Gy/12 d	1973–1993 High grade glioma (GBM and AA) A 61 pts B 135 pts C 39 pts D 59 pts
Donahue, RTOG 1997 [4] C, phase I/II	See ref 25 Comparison of different histopathologic subtypes Effect of oligoastrocytic component	Subgroups from ref 25. A 109 AA B 24 AA /oligoastrocytoma
Huncharek 1998 [8] M	Radio-sensitizer **A:** RT **B:** RT + misonidazol	9 trials 1 700 pts with GBM and AA A 711 pts B 1 086 pts
Sneed 1997 [22] L	Evaluation of BRT **1.** In recurrent disease **2.** As boost to conventional radiotherapy in primary disease	High grade malignant glioma 1. Recurrent glioma 2. A WHO grade III B WHO grade IV
Matsumoto 1997 [18] R	BRT with Ir-192 **A:** RT 2Gy/fr to 51.1 ± 12.4 Gy **B:** RT 2Gy/fr to 51.1 ± 10.8 Gy + BRT 50.2 ± 13.2 Gy, dose rate 0.3–0.4 Gy/h	1987–1995 High grade glioma III–IV (Kernohan) A 50 pts B 33 pts
Laperriere 1998 [17] C	BRT with Ir-125 seeds **A:** RT 2Gy/fr to 50 Gy/5w **B:** RT same as A + BRT 60 Gy, dose rate 0.7 Gy/h	1986–1996 High grade glioma 140 pts A 69 pts B 71 pts
Pickles 1997 [19] C	Intermediate LET with pions **A:** RT 2 Gy /fr to 60 Gy/6 w **B:** RT pions to 33–34.5 Gy π/ 1 fr/d, 15 fr/3 w	1988–1994 High grade glioma 81 pts (Kernohan) A 41 pts B 40 pts

Results	Conclusion/Comments
Shorter RT time suggested for pts with poor prognosis	Important discussion on cost-benefit. **L2**
OS% at 2 y A 21 B 19 C 15 D 24 ns	Only age a sign prognostic factor. **R3**
Median survival time, y A 3 B 7.3 p=0.02	PAD important prognostic factor. Oligoastrocytic component better prognosis. **C1**
The survival advantage at one year in B is approx 8%	A small but significant benefit of radiosensitizer is demonstrated in this large meta-analysis. **M2**
Survival time, m 1. 5.5–18 2. A 36 B 18–19	Important review. BRT is considered to prolong life for pts with grade IV but not grade III glioma and can be used in recurrent disease. **L1**
Median survival time, m A 12.2 B 23.7 Sign p=0.0145 Tox: Radionecrosis was seen in 9 pts in B	Selected, good performance patients with tumours situated in non eloquent areas may benefit from BRT. **R3**
Median survival time, m A 13.2 B 13.8 ns Toxicity: 15 complications reported in BRT arm	In a randomized study no improvement with BRT. **C2**
Median survival time, m A 10 B 10 ns No difference in toxicity	No therapeutic gain in this study but it is an interesting approach. **C2**

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Overview 1 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Laperriere 2002 [16] L	Systematic review concerning survival benefit from post operative RT in high grade glioma. Literature review covering 1983–2000 **A:** 6 randomized studies comparing conventional RT with no radiation. Statistical analysis of pooled material **B:** 6 randomized studies of hyper-fractionated RT compared with conventional RT. Statistical analysis of pooled material. **C:** Review concering hypofractionation and brachytherapy.	A 6 trials published 1976–91 794 pts B 6 trials published 1982–98 979 pts

Results	Conclusion/Comments
A. Significant survival benefit with postoperative conventional RT compared to no RT, (RR 0.81 P<0.000001). B No survival benefit with hyper-fractionated RT compared to conventional RT (RR 0.89 P = 0.27).	This well performed review with pooling and statistical analysis of study results concludes that postoperative external beam RT (50–60 Gy in fraction sizes of 1.8–2.0) is recommended as standard therapy for patients with malignant glioma. For older patients the same survival benefit can be achieved with shorter course RT with higher dose per fraction. **L1**

Overview 2 *Brain tumours. Low grade malignant glioma – radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Karim, EORTC 1996 [10] C	**A:** RT 1.8 Gy/fr, 25 fr to 45.5 Gy/ 5 w **B:** RT 1.8 Gy/fr, 33 fr to 59.4 Gy/6.5 w	1985–1991 Low grade glioma I–II (WHO) 379 pts A 171 pts B 172 pts
Kiebert, EORTC 1998 [11] C	QoL analysis based on ref 10.	See ref 10.
Karim, EORTC 2002 [9] C	Evaluation of postoperative RT **A:** RT 1.8 Gy/fr, 30 fr to 54 Gy/6 w **B:** no RT	1986–1997 Low grade glioma 290 pts A: 150 pts B: 140 pts
Trautmann 1996 [23] L	The role of RT in low-grade glioma.	Low-grade glioma (WHO) in comparison to other classification systems
Kreth 1997 [14] R	BRT risk analysis BRT with I-125 seeds Permanent (60 Gy) or temporary (100 Gy)	Low grade glioma 594 pts

BRT: brachytherapy; fr: fraction(s); m: month(s); ns: no significant; OS: overall survival; pts: patient(s); PFS: progression free survival; QoL: quality of life; RT: radiotherapy; w: week(s); y: year(s)

Results	Conclusion/Comments
OS% **PFS%, at 5 y** A 58 47 B 59 ns 50 ns	No benefit with a higher radiation dose. Tumour size is an important prognostic factor. **C1**
A worse QoL with longer treatment time.	Shorter treatment schedule gives better QoL with equal survival in patients with low grade glioma. **C1**
OS% **PFS%, at 5 y** A 63 44 B 66 37 ns p=0.02	This is an interim analysis. After a pathology review only 172 (74%) patients were confirmed as low grade glioma (WHO grade II). Eight cases had grade I, 48 grade III and 4 cases a grade IV glioma. A reanalysis of the 172 patients with grade II glioma showed limited statistical power. Thus, this study gives no statistical evidence that radiotherapy prolongs life for patients with low grade glioma. **C3**
WHO I No benefit from RT WHO II Retrospective studies have shown conflicting results and randomized studies are lacking.	No significant evidence yet that radiotherapy prolongs life for patients with low grade glioma. Radiotherapy can be used to treat symptoms. **L1**
Median survival time 44 m. Overall complication rate 7.5% Temporary BRT complications < 3%.	The method is limited by complications. Temporary implants better than permanent. The method is best for small tumours. **R1**