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EORTC Radiation Oncology Group

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Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase-II and observation study

EORTC protocol 22042-26042

(EudraCT number 2005-005551-18)

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Protocol summary

Title of the Study	**Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase-II and observation study** **(EORTC 22042-26042)**
Objective(s)	To assess the impact of high-dose radiotherapy (RT) on progression-free survival (PFS), treatment tolerance, and post-treatment global cognitive functioning in patients with a diagnosis of either atypical (grade WHO II, phase II study) or malignant (grade WHO III, registration study) meningiomas.
Methodology	For patients with atypical (WHO grade II) meningioma, the study is designed as a stratified phase II with stratification for the resection status scored according to Simpson's guidelines (Simpson's stages 1-3 vs 4-5). A separate Fleming 1-stage design is applied to each of the two strata separately, with specific objectives expressed in terms of the 3-year progression-free survival rate. The patients with malignant (WHO grade III) meningioma are registered as a separate group and will be treated and followed according to the protocol but no specific statistical design is planned due to the small number of such patients expected to enter the study. The duration of accrual is driven by the phase II trials.
Number of patients Number planed (statistical design) Number analyzed	A total of 64 patients with atypical (WHO grade II) meningioma will enter the phase II: 25 with Simpson's stage 1-3 and 39 with Simpson's stage 4-5. These numbers are determined from Fleming designs with type I and type II error rates ≤10%, with parameters P0=70% and P1=90% for the group with Simpson's stage 1-3 and P0=50% and P1=70% for the group with Simpson's stage 4-5. These patients will need to be eligible and to have started treatment. It is foreseen than 6-13 grade-III patients will be registered in the present study during the accrual period of the phase II, which is estimated to last approximately 3 years. The primary analysis of the efficacy endpoints will be on all eligible cases who started irradiation and using the histological classification by the local pathologist.
Diagnosis and main criteria for inclusion	To enter the study, patients should present with ♦ Patients with WHO grade-II or WHO grade-III meningioma (local pathology) ♦ Complete or subtotal resection as assessed by the surgeon after verification with a postoperative MRI and according to Simpson guidelines. All Simpson's stages are thus allowed. ♦ Age between 18 and 70 years ♦ WHO performance status 0-2

	♦ No optic nerve sheet tumors nor neurofibromatosis type II ♦ No previous radiation therapy to the meninges or brain ♦ No second malignancies ♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial ♦ Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
Treatment Test product, dose and mode of administration	The treatment dose will be determined in function of the Simpson's stage. Irrespective of WHO tumor grade patients with Simpson stage 1-3 will receive 60 Gy to the CTV1 and those with Simpson stage 4-5 will be treated with 60 Gy to CTV1 followed by a 10 Gy boost to the CTV2 (total, 70 Gy). Volumes and prescribed dose should be according to the ICRU-50 report. ♦ GTV: postoperative tumor residual (CT or MRI). ♦ CTV1: GTV and/or subclinical microscopic tumor (may include the pre-operative tumor bed, peritumoral edema, hyperostotic changes if any, and dural enhancement or thickening as seen in the CT/MRI at diagnosis) + 10 mm or less, see dose constraints below. ♦ CTV2: GTV + 5 mm margin or less (see dose contraints, below). ♦ PTV1 & PTV2: CTV1 & CTV2 + 5mm margin (3 mm for stereotactic irradiation). These volumes needed to cover the CTV1 & CTV2 with the 95% isodose line, respectively. Fractionation: 2 Gy daily fractions, 5 fractions a week Radiation quality: photon (> 4 MV) beams either conformal, stereotactic, or intensity-modulated radiation therapy (IMRT). Dose constraints (total dose): ♦ optic pathways: 56 Gy (average); 60 Gy (maximum). ♦ Pituitary gland: 56 Gy. ♦ Brainstem: central, 54 Gy; surface, 64 Gy.
Duration of treatment	The treatment duration is therefore 6 weeks for Simpson's stage 1-3 and 7 weeks for Simpson's stage 4-5.
Reference therapy, dose and mode of administration	Not applicable

Criteria for evaluation	
Efficacy	The primary trial endpoint is the 3-year progression-free survival rate in each stratum of the phase II study. Progression-free survival is counted from entry on study until the first event of either death or progression (as demonstrated by an MRI showing either appearance of new lesions or increased in tumor size by 25% using 3 dimensions) Overall survival is a secondary endpoint and is measured from date of entry to date of death, irrespective of the cause. For both endpoints, the patients not having experienced the event(s) of interest are censored at the date of most recent follow-up.
Safety	Acute and long term toxicity will be scored according to the NCI-CTCAE version 3.0. Neurological function will be measured by the Mini-Mental Status Evaluation.
Statistical methods	The 3-year progression-free survival rates in each group will be estimated by the Kaplan-Meier in the eligible patients who started treatment. In each stratum, the treatment will be judged successful if the lower bound of the 1-sided 90% confidence interval around the estimated 3-year PFS rate is greater than the specified value P0. Additionally, 2-sided 95% confidence intervals will be provided for each subgroup (WHO grade II Simpson's stage 1-3, WHO grade II Simpson's stage 4-5 and WHO grade III) Overall survival will be estimated by Kaplan-Meier method in each patient group. The frequency of each toxic event will be tabulated on all patients who started treatment, irrespective of eligibility. No formal comparison between groups will be performed[2]
Translational research	Genotyping for known chromosomal losses or gains using FISH on paraffin embedded material will be undertaking as well as construction of tissue arrays. The translational research is optional.

1 Background and introduction

Meningiomas are the second most common primary brain tumor and represent approximately 15 - 26% of all intracranial neoplasms, with an annual incidence rate of 6 per 100 000 population (Ref. 1). Approximately, 5 - 10% of these extra-axial tumors correspond to specific histological subtypes that are associated with less favourable clinical outcome (Ref. 2, Ref. 3, Ref. 4). Non-benign histology was associated with a local failure-relative risk of approximately 2 on multivariate analysis in a large meningioma patients cohort (Ref. 5). Non-benign histology has a strong impact on survival as shown in the largest meningioma trial ever published by the Helsinki group (Ref. 6). Kallio et al. reporting on 935 meningioma patients reported a 4.2-fold relative excess risk of death for patients with malignant tumors (Ref. 6). The median overall survival of malignant meningioma patients has been reported to be as low as 7.2 months (Ref. 7). Although benign meningiomas are slowly growing tumors, atypical or malignant meningiomas are associated with a locally more aggressive behaviour with early recurrence or tumor progression. As a result, surgical excision rarely cures the patient and adjuvant treatment is thus needed. Due to the rarity of non-benign meningiomas and the way they are histologically classified, the data on the role of surgery and radiation therapy is difficult to interpret. More specifically, the timing of radiotherapy, the dose that should be administered and the definition of target volumes are controversial.

1.1 Histological classification of meningiomas

Originally, the 1979 WHO classification recognized only two types of meningiomas, classic and anaplastic (Ref. 8). The anaplastic or malignant grade was given to any meningioma that displayed anaplastic features 'yet has not developed in frank sarcoma'. The three-grading system was introduced with the revised 1993 WHO classification, but the precise definition of atypia was not formulated (Ref. 9). Identically, the new 2002 WHO classification relies entirely on the morphological classification of meningiomas, certain subtypes are given the WHO grade of II or III (Ref. 1) although several studies have not demonstrated a correlation between histological subtypes and tumor recurrence (Ref. 10, Ref. 11). More specifically, clear cell and chordoid subtypes are considered WHO grade II (atypical) meningiomas and rhabdoid, papillary and anaplastic histological features classify these tumors as WHO grade III (malignant) meningiomas (Ref. 1). Several alternative grading schemes were published, some based on large series (Ref. 11, Ref. 12, Ref. 13, Ref. 14).

Interestingly, a grading scheme of six histological parameters, each scored from 0 to 3 (absent, mild, moderate and marked) has been applied by several investigators with a good correlation relative to clinical outcome (Ref. 11, Ref. 13, Ref. 14, Ref. 15). This classification contained 4 grades (I-IV) identically to the glioma grading system, defined by a cumulative score: benign (0-2), atypical (3-6), anaplasic (7-11) and sarcomatous (>11). Parenthetically, the 1979 WHO classification is often credited for this grading system, although it actually makes no mention of it. The problems associated with this type of classification were the assumption that all six variables are of equal importance, the imprecision of the 'sarcomatous' (grade IV) subtypes and the possible promotion of overgrading as only 11 points are necessary to define grade IV meningiomas. Notwithstanding the architectural pattern, specific histopathological features are currently required for the diagnosis of WHO grade II or III meningiomas.

In a retrospective series of 581 patients who underwent gross total resection in the Mayo Clinic, the most significant prognostic parameter in multivariate analysis was the maximal mitotic rate ≥ 4 per 10 high-power fields among 10 histological parameters (Ref. 16) bearing in mind that high mitotic

counts can be achieved after embolization (Ref. 17). This criterion was also a major prognostic factor in other series (Ref. 10, Ref. 12, Ref. 18, Ref. 19). As a result, this maximal mitotic rate alone (≥ 4 mitosis per high-power field [HPF]) usually allows a diagnosis of atypia in the absence of other features, such as increased cellularity, architectural sheeting (i.e. patternless pattern), macronuclei and small cell formation (Ref. 20). Likewise, the presence of at least 3 of the latter 4 variables was associated with a statistically significant decreased progression-free survival in the Mayo study (Ref. 16). As a result, in the absence of aforementioned maximal mitotic rate, the diagnosis of atypia can be made also if at least three of these four features are present. Tumors are usually classified as malignant if they have either of the following criteria: (1) excessive mitotic rate (≥ 20 HPF), or (2) dedifferentiation or frank anaplasia on light microscopy. Even with these strict histological criteria, a correct histopathological diagnosis cannot be made in a substantial number of cases (≈ 15%) (Ref. 21).

Finally, most series have reported a strong association between histological grade and gender, with male presenting more frequently with non-benign meningioma (roughly 3 – 4 times) than females (Ref. 13, Ref. 16), while others have observed an equal male/female ratio (Ref. 14, Ref. 15).

The significance of brain invasion is somewhat controversial (Ref. 22). Moreover, this criteria is difficult to evaluate as in most cases, brain parenchyma is lacking or is unsampled. Simple perivascular extension along Virchow-Robin spaces is usually not considered as brain invasion, whereas finger-like or knobby protrusions into underlying cerebral or cerebellar cortex are considered a characteristic of brain invasiveness. This invasiveness commonly produces a gliotic reaction. In the Mayo series, brain invasion was strongly associated with decreased recurrence-free survival on multivariate analysis (Ref. 16). Although this criterion was adversely associated with outcome in several series (Ref. 16), it has not been assessed in other large clinical series (Ref. 11, Ref. 12, Ref. 13, Ref. 14, Ref. 15). Currently, brain invasion is not a criterion *per se* for the grading of meningiomas in the new WHO classification (Ref. 1).

1.2 Current policy for non-benign meningiomas after surgery

Unlike their benign counterpart, the management of atypical or malignant meningiomas rarely depends on patient's age, on the associated signs or symptoms and nor on the site or size of the tumor. Although asymptomatic benign meningioma can be observed in a substantial number of cases (Ref. 20), and a wait and see policy is appropriate even for non-convexity anatomic site lesions (Ref. 23), non-benign tumors rarely are asymptomatic. As such, the signs and symptoms associated with these latter tumors usually require immediate treatment.

Surgery is the treatment of choice since radical resection (gross total resection *vs.* subtotal resection) may be associated with increased tumor control for atypical (Ref. 2, Ref. 24) and malignant (Ref. 2, Ref. 25, Ref. 26, Ref. 27) meningiomas. Ojemann *et al.* reported on 22 primary or recurrent malignant meningioma patients and observed that tumor control following radio-surgery was significantly greater in patients with smaller-sized tumors (Ref. 26). Likewise, in Dzuik's analysis, patients whose disease was completely resected had a significantly greater 5-year local control than those who underwent subtotal resection (39% *vs.* 0%) (Ref. 25). For atypical meningiomas, gross total resection was also associated with a significantly lower recurrence rate in the Cleveland series (Ref. 24). Palma *et al.* reported on 71 non-benign meningiomas and observed that the degree of surgical resection correlated significantly with overall survival in multivariate analysis (Ref. 2). Noteworthy, all series assessing the outcome of non-benign meningiomas are retrospective, have methodological problems or may suffer from biais (Ref. 28, Ref. 29). The number of patients in these studies is small and the studied cohorts contain potentially heterogeneous population treated with various modalities. Moreover, the studied endpoints vary between studies (local control, disease free and overall survival). As such, the ASCO level of evidence can be estimated as V and thus the data should be interpreted cautiously.

Many other series have not assessed the degree of surgical resection (Ref. 30) or found no benefit in a gross total resection in atypical (Ref. 31, Ref. 32) or malignant meningioma (Ref. 31, Ref. 32). This disclaimer aside, it must also be stressed that the degree of surgical resection has been evaluated retrospectively from the operative notes and was assessed differently in these series. Some authors have equated gross total resection to Simpson grade II and III (Ref. 24), while others have not used specifically this classification but have simply defined the surgery as complete or non-complete (Ref. 32). Others did not specify the method of their evaluation of the degree of surgical resectability (Ref. 25, Ref. 31). The degree of surgical resection is usually determined with the Simpson grading system. Donald Simpson, in a seminal paper, described the local failure rates of 229 meningioma patients after surgical excision (Ref. 33). In essence, he showed that the extent of dura management is prognostic for recurrence. The 5-year local failure rate was 9% for grade I excision (removal of tumor and all dural attachments including bone if necessary); 19% for grade II excision (removal of tumor and coagulation of dural attachments); and 29% for grade III excision (removal of tumor). Although this analysis was retrospective and patients were treated before the advent of modern imagery (CT and MRI) and microsurgery, the prognostic importance of the extent of tumor and dural resection has been confirmed by several subsequent studies (Ref. 2, Ref. 5, Ref. 6, Ref. 34, Ref. 35).

Noteworthy, dura matter invasion of benign meningioma can be observed around the dura in the vicinity of the tumor attachment zone. Borovitch *et al.* reported on 14 meningioma patients who underwent radical resection with excision of a radial strip of dura from the line of attachment of the tumor. Clusters of meningioma cells or nodes protruding from the inner aspect of the dura was observed in all patients (Ref. 36). Strips of convexity dura mater taken from 10 control-neurosurgical patients without meningioma did not exhibit these meningotheliomatous conglomerates. As such, regional multiplicity of meningioma may explain some of the observed recurrences of these tumors after radical resection. This author proposes an even higher grade of total resection, ‘Simpson 0’ which would include a wide dural excision around the meningioma attachment zone (Ref. 37).

In summary, no prospective data have confirmed the prognostic importance of radical resection in non-benign meningiomas. A literature overview indicates that for these tumors the recurrence/progression rate following subtotal excision (71%) is higher than following total resection (57%) (Ref. 25). As such, complete surgical resection appears crucial for the long-term tumor control.

1.3 Rationale of adjuvant radiotherapy

The majority of patients with non-benign meningiomas treated with surgery alone will ultimately recur. In a multi-center overview of the surgical results, the reported recurrence rate was 50% and 90% for sub-totally and totally excised patients, respectively (Ref. 27). Most importantly these recurrences have a major impact on the patient’s outcome, as local recurrence negatively impacts overall survival in benign (Ref. 7, Ref. 33, Ref. 38, Ref. 39) and non-benign meningiomas alike. The reported 5-year overall survival rates for non-benign meningiomas is 28 - 70% (Ref. 2, Ref. 13, Ref. 25, Ref. 32, Ref. 40, Ref. 41, Ref. 42). For these aggressive tumors, survival is usually significantly shorter for patients who underwent partial resections at first presentation (Ref. 2, Ref. 42). Thus, adjuvant treatment is justified. Medical therapy is ineffective in meningioma in general.

For meningiomas that recur after surgery and radiotherapy, several experimental therapies have been assessed in small case-series, including hydroxurea (Ref. 43, Ref. 44) or temozolomide (Ref. 45) chemotherapy, interferon alpha (Ref. 46), or anti-progestational drug (Ref. 47, Ref. 48), with limited success. Early attempts with traditional chemotherapy agents, such as cyclophosphamide, adriamycin and vincristine (CAV) have been disappointing (Ref. 49). The results from a large multicenter, placebo-controlled randomised Phase III trial (SWOG 9005) of

mifepristone could not confirm the preliminary favourable results suggested by previous studies (Ref. 50) and it is thus doubtful that this agent will have any major impact in the treatment of this tumor. Some authors offer concurrent chemotherapy with radiotherapy (Ref. 51). For non-benign meningiomas, all patients progressed during chemotherapy (Ref. 44). Notwithstanding the absence of notable antitumoral activity for meningioma recurrences, these agents have no ascribed value in the adjuvant setting.

Although meningioma is traditionally regarded as being radio resistant, radiation therapy is an effective adjuvant treatment for benign meningiomas and is thus the only accepted form of adjuvant therapy (Ref. 52). The role of radiotherapy is currently evolving. It is usually administered after incomplete resection, after recurrence and when tumor histology reveals atypia or malignancy. For meningioma, numerous retrospective studies have reported a beneficial effect of adjuvant radiation on recurrence free- and overall survival rates, especially after subtotal resection (Ref. 53, Ref. 54, Ref. 55, Ref. 56, Ref. 57). However, none of these studies were randomised, controlled nor prospective. As a result, substantial controversies have arisen concerning the use of immediate post-operative radiotherapy for meningioma in the neuro-oncology community. An ongoing prospective phase III trial has recently been launched (EORTC 26021-22021) that assesses the value of post-operative radiotherapy after non-radical surgery for benign meningioma. This study is currently recruiting and will evaluate both tumor recurrence and quality of life (QoL).

For non-benign histology, the same controversy exists. There are no published prospective trials and the published data consists exclusively in retrospective studies. A small retrospective study demonstrated that when radiation therapy is administered for recurrent lesions, adjuvant radiotherapy (after re-excision) significantly improves the 2-year (50% *vs.* 89%; p=0.002) but not the 5-year disease-free survival (Ref. 25). The use of this modality may obviate the need for further surgical procedures in non-benign meningiomas and may offer a beneficial treatment option for patients with a high risk of tumor recurrence (i.e. non-benign histology). The outcome of patients treated with radiation therapy is however not optimal. Milosevic *et al.* reported on 59 atypical and malignant meningioma patients treated with radiotherapy at presentation or recurrence (Ref. 32). Five-year overall survival was 28%. In this cohort, only 10% of the deaths were unrelated to the disease. Other series resection from the two major US cancer centres, the University of California, San Francisco and the MD Anderson Cancer Centre including both atypical and malignant meningiomas treated with radiation after subtotal resection confirm these results with an estimated 5-year survival of 58% (Ref. 41) and 40% (Ref. 42), respectively.

Given the need of more effective therapies for this patient population, it is of very important to optimize the only adjuvant treatment available.

One therapeutic strategy would be to administer a higher dose to the tumor, building on a dose response relationship observed by several authors. A single high dose of radio surgery (SRS), with median maximum dose of 30.1 ± 6.1 Gy, was administered to 30 patients (atypical, 18 patients; malignant 12 patients) in the Pittsburgh series (Ref. 21). An encouraging clinical outcome was reported for atypical and malignant meningioma alike. The 5-year progression-free survival was 83 ± 7% and 72 ± 10% (p=0.018) for atypical and malignant meningiomas, respectively. Likewise, Stafford *et al.* reported on 21 atypical or malignant meningioma patients treated with SRS at the Mayo clinic (Ref. 58). The administered median maximal dose was 32 Gy (range, 20 - 60), depending on the tumor volume. The observed 5-year local tumor control were 68% for atypical and 0% for malignant, respectively (p <0.0001). Importantly, a tumor margin dose > 16 Gy was associated with a significantly increased local control on univariate analysis. Retrospective external beam radiotherapy studies suggested that higher doses of external radiotherapy may increase the local tumor control and survival in both WHO grade 2 and grade 3 (Ref. 30, Ref. 31, Ref. 32, Ref. 41) (Table 1). Goldsmith *et al.* reported on 23 WHO grade 2 and 3 patients (treated with radiation therapy (median dose, 54 Gy) as adjuvant to subtotal resection (Ref. 41). The median follow-up was 40 months. The 5-year progression-free survival was significantly increased when a higher dose was administered (67% *vs.* 17%, p=0.01). Likewise, Milosevic *et al.* reported on 59

WHO grade 2 and 3 patients (median age, 58 years) irradiated (median, 50 Gy) immediately after diagnosis and after at least 1 recurrence in 24 and 35 patients, respectively (Ref. 32). After a median follow-up of 40 months (range, 7 - 114), a higher radiation dose (> 50 Gy) was independently associated with an increased 5-year cause-specific survival by multivariate analysis (42% *vs.* 0%, $p<0.01$). An improved survival was also reported by Coke *et al.* in 17 patients (grade WHO 2, 9 patients; grade WHO 3, 8 patients), the majority of the patients (n=15) was treated with postoperative radiotherapy (median dose, 61 Gy) (Ref. 30). The median follow-up was 87 months. Three out of 5 patients treated with less than 54 Gy to the tumor died of recurrent disease, whereas only 1 of the 12 patients treated with higher dose died of disease. Hug *et al.* reported on 31 (grade WHO 2, 15; grade WHO 3, 16) patients treated with high dose photon/proton therapy (Ref. 31). Mean doses for atypical and malignant meningioma were 62 Gy (range, 50 - 68) and 58 Gy (range, 40 - 72) Gy, respectively. The average follow-up was 59 months (range, 7 – 155). They report significantly increased local control with radiation doses ≥ 60 Gy for grade WHO 2 as well as for grade 3 meningiomas. For atypical meningioma, the 5-year local tumor control with radiation dose <60 and ≥ 60 Gy was 0% and 90% ($p=0.025$), respectively. For malignant meningiomas, the corresponding values were 0% and 100% ($p=0.006$), respectively. Interestingly, the University of Florida data could not confirm this dose-response relationship (Ref. 59).

In summary, limited retrospective data suggest superior local tumor control for non-benign meningiomas treated with higher dose of radiation therapy. One should remember that all these series are retrospective and involve only a small number of patients. Moreover, these publications are plagued by patients (age, performance status) and treatment heterogeneity (surgery, dose policy, treatment indications). The outcome assessments vary widely and no clear definition of non-benign histology is defined in these series (see Histological classification of meningioma, chapter 1.1). In consequence, caution is needed in drawing any definite conclusions on a potential radiation dose response relationship and a subsequent benefit for patients with atypical or malignant meningiomas. Notwithstanding this possible dose response relationship, administering a higher dose to these locally aggressive tumors may translate into a better local control. No prospective dose-escalation studies for meningioma have been published.

Retrospective studies have shown that high dose proton beam radiation therapy (with or without photons) for meningioma is safe providing dose constraints are strictly implemented and respected. Weber *et al.* reported on 16 meningioma (2 patients with grade WHO 2 meningioma) patients treated with spot-scanning proton beam therapy (Ref. 60). The median prescribed dose was 56 CGE (range, 52.2 – 64) and the median follow-up was 34.1 months (range, 6.5 – 67.8). The 3-year toxicity-free survival was 76.2%. Three patients presented with a radiation-induced optic neuropathy (SOMA grade 3, 1 patient), retinopathy (SOMA grade 2, 1 patient) and brain necrosis (CTCAE grade 3, 1 patient), respectively. For the 2 former patients, the maximum doses to the optic nerve and retina were 66.8 and 55.9 CGE, respectively. The ophthalmologic late toxicity was reversible. Likewise, Wenkel *et al.* reported on 46 meningioma patients treated with combined photon and proton beam therapy (median dose, 59 CGE; range, 53.1 – 74.1) (Ref. 61). After a median follow-up of 53 months (range, 12 – 207), the 10-year survival rate without severe toxicity was 80%. Four patients developed severe ophthalmologic and neurological toxicity, respectively. All patients with ophthalmologic toxicity received doses higher than those allowed for the optic nerve structure in the modified protocol (≤ 54 CGE). Finally, Noël *et al.* reported on 51 meningioma patients treated with combined photon and proton beam therapy (median dose, 60.6 CGE; range, 54 – 64) (Ref. 62). Two patients presented with SOMA grade 3 complications: 1 patient presented a pan-pituitary insufficiency (median dose to the pituitary gland, 60.6 CGE) and another experienced severe hearing loss, requiring a hearing aid apparatus (maximal dose to the inner ear, 59.4 CGE). In all 3 series, patients treated with high dose conformal irradiation (proton or combined photon and proton beam therapy), with administered OAR-doses within the dose-constraints limits defined by the various protocols, did not present any severe toxicity.

The need for conformal treatment when administering high-dose radiation to these patients cannot be over emphasized. Using 2D photon therapy ('conformal' techniques used in less than 30% of patients), a median dose of 61 Gy administered to grade WHO 2 and 3 patients resulted in substantial post-treatment toxicity (Ref. 30). CT simulation was only done in a minority of patients. It is axiomatic that the treatment induced toxicity is closely related to the delivered dose, the volume irradiated and the percentage of patients with tumors in close vicinity to OARs. Applying a single high-dose with radio surgery (median, 29 Gy; range, 10 – 50) resulted in substantial radiation induced toxicity (47%) in a cohort of patients presenting with mainly skull-base tumors (falx tumor site, 2/17 patients) (Ref. 63). If the target volume is appropriately defined by the implementation of pre-defined margins and the OARs dose-constraints diligently respected, the delivery of high dose radiation with highly conformal radiation techniques should be safe.

All the above mentioned meningioma studies with a substantial follow-up have shown that delivering approximately 60 Gy is feasible (Ref. 60, Ref. 61, Ref. 62). Administering 70 Gy to target volumes in the brain did not result in increased acute toxicity in prospective randomised trials. Brain tumor dose-escalation studies using 2D radiation planning and delivery demonstrated that administering high dose to the target is feasible with an acceptable acute and late toxicity profile in glioblastoma (GBM) patients.

The definitive results of the RTOG 83-02 phase I/II randomised study of hyperfractionated and accelerated hyperfractionated radiotherapy with carmustine chemotherapy showed an acceptable acute toxicity rate. The actuarial 5-year severe toxicity rate (grade RTOG 3-4) of 3% in the lowest total dose arms (48 and 54.4 Gy), 4% in the intermediate dose arms (64.8 and 72 Gy) and 5% in the highest dose arms (76.8 and 81.6 Gy) (Ref. 64) did not differ significantly (p=0.54). No grade 5 radiation-induced toxicity was observed in the hyperfractionation arms. Forty percent of patients only had a tumor of less than 5 cm by central review, suggesting that administering a high dose to a substantial volume is feasible with hyperfractionation. Another study (RTOG 94-11) assessing the toxicity of high dose delivery (hyperfractionated radiotherapy) with concurrent chemotherapy (64 and 70.4 Gy delivered as a function of tumor volume) reported an absolute severe toxicity rate of less than 2% in 108 GBM patients (Ref. 65). The reported acute toxicity was again acceptable. More recent studies have shown that the administration of very high-dose 3D CRT (up to 90 Gy) results in an acceptable acute toxicity rate (Ref. 66, Ref. 67). The greatest caution is needed when comparing various dose levels with late complication rates for GBM patients treated with high-dose irradiation. Most of these GBM patients will not live long enough to develop any radiation-induced morbidity. Moreover, hyperfractionated regimen do not result, when compared to conventional fractionated treatment, in the same toxicity profile, with the former scheme theoretically separating early and late effects, although this late OAR-sparing effect is questionable (Ref. 68, Ref. 69, Ref. 70). Overall, the administration of 70 Gy with highly conformal radiotherapy should be feasible and should not generate unacceptable radiation-induced toxicity.

Table 1. Outcome of grade WHO 2 and 3 patients following external beam radiotherapy to either low or high target dose.

Authors (Ref)	Number of patients	Radiation dose	Outcome	P value
Goldsmith (Ref. 41)	23	< 53 Gy	5-year PFS 17%	0.01
	(grade WHO 2 &3)	≥ 53 Gy	5-year PFS 67%	
Milosevic (Ref. 32)	59	< 50 Gy	5-year CSS 0%	<0.01
	(grade WHO 2 &3)	≥ 50 Gy	5-year CSS 42%	
Coke (Ref. 30)	17	< 54 Gy	3/5 death	-
	(grade WHO 2 &3)	≥ 54 Gy	1/12 death	
Hug (Ref. 31)	15	< 60 Gy	5-year LC 0%	0.025
	(grade WHO 2)	≥ 60 Gy	5-year LC 90%	
Hug (Ref. 31)	16	< 60 Gy	5-year LC 0%	0.006
	(grade WHO 2)	≥ 60 Gy	5-year LC 100%	

PFS: Progression-Free Survival; CSS: Cause-Specific Survival; LC: Local Control

Application of radiotherapy to meningioma patients has evolved in the past decade with the development of radiological imagery and conformal (particularly stereotactic) methods for the planning and delivery of therapy. Tumor delineation during CT-assisted planning can be difficult as a result of its poor-soft tissue contrast. Additionally, X-rays from CT are preferentially absorbed by thick layers of bone such as those found in skull-base location, causing imaging artefacts which impair the ability to clearly delineate target volumes in this location (Ref. 71). MRI provides superior soft-tissue resolution and visualization of tumor invasion in surrounding soft tissues. In addition, MRI provides 3D reconstructed images in non axial planes (sagittal and coronal), thus allowing optimised representation of the tumor volume. On the other hand, CT enables the visualization of tumor invasion of the bone and provides the electron density information necessary for heterogeneity correction of the dosimetry computation. As a result, the fusion of CT and MRI scans contains complementary informations and could thus optimise tumor definition.

Several studies have shown that CT-MRI co-registration during radiotherapy planning induced substantial tumor volume variations, when compared to CT-based only tumor delineation (Ref. 72, Ref. 73). Improved imagery (MRI and CT) have possibly influenced the better outcome observed after RT in benign meningioma, as reported by Goldsmith *et al* (Ref. 41). For this study, the routine registration of the diagnostic and/or post-operative MRI in the radiotherapy planning system will be strongly recommended in order to accurately localise and target the tumor.

Traditionally, two-dimensional (2D) radiation therapy was planned after reporting manually the target volume on orthogonal radiographs. Dosimetric calculations were made on the isocenter-axial slices of the different fields giving thus the dose deposition on a ‘tumor’ surface and not a volume. Limitations associated with 2D panning thus consist among many others, of lack of realistic appreciation of tumor- and organ at risk (OAR)-volumes, failure to compute the dose throughout the volumes of interest and restriction of treatment to coplanar beams only. These 2D planning and delivery techniques have be administered to atypical and malignant meningioma patients accrued in all the retrospective series mentioned above (Table 1). On the contrary, 3D conformal radiotherapy (3D CRT) involves the delivery of radiation to a defined 3D target volume as opposed to target area with 2D planning. The use of imagery tools, such as CT or MRI, and advanced treatment planning software have enabled improved tumor definition enabling the physician to conform or shape the radiation volume more precisely around the target while minimizing the dose to the adjacent OARs. As a result, 3D CRT may result in substantial reductions in acute and late radiation-induced toxicity. It has also allowed for safe escalation of radiation dose with resulting improved local

tumor control compared to conventional radiotherapy for some tumor types. Narayan *et al.* reported on 11 patients with optic nerve sheet meningioma treated with 3D CRT (Ref. 74). The 50% isodose line usually spared the major OARs in direct vicinity of the tumor (lens, cavenous sinus and pituitary gland). After a median follow-up of 51.3 months, late toxicity was rare and the visual outcome excellent. Sophistication of the delivery techniques has been achieved with stereotactic radiation therapy (SRT). SRT was developed using the precision of radio surgery but exploiting fully the radio biologic advantage of fractionation. Several retrospective studies have shown that SRT is safe and effective for this tumor type (Ref. 75, Ref. 76). Likewise, intensity modulated radiotherapy (IMRT) is an advanced form of 3D CRT that can be delivered to meningioma (Ref. 77, Ref. 78). Pirzkall *et al.* reported on 20 skull base patients treated with IMRT to a median dose of 55.8 – 58.2 Gy (Ref. 77). After a median follow-up of 36 months, the majority of patients (60%) with pre-existing neurological symptoms improved. There was no radiation-induced peri-tumoral oedema or new onset of neurological deficits. All these modern radiation delivery techniques (3D CRT, SRT and IMRT) are roughly equally conformal for the treatment of brain tumors. Chan *et al.* reported on a dose comparative study of 5 GBM patients (Ref. 79). The treatment of these patients was planned with 3D CRT and IMRT. With both the 3D CRT and IMRT plans, the planned dose (60 Gy) was delivered with doses to the OARs below the tolerance threshold. As such, these different modes of radiation delivery will have no impact on the endpoints of this study. Thus, with modern image-based conformal radiation techniques, including SRT and IMRT, the delivery of high dose radiation is safe and efficacious.

In view of the overall quality of the data in the literature, it was decided to perform a new prospective study assessing the efficacy and toxicity of high dose radiotherapy, using 3D CRT, SRT or IMRT, for grade 2 and 3 meningiomas. This will be the first phase II study addressing this question.

1.4 Prognostic factors for non-benign meningioma

1.4.1 Atypical vs. malignant meningioma

Because of the rarity of this disease, recognized prognostic factors are not available for grade WHO 2 and 3 meningiomas. It is usually admitted that the WHO histological grade (3 *vs.* 2) is associated with an adverse outcome. Palma *et al.* reported on the long-term prognosis of 71 atypical and malignant meningioma patients treated with surgery only (Ref. 2). The two groups were compared with respect to overall- and recurrence-free survival and median time to recurrence. The 10-year overall survival was significantly better for patients with atypical (79%) when compared to malignant (34.5%) tumors. Similarly, the recurrence-free survival and median time to recurrence (5 *vs.* 2 years) were significantly longer in patients with atypical than with malignant meningiomas. In the two published non-benign meningioma SRS series, a significantly improved clinical outcome was observed for atypical compared to malignant meningiomas (Ref. 21, Ref. 58). In the Princess Margaret Hospital series, a trend for an improved 5-year cancer-specific survival (CSS) was observed for atypical histology when compared to malignant histology (51% *vs.* 27%, univariate analysis p=0.09) (Ref. 32). The difference whas however not significant in multivariate analysis. Hug *et al.* however reported an identical 8-year local tumor control rate (19% *vs.* 17%) for grade WHO 2 and 3 tumors. Likewise, Coke *et al.* did not observe a detrimental effect of histological malignancy on survival. Ten-year overall survival was 58% and 60% for grade WHO 2 and 3 meningioma, respectively (Ref. 30). These conflicting results illustrate how heterogeneous these retrospective studies likely are with respect to tumor histology. No clear definitions of the grading or of the resection completeness are clearly given in these series.

1.4.2 Extent of resection

Similarly to benign meningiomas, sub-total resection of malignant meningioma is associated with a significantly increased recurrence rate compared to total resection (Ref. 26). In the Baylor College series, the risk ratio for recurrence was 2.71 (p=0.014) when Simpson 1-3 were compared to Simpson 4 or more tumors (Ref. 25). Likewise, in the Goyal *et al.* series (Ref. 24) the 10-year overall survival was higher in patients with atypical tumors who underwent gross total resection (87%) than in those who did not have total excision (75%). Although this difference was not statistically significant for survival, it was for local control (87% vs. 17%, p=0.02). Similarly, Palma *et al.* observed that a Simpson Grade 1 resection for atypical or anaplastic leads to improved survival times (Ref. 2). Once recurrence develops, prognosis is poor as a result of the high likelihood of treatment failure (Ref. 25, Ref. 31).

1.4.3 Age

It has been shown that age less than 58 years was a significant predictor of 5-year CSS on multivariate analysis for both atypical and malignant meningioma (Ref. 32). This prognostic factor has not been assessed by other authors (Ref. 2, Ref. 24, Ref. 25, Ref. 30, Ref. 59).

1.4.4 Gender

It was suggested that male gender is associated with an increased risk of tumor recurrence in meningioma, possibly as a result of the association of male gender with high-grade (atypical/brain invasive) tumors (Ref. 16). For non-benign histology, gender was not significantly prognostic for survival and local control (Ref. 24). This factor has not been assessed by other authors (Ref. 2, Ref. 25, Ref. 30, Ref. 32, Ref. 59).

1.4.5 Pathology

Molecular prognostic markers have been described in benign and non-benign meningiomas. Perry *et al.* reported on 117 archival meningioma samples (benign, 42 cases; atypical, 52 and anaplastic, 23 cases) and determined the CDKNA (p16) deletion status (Ref. 80). This inactivation of the cell-cycle regulator, located on chromosome 9, has been observed in some atypical and the majority of anaplastic meningiomas. The CDKNA deletion was significantly associated with a shorter survival in the anaplastic meningioma cohort, with a risk ratio for death of 6.79. Conversely, the absence of this deletion identified a subset of anaplastic meningioma patients with a prolonged survival. It has been shown that a high MIB-1 labeling index may be associated with a poor prognosis. The same group evaluated primary GTR meningiomas from 425 patients with DNA flow cytometry, immunostaining for MIB-1, and determination of p53 protein expression (Ref. 81). Although p53 status was not associated with clinical outcome, an elevated MIB-1 labeling index of $\geq$4.2%, identified in 8% of cases, was strongly associated with decreased relapse-free survival in univariate analysis (p=0.0001). Caution should be taken when using the MIB-1 labeling index since substantial overlap exists for benign, atypical and anaplastic meningiomas (Ref. 82). Some series did not find a correlation between MIB-1 labeling indexes and clinical outcome (Ref. 83, Ref. 84).

Chromosomal and genetic aberrations differ with meningioma subtypes. Allelic loss at chromosome 22q is found roughly in 50% of WHO grade 1 meningiomas (Ref. 85). Allelic loss at additional chromosomal loci is associated with atypia and anaplasia in meningiomas. Lee *et al.* reported on 43 benign and non-benign meningiomas. The mean number of alleles with loss of heterozygocity (LOH) was 1.5 +/- 1.2 for benign meningiomas, 6.7 +/- 2.7 for atypical meningiomas, and 8.3 +/- 2.3 for anaplastic meningiomas ($p < 0.001$) (Ref. 86). Likewise, the Pitié-Salpétrière group reported on 51 benign and non-benign meningiomas. LOHs on chromosomes 1p, 9p, 10q, 14q, and 22q, a deletion of CDKN2A, and telomerase activity was assessed (Ref. 87). LOH on chromosomes 22q, 1p, and 10q, as well as telomerase activity were significantly related to the WHO histological

grades of the lesions. Moreover, the LOH on chromosome 1p, 9p, or 10q; and telomerase activity, as well as histological and Simpson grade; were significantly correlated with a shorter PFS time. It thus seems that genetic changes are associated with meningioma progression (Ref. 88) but these genetic abnormalities have not been studied on prospective-collected pathology material. The EORTC planned study for benign meningiomas (26021/22021) and this study (atypical and malignant meningiomas) gives a unique opportunity to undertake a number of translational research projects on prospectively collected tumoral tissues (paraffin block and frozen material).

In summary, it is unclear if the clinical outcome of patients with grade WHO 3 tumors is significantly worse than that of grade WHO 2 meningiomas. Clinical characteristics (age, gender) do not seem to have a major impact on outcome for non-benign meningioma patients. The absence of total gross resection (Simpson 1-3) apparently negates the overall prognosis of grade 2 and 3 meningioma patients, alike. Because of the possible influence of the extent of resection on the clinical outcome, it was decided to stratify for resection and administer a higher dose to patients with subtotal resection. Atypical (grade WHO 2) tumors will be eligible for this study. Malignant meningioma is a rare disease, accounting only for 1-2% of all meningiomas. It is thus questionable if a prospective phase II study could be carried out with a sufficient number of eligible patients. Despite the unknown significance of a WHO grade 3 in meningiomas, it is of importance to prospectively assess the outcome of these rare tumors. As such, malignant (grade WHO 3) will be registered in the present study, with no dose escalation (i.e. 60 Gy to the tumor bed).

1.5 Target volumes

The definition of target volumes is essentially based on the ICRU 50/62 recommendations (Ref. 89). Target definition with respect to meningioma margins has not been prospectively addressed in the literature. Although the atypical (grade WHO 2) meningiomas do not infiltrate normal brain, adjacent bone structures and dura can be involved. Not infrequently, perivascular extension along the Virchow-Robin spaces happens. Therefore both CT and MRI are mandatory diagnostic techniques to delineate visible tumor and form the starting point for target volume definition (Ref. 71) (see Rational of adjuvant radiotherapy, chapter 1.3). Substantial differences and uncertainties exist, however, in a consistent delineation of macroscopic disease between both techniques. Khoo et al. reported on 7 skull base meningioma patients imaged with CT and MRI. In this series, MRI appeared to define target volumes that were larger but not inclusive of those defined by CT (Ref. 90). For the delineation of the gross tumor volume (GTV) for treatment planning it is therefore necessary to pragmatically define the tumor extension with maximum information by using both techniques. The high dose delivery in this study requires an optimal precision of treatment delivery, which demands in turn a greater accuracy of tumor delineation to avoid marginal target misses.

Although no reliable data exist, when applying fractionated irradiation, most radiation oncologists consider that sub clinical disease (i.e. Clinical Target Volume, CTV) need to be anticipated approximately 1 cm beyond dural thickening. This is not the case in normal brain and bony structures unless frank brain or bone invasion is documented. In order to limit the radiation induced toxicity after high dose radiotherapy for macroscopic disease (see Toxicity, chapter 1.6), it is necessary to tighten the margins around the GTV. CTV will be defined by adding 1 cm (CTV1) and 0.5 cm (CTV2) during the first part of the irradiation and cone-down, respectively. Various studies have shown undisputedly that rigid face masks or stereotactic relocable frames offer a high level of geometric accuracy.

Kortmann et al. reported on a quantitative assessment of the accuracy of field alignments in 95 patients presenting with difficult positioning (Ref. 91). In this series, conventional radiotherapy (2D) was administered. The observed precision (standard deviation) was 2.5 mm, with patient immobilization using a thermoplastic face mask. The same group reported on the geometric accuracy of SRT in 20 brain tumors patients (Ref. 92). SRT was administered with a stereotactic

target positioning device. Ninety-five % of all absolute deviations were between less than 4.6 mm. The Royal Marsden group have shown that a precision of 1 mm could be achieved using a Gill-Thomas-Cosman frame (Ref. 93). As such, a 5 and 3 mm setup precision will be assumed for 3D CRT and SRT, respectively. These margins can however be tightened, depending on departments' policy to define the institutional safety margin with respect to their radiation therapy techniques.

1.6 Toxicity

1.6.1 Radiation-induced toxicity with conventional dose fractionated radiotherapy

Radiation-induced toxicity after radiotherapy is infrequent and range between 2% (Ref. 94) and 30% (Ref. 63). Radio surgery probably induced more treatment related morbidity (Ref. 95) when compared to fractionated radiotherapy (Ref. 75, Ref. 76). In two large series of patients with benign meningiomas, significant long-term toxicity was reported in 2% (Ref. 94) and 4% (Ref. 41), respectively. The dose to the tumor dose ranged from 50 to 55 Gy in the first study (Ref. 94), in which 50% of the tumor were in the more favourable para-sagittal or cortical location, and the median target dose was 54 Gy in the second study (Ref. 41). These data indicates that radiation-induced morbidity is unusual but possible even with 'standard' dose radiotherapy.

1.6.2 Radiation-induced toxicity with high-dose fractionated radiotherapy

Among other factors, such as tumor location and irradiated volume, the complication rate is closely related to the administered dose. As mentioned earlier (see Rational of adjuvant radiotherapy, chapter 1.3), patients with non-benign meningiomas have been treated at a higher dose. Only one of these these series reported unusual treatment-related toxicity (Ref. 2, Ref. 24, Ref. 25, Ref. 30, Ref. 31, Ref. 32). Katz et al. reported on 36 patients (atypical, 27 patients; malignant 9 patients) treated with an aggressive radiotherapy schedule consisting of 60 Gy (at 1.5 Gy per fraction twice daily), with or without a radio surgery boost (median dose, 12.5 Gy) (Ref. 59). This radiation regimen was chosen because it appeared well tolerated in GBM (Ref. 96). A shrinking field technique was used in most cases. One third of the patients developed a severe complication: 6 patients presented with a grade NCI-RTOG 3 and 4, respectively. No grade 5 complication (i.e. death attributed to treatment) was observed. The majority (10/11) of these patients presented clinically with persistent radio-necrosis (median time of steroids administration, 1 year). The complication rate for those treated with accelerated hyperfractionated radiotherapy was significantly higher (grade 3, 0% vs. 55%; grade 4, 0% vs. 27% for non- and accelerated hyperfractionated radiotherapy, respectively). It is likely that the radiation-induced toxicity could not be optimally assessed in these retrospective series, excluding the University of Florida data (Ref. 59). As a result, all high-dose radiotherapy published data focus on tumor control and complication rates are scarce. Identically, the Boston group reported a high complication rate after combined photon and proton radiotherapy (median dose, 59 Gy; range, 53.1 – 74.1) for benign meningiomas in their prospective series (Ref. 61). The 10-year survival without significant grade 3-4 morbidity was 80%. As a result of the observed toxicity, the optic structures-dose constraints were substantially modified (from $\leq$ 62 Gy to 54 Gy) during accruing period.

All these data undisputedly show that great care should be advised in delivering high-dose radiotherapy to those patients. Strict dose constraints (see Normal tissue sparing, chapter 5.1.7) should be implemented and the target volume should be precisely defined (see Target volume definitions, chapter 5.1.2) in order to avoid significant radiation-induced toxicities.

1.6.3 Radiation-induced secondary tumors

Induction of neoplasms by fractionated radiotherapy for various primary diseases, like meningioma, pituitary adenoma, craniopharyngeoma, medulloblastoma, leukaemia and tinea capitis has been noted both after low and high irradiation doses. Various types of secondary tumors have been reported, such as astrocytoma, GBM, gliosarcoma, ependymoma, meningioma and outside the cranium leukaemia, lymphoma, thyroid carcinoma, peripheral fibrosarcoma. These consequences are infrequent but possible. The overall risk for radiation-induced cancers has been estimated around 2-10% for all adults treated with radiotherapy (Ref. 97).

The consensus criteria for identifying radiation induced cancers are: 1) the tumor must appear in the irradiated area, 2) the tumor was not present prior to irradiation, 3) a proper number of years latency must have elapsed between irradiation and the appearance of the tumor (usually five years or more (Ref. 98)), 4) the radiation-induced tumor must be histologically proven and must distinctly differ from the original histology, 5) there must be no concerns to a genetic multiple predisposition syndrome (Ref. 99).

1.7 Conclusions

The overall policy in the treatment of non-benign meningiomas is controversial. It usually includes aggressive surgical resection of the tumor and of its dural attachments. If complete resection of the tumor is not possible or if it is deemed to be associated with an unacceptable morbidity, surgery should be more reserved. Post-operative radiation might reduce the local tumor recurrence rate for these aggressive tumors. A dose-response relationship has been suggested by several retrospective studies although this issue is controversial. Considering the lack of prospective data and the controversy around the dose escalation issue for this tumor entity, it was decided to perform the present prospective phase II study. There is no prospective study addressing the potential local control benefit of adjuvant high-dose radiotherapy for non-benign meningiomas weighted against the potential radiation induced toxicity. Atypical (grade WHO 2) patients will be accrued in this study. A separate observation study will be initiated for malignant (grade WHO 3) meningiomas, as this tumor type is rare (see Prognostic factors in meningiomas, section 4.1.5). No dose-escalation policy is planned for malignant meningiomas.

2 Objectives of the trial

2.1 General objectives

The objectives of this study are to assess the impact of high-dose radiotherapy (RT) on progression-free survival (PFS), treatment tolerance, and post-treatment global cognitive functioning in patients with a diagnosis of either atypical (grade WHO II) or malignant (grade WHO III) meningioma.

The atypical meningioma patients will be entered in one of two strata of a non-randomized phase II study, depending on the Simpson’s stage achieved by surgery. The malignant meningioma patients will be registered in a separate stratum. For the latter group, no strict statistical design is planned due to the expected small patient number.

This study is the first one assessing the value of post-operative high-dose radiotherapy in grade II and grade III meningioma patients and the results will serve as a basis for designing future studies in this disease. If the patient accrual rate is high enough and if dose escalation to 60 or 70 Gy demonstrates sufficient activity with acceptable toxicity, a phase III trial might be considered in the future.

2.2 End-points

The primary trial endpoint is progression-free survival where progression is defined on the basis of tumor growth or appearance of new lesions (see chapter 7 for exact definition).

The secondary trial endpoints are acute and late effects classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 3.0 (NCI CTCAE v3.0), mini-mental status (MMSE) and overall survival.

Quality of life is not an endpoint in this study since the trial is not randomized and is of relatively small size.

3 Patient selection criteria

Patients will be registered between surgery and the start of radiotherapy without exceeding 6 weeks time interval.

- **Histologically proven newly diagnosed atypical grade WHO grade II** meningioma ($\geq$ 4 mitosis per high-power field [HPF] or the presence of at least 3 of the latter 4 variables: cellularity, architectural sheeting (i.e. patternless pattern), macronuclei and small cell formation) (see section 3.2 below for definition)

OR

- **Histologically proven newly diagnosed malignant WHO grade-III meningioma** (see section 3.2 below for definition)

(as assessed by the local pathologist)

AND all of:

- Complete or subtotal resection as assessed by the surgeon after verification with a postoperative MRI and according to Simpson guidelines (see section 3.4 below for definition). The patients will be stratified according to the resection status: complete excision (Simpson's stages 1-3) versus incomplete excision (Simpson's stages 4-5)
- Age between 18 years and 70 years
- WHO performance status 0-2
- All locations except optic nerve sheets tumors
- No neurofibromatosis type II patients (NF-2)
- No previous radiotherapy to the brain or meninges interfering with the protocol treatment plan
- No clinical evidence of second malignancies, except a history of cervix carcinoma in situ and basocellular carcinoma
- Women of reproductive potential must use effective contraception for the whole duration of the treatment and must not be pregnant or lactating.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Patients can be registered in this trial only once.

3.1 WHO grading of meningiomas

For assessing eligibility for entry, on study, the specimens will be signed out by the pathologist at the treating institution according to the criteria of the WHO (Ref. 1). These criteria read as follows:

- WHO definition of **atypical meningioma (WHO grade II)**: a meningioma with increased mitotic activity or three or more of the following features: increased cellularity, small cells with high nucleus/cytoplam ration, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of «spontaneous» or «geographic necrosis».
- WHO definition of **anaplastic (malignant) meningioma (WHO grade III):** a meningioma exhibiting histological features of frank malignancy far in excess of the abnormalities present in atypical meningioma.

After entry on study, the diagnostic pathology will be reviewed centrally (see chapter 15.3 – Pathology review).

3.2 Simpson's guidelines for assessing resection level

The resection level will be assessed by the surgeon after verification with a postoperative MRI and will be classified according to Simpson guidelines as

Table 2. Simpson grading

Radical	
Stage 1 :	complete excision, including dura and bone.
Stage 2 :	complete excision + supposed reliable coagulation of dural attachment.
Non-radical	
Stage 3 :	complete excision but insufficient dural coagulation or bone excision (non visible on MR, according to surgeon's opinion).
Stage 4 :	incomplete excision, macroscopic rest visible (on MRI).
Stage 5 :	biopsy only (visible on MRI).

4 Trial Design

For patients with atypical meningioma (grade II) the trial is designed as two parallel non-randomized phase-II trials with progression-free survival rate at 3-years as primary endpoint, in respectively patients with Simpson's stage 1-3 resection and patients with Simpson's stage 4-5 resection.

A separate one-stage Fleming design will be applied each to the two strata of patients. The criteria for success are respectively to demonstrate that the 3-year progression free survival is superior to 70% for patients with Simpson's stage 1-3 and that it is superior to 50% for patients with Simpson's stage 4-5.

With such a design, a total of 25 patients with Simpson stage 1-3 grade II meningiomas and 39 patients with Simpson stage 4-5 meningiomas are needed (total phase II study, 64 patients).

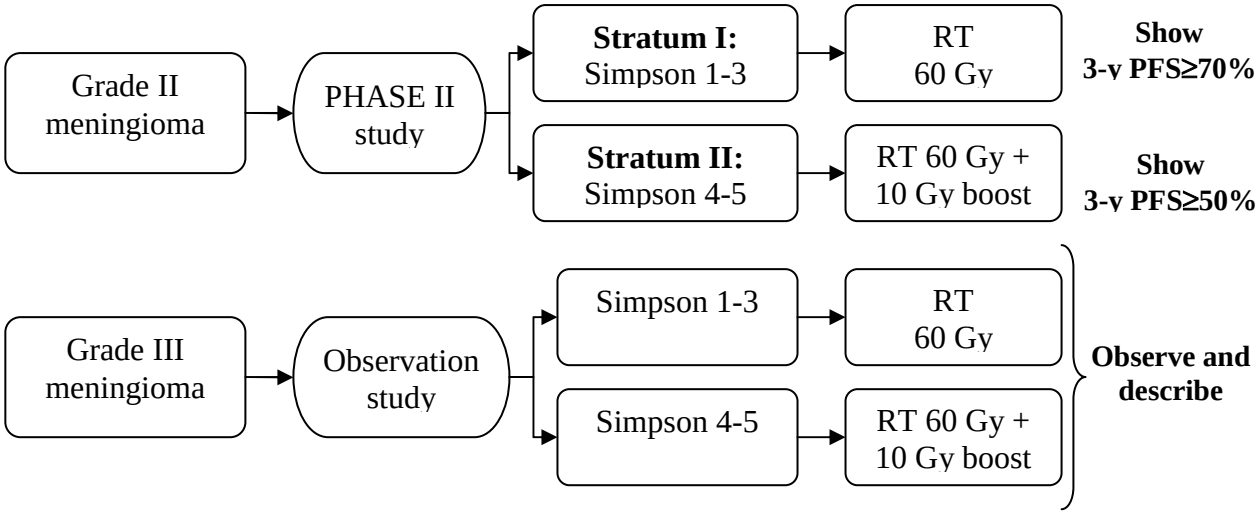
For the grade III meningiomas, given the small numbers expected to enter the trial, the patients will be registered only and treated and then followed-up similarly to the grade II meningiomas (see chapter 6). No specific statistical design, decision rule, or sample size is defined for this small group and only descriptive statistics will be produced.

The trial duration will be driven by the phase II study. It is foreseen than 6-13 grade-III patients will be registered during the accrual period of the phase II.

Patients need to be eligible and to have started treatment. The local pathology will be used for assessing eligibility.

Accrual to the phase II is anticipated to last 3 years.

Trial scheme:



5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Guidelines for Radiotherapy (including 3DCRT, IMRT and SRT)

5.1.1 Equipment

Linear accelerator (Linac) X-ray beams with nominal energy of at least 4 MV and not greater than 20 MV should be used. Three dimensional conformal therapy (3D CRT) is mandatory. Intensity modulated radiotherapy (IMRT) and fractionated stereotactic radiotherapy (with or without IMRT) is permitted in this study.

5.1.2 Definition of target volumes

The Gross Tumor Volume (GTV) is defined as the visible tumor which is the region of enhancement on post-operative brain MRI (T1Gado+) and planning CT-scan (with iodine contrast). If bone is involved, a CT bone window (setting) is strongly advised. Clearly thickened dural trails and hyperostotic bones are as much as appropriately included; enhancing dura without being thickened is not included.

The Clinical Treatment Volume 1 (CTV1) is defined as the GTV and sub clinical microscopic tumor (may include the pre-operative tumor or post-operative tumor bed, peritumoral edema, hyperostotic changes if any, and dural enhancement or thickening as seen in the CT/MRI at diagnosis) plus a 3D 10 mm margin (in all directions but not extending outside the patient) or less (see dose constraints, chapter 5.1.7).

The CTV2 is defined as the GTV and sub clinical microscopic tumor (may include the pre-operative tumor bed, peritumoral edema, hyperostotic changes if any, and dural enhancement or thickening as seen in the CT/MRI at diagnosis) plus a 3D 5 mm margin (but not extending outside the patient) or less (see dose constraints, chapter 5.1.7).

The Planning Treatment Volume 1 (PTV1) is defined as the CTV1 plus a 3D margin depending on the institutional planning values (usually, 5 mm for 3D-CRT/IMRT and 1-5 mm for SRT) to account for day-to day setup variation related to the ability to immobilize the patient and the physiologic motion of the CTV, or less depending on dose constraints (see chapter 5.1.7).

The PTV2 is defined as the CTV2 plus a 3D margin depending on the institutional planning values (usually, 5 mm for 3D-CRT/IMRT and 1-5 mm for SRT) to account for day-to day setup variation related to the ability to immobilize the patient and the physiologic motion of the CTV, or less depending on dose constraints (see chapter 5.1.7).

In patients with no visible tumor (Simpson 1-3), the GTV=CTV should be estimated on the basis of the preoperative imaging demonstrating the meningioma attachment and the information in the surgeon's operative report on tumor attachment and microscopic tumor residue. The centre of the CTV should coincide as accurately as possible with the centre of the dural attachment. The definition of the CTV is at the discretion of the treating radiation oncologist and neurosurgeon.

5.1.3 Treatment planning

Treatment planning CT as well as a post-operative MRI scans are mandatory for (volume-based) 3D treatment plans (3D CRT, IMRT and SRT). Treatment portals will be defined by virtual simulation.

Fusion between the treatment planning CT and the post-operative MRI as obtained shortly before the registration is strongly recommended (see Definition of target volumes, chapter 1.5).

Multi-leaf collimators or secondary collimation with shielding blocks are mandatory in order to ideally conform to the PTV.

Treatment planning should conform to ICRU 50/62 rules for coverage of GTV, CTV and PTV (Ref. 89). Additionally, organs at risk (OAR) should be delineated according to the ICRU 62 rules: brain stem, optic chiasm, both optic nerves, pituitary gland, both eyes and both inner ears (cochleae), whenever appropriate depending on the location of the primary tumor.

5.1.4 Timing of radiotherapy

Treatment with radiotherapy should start within 6 weeks after surgery.

5.1.5 Target dose

Prescription point: Dose prescription for the PTV will be at or near the centre of this volume following recommendations of ICRU 50/62 reports (Ref. 89).

Dose definition: The absorbed dose is specified as Gy.

Tissue heterogeneity: Inhomogeneity correction for bone and soft tissue density variation will be applied.

Prescribed dose and fractionation:

- The prescribed dose for the CTV is 60 Gy in 30 fractions (Simpson's stages 1-3) or 70 Gy in 35 daily fractions (Simpson's stages 4-5) in one course.
- Fraction size is 2Gy

- One fraction given per day, five fractions per week so that overall treatment duration should be 6-7 weeks
- Dose specification and homogeneity requirements in the PTV (–5% +7%) have to be in accordance with the ICRU guidelines.
- Interruptions: Patients requiring an interruption in radiotherapy will not receive additional fractions in order to compensate for potential tumor cell repopulation during the treatment gap. (hyperfractionation is not allowed).

5.1.6 Treatment technique

Techniques which allow shielding of normal tissue are encouraged providing they do not compromise treatment of the intended PTV.

Patient position: The patients may be treated in the most appropriate position as long as an optimal fixation can be obtained.

Thermoplastic face mask for 3D CRT and relocable stereotactic frame for SRT is mandatory.

As a minimum to insure correct, reproducible positioning of the patient, orthogonal (AP and lateral) DRRs and corresponding orthogonal portal images (film or electronic) are required.

Field shaping: Shall be done with blocks or multi-leaf collimators which are at least 5 HVL thick.

5.1.7 Normal tissue sparing

It is important to protect OAR whenever possible. Such shielding must be weighted against the possibility of sub-optimal treatment of the target volume. The recommended upper dose limits for different organs are the following:

1. Optic chiasm, optic nerves and tracts should not receive higher (maximum) doses than 60 Gy at 1.8 - 2 Gy/fraction/day (median dose, 56 Gy).
2. The brainstem should not receive higher (maximum) doses than 64 Gy at the surface of this OAR and 54 Gy centrally 1.8 - 2 Gy/fraction/day.
3. The hypothalamus/pituitary should not receive higher (maximum) doses than 56 Gy at 1.8 - 2 Gy/fraction/day. If clinically indicated based on the position of the PTV, the radiation oncologist has the option to relax the hypothalamus/pituitary's dose constraints.
4. The cochlea should not receive higher (maximum) doses than 50 Gy 1.8 - 2 Gy/fraction/day. If clinically indicated based on the position of the PTV, the radiation oncologist has the option to relax the cochlea's dose constraints.

5.1.8 Dose calculation and reporting

Isodose distributions will be calculated through the target in three planes, transverse, coronal and sagittal planes. Recording of integral doses to GTV, CTV PTV and OAR including dose volume histograms is mandatory.

Portal imaging or portal films, if needed using the double exposure technique, will be used for verification.

5.2 Medical concomitant treatments

5.2.1 Concomitant medications

In the case report forms use of corticosteroids, anti-epileptic drug and anti-emetics will specially be recorded with date of start and end of therapy.

5.2.2 Anti-emetics

Prophylactic anti-emetics will be administered at the discretion of the treating physician.

5.2.3 Corticosteroids

Use of corticosteroids around the time of radiotherapy is left to the discretion of the treating physician according to local protocol/custom.

5.3 Expected acute radiation toxicities

Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals or eyes should be observed and treated symptomatically. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.

5.4 Treatment interruptions/Treatment withdrawal criteria

Treatment will be delivered daily for all radiation fractions except for weekends. Up to three days of treatment interruptions are permitted for any reason. Interruptions of 3 to 5 treatment days will require notification to the Study Chairman and patients will be regarded as eligible for evaluation. Treatment breaks of more than five treatment days will be considered a protocol violation.

Reasons to terminate protocol treatment before normal completion are:

- Evidence of disease progression during treatment
- Unbearable toxicity
- Patient refusal to pursue the treatment

5.5 Treatment in case of tumor progression

After tumor progression, all further therapy is left at the discretion of the treating physician.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Before treatment start

The following evaluations have to be done:

- Local histology certifying meningioma WHO grade II or III. Mitotic index and if possible, MIB-1 index and, in women the progesterone/estrogen receptor status.
- Contrast enhanced pre and post-operative MRI in at least 2 plans. The post-operative MRI brain study should be done within 48 hours of the operation.

- Complete medical history including medications
- Physical examination including the performance scale evaluation (WHO performance scales see Appendix B)
- Mini-Mental Status Examination (MMSE, see Appendix F)

6.2 During the treatment

The patients should be clinical examined weekly during the treatment for:

- Performance status evaluation (WHO-ECOG)
- Concomitant medications
- Acute adverse events scoring according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf) grading system.

6.3 During the follow-up

6.3.1 The first follow-up

The first follow-up will be 6 weeks after the last irradiation and will focus on possible acute irradiation toxicity (see table in chapter 6.4). The following evaluation will be performed:

- Clinical examination, performance status evaluation (WHO-ECOG), interim medical history.
- Concomitant medications
- Mini-Mental Status Examination (MMSE, see Appendix F)
- Acute adverse events scoring according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf) grading system.
- No MRI is requested.

6.3.2 The further follow-up

The next follow-up will be at 6 months after entry on study, then at month 12 and then annually.

Until disease progression, every scheduled follow-up visit includes the following evaluation (see table in chapter 6.4).:

- Clinical examination, performance status evaluation (WHO-ECOG), interim medical history.
- Concomitant medications
- Mini-Mental Status Examination (MMSE, see Appendix F)
- Late adverse events scoring according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf) grading system.
- Contrast enhanced (gadolinium) MRI (T1, T1 Gado, T2) with slice thinkness of 3-5 mm.

After disease progression, the patients will only be followed-up for survival.

6.4 Summary table

	Baseline prior to entry	At 6 weeks after the last day of irradiation	Follow-up at 6 months after entry	Follow-up at month 12 and then yearly
Histological diagnosis	X			
MRI brain study (Gd+)	X	NO	X	⌂
Medical history	X	X	X	⌂
Physical examination	X	X	*	*
Performance Status	X	X	X	⌂
Concomitant medication	X	X	X	⌂
Mini-mental status	X	X	X	⌂
Adverse events scoring (CTCAE v.3.0)	X (acute)	X (acute)	X (late)	⌂ (late)
Survival		X	X	X

X Mandatory

* Recommended

⌂ Until tumor progression

7 Criteria of evaluation

7.1 Tumor progression

The maximum diameters in millimetres will be measured in three perpendicular directions. From this the volume can be calculated by the formula 1/6 x 3,14 x length x width x height.

Attributing to possible inaccuracy of volume measurement is the difficulty to delineate the visible extensions due to the gradual transition of tumor into dural hyperaemia. Only clear dural thickening at the distinction of the investigator is to be considered tumor. Merely after a 25% increase of the calculated 3D-volume a decisive event is registered. This volume increase - or tumor recurrence in post-MRI Stage 3 disease - must at least exceed 0.065 cc (this is the volume of a 5mm-diameter sphere) in order to prevent valuation of subtle and possibly false positive tumor growth, as a consequence of 2-3 mm slice thickness and observer bias.

7.2 Progression-free survival

Progression-free survival will be counted from the date of randomization until the date of the first event of either progression or death due to any cause. Patients alive without progressive disease at the time of data analysis will be censored at the time of the most recent follow-up visit.

7.3 Overall survival

Overall survival is counted from the date of randomization. Patients who die are reported as events, irrespective of the cause of death. Patients without the event of interest are censored at the time of most recent follow-up visit

7.4 Adverse events

Side effects (acute and late) of the treatment will be assessed using the International Common Toxicity Criteria (CTC), version 3.0 scoring system. A copy of the CTC can be accessed from the CTEP home page (http://ctep.info.nih.gov/reporting/ctc.html). A link to this page is provided on the EORTC web site (http://www.eortc.be/;). If the location is moved to another site, this link will be updated. Investigators who do not have any access to Internet can contact the EORTC Data Center to receive a copy by mail.

7.5 Evaluation of neurologic function

Short cognitive screening with the *Mini-Mental State Examination* (Ref. 100) will take place at randomisation and then at every scheduled follow-up visit as indicated in chapter 6. This 30-point test includes questions on orientation to time and place, registration, attention, calculations, recall, language, and visual construction (See Appendix F).

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

For patients with atypical meningioma (grade II) the trial is designed as two parallel non-randomized phase-II trials with progression-free survival rate at 3-years as primary endpoint.

The trial is therefore stratified in two groups: the patients with Simpson's stage 1-3 resection and patients with Simpson's stage 4-5 resection.

A separate one-stage Fleming design (Ref. 101) will be applied each to the two strata of patients with WHO grade II disease. The criteria for success are respectively to demonstrate that the 3-year progression free survival is superior to 70% for patients with Simpson's stage 1-3 and that it is superior to 50% for patients with Simpson's stage 4-5.

With such a design, a total of 25 patients with Simpson stage 1-3 grade II meningiomas and 39 patients with Simpson stage 4-5 meningiomas **eligible and starting treatment** are needed (total phase II study, 64 patients).

For the grade III meningiomas, given the small numbers expected to enter the trial, the patients will only be followed-up similarly to the grade II meningiomas. No specific statistical design, no decision rule and no sample size are defined for this small group. Only descriptive statistics will be produced. The trial duration will be driven by the phase II study. It is foreseen than 6-13 grade-III patients will be registered during the accrual period of the phase II.

Accrual to the phase II is anticipated to last 3 years.

All patients need to be followed for a minimum of 3 years or until death or progression of the disease. Ineligible patients and those who do not start treatment need to be replaced in the sample.

8.1.1.1 Parameters of the design for WHO grade II and Simpson's stage 1-3

For Simpson stage 1-3 grade II meningiomas,

- A 3-year PFS rate of 70% is considered too low (P0 = 70%) to warrant further testing of 60Gy irradiation whereas a 3-year PFS rate of 90% (P1=90%) would be considered enough to warrant further study of the treatment
- The type I error rate (α) is 0.09
- The type II error rate (β) is 0.098
- With this design, there is therefore 9% risk of considering that the irradiation is sufficiently active if the true progression-free survival rate at 3 years is in fact only 70% and there is 9.8% risk of failing to demonstrate it is sufficiently active, if the true progression-free survival rate at 3 years is 90%
- The treatment will be considered active enough if for Simpson stage 1-3 grade II meningiomas the lower bound of the 1-sided 90% confidence interval of the 3-year PFS rate estimated by Kaplan-Meier (using log-log transform) is >70%

8.1.1.2 Parameters of the design for WHO grade II and Simpson's stage 4-5

For Simpson stage 4-5 grade II meningiomas,

- A 3-year PFS rate of 50% is considered too low (P0 = 50%) to warrant further testing of 70Gy irradiation whereas a 3-year PFS rate of 70% (P1=70%) would be considered enough to warrant further study of the treatment
- The type I error rate (α) is 0.10
- The type II error rate (β) is 0.094
- With this design, there is therefore 10% risk of considering that the irradiation is sufficiently active if the true progression-free survival rate at 3 years is in fact only 50% and there is 9.4% risk of failing to demonstrate it is sufficiently active, if the true progression-free survival rate at 3 years is 70%
- The treatment will be considered active enough if for Simpson stage 4-5 grade II meningiomas the lower bound of the 1-sided 90% confidence interval of the 3-year PFS rate estimated by Kaplan-Meier (using log-log transform) is >50%.

8.1.2 Registration and stratification

Patients will be centrally registered but not randomized (for practical details, see chapter on registration procedure).

At registration, the patients will be grouped according to the WHO tumor grade and the resection's Simpson's stage as:

- WHO grade II, Simpson's stage 1-3
- WHO grade II, Simpson's stage 4-5
- WHO grade III, Simpson's stage 1-3
- WHO grade III, Simpson's stage 4-5

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

8.2.1.1 Progression-free survival (primary endpoint)

Progression-free survival will be counted from the date of registration until the date of the first event of either progression or death due to any cause. Patients alive without progressive disease at the time of data analysis will be censored at the time of the most recent follow-up visit.

8.2.1.2 Overall survival (secondary endpoint)

Overall survival is counted from the date of registration. Patients who die are reported as events, irrespective of the cause of death. Patients without the event of interest are censored at the time of most recent follow-up visit.

8.2.1.3 Adverse events (secondary endpoint)

Side effects of the treatment will be assessed using the NCI-CTCAE version 3.0. The analysis will focus on the worst grade of acute adverse events reported by the patients, as well as the worst grade of late adverse events (i.e. reported on follow-up forms to have occurred 3 months or more after the end of irradiation).

8.2.1.4 Mini Mental-State Examination (MMSE, secondary endpoint)

The Mini Mental State Examination (MMSE) is a brief, standardized tool to grade patients' cognitive function. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30.

Since its creation in 1975 by Folstein et al (Ref. 102), the MMSE has been validated and extensively used in both clinical practice and research.

Following Tangalos et al. (Ref. 103) and as previously used by Brown et al (Ref. 104) a decline of more than 3 points in the MMSE score will be considered to represent clinically significant deterioration.

Following Brown et al, the patient's cognitive function will be considered 'impaired' if the MMSE score is 26 or less and 'normal' if it is 27 or more.

The evolution of the MMSE evaluation over time will be interpreted in the light of attrition induced by the fact that patients are assessed only until progression. All MMSE results will thus be conditional on the patients being otherwise free of progression.

8.2.2 Analysis populations

- Intention-to-treat population: all patients entered in the study
- Per protocol population: all patients who are eligible and have started the planned treatment (at least one fraction of irradiation)
- Safety population: all patients who have started the planned treatment (at least one fraction of irradiation)

A patient will be considered to be eligible if he/she did not have any major deviations from the patient entry criteria listed in chapter 3 of the protocol. Eligibility will be assessed by the Study Coordinator based on the review of each patient file.

For eligibility and stratification (WHO II vs WHO III), the histology assessed by the local pathologist will be considered.

8.2.3 Statistical methods

8.2.3.1 Primary analysis population

The primary analysis of the efficacy endpoints (progression-free survival and overall survival) will be performed in the per protocol population.

The primary analysis of the safety endpoints (acute and late adverse events) will be performed in the safety population.

Each analysis will be performed separately in the four groups defined in section 8.1.2, but for the efficacy endpoints and the grade III meningiomas in whom, due to small numbers, the analysis will be carried out in the pooled group of grade III meningiomas, irrespective of Simpson's stage.

8.2.3.2 Analysis methods for activity endpoints

The primary endpoint, progression-free survival rate at 3 years, will be estimated by the Kaplan-Meier technique (Ref. 105). The variance will be estimated by the Greenwood formula (Ref. 106). The one-sided lower 90% confidence interval will be calculated using Log-Log transform to assess the primary protocol conditions for success. The same method will be used for estimating the 2-sided 95% confidence intervals.

The secondary endpoint overall survival will be analyzed by the same methods as the primary endpoint, but the 1-sided 90% confidence interval will not be displayed (the confidence intervals will be 2-sided at 95%).

8.2.3.3 Analysis methods for safety endpoints

The frequency of the worst grade of acute adverse events reported by the patients will be tabulated in each of the four patient groups described in section 8.1.2.

The worst grade of late adverse events (i.e. reported on follow-up forms to have occurred 3 months or more after the end of irradiation) will also be tabulated. The time to the occurrence of any severe late adverse events will be estimated by Kaplan-Meier method, with the time counted from entry on study to the first reported late adverse events grade 3 or 4 and with censoring at the time of last examination of the patients who did not report any such event. The rate of late severe adverse events will be estimated similary by means of cumulative incidence curves (Ref. 107) with 2-sided 95% confidence intervals at specified time points.

No formal statistical tests will be performed.

8.2.3.4 Analysis methods for the Mini mental-state examination (MMSE)

The proportion of patients with 'normal' and 'impaired' MMSE score at baseline and at key time-points of evaluation (eg. Baseline, year 1, year 2 etc..) will be displayed in the four patient groups defined in section 8.1.2.

Similarly to Brown et al. (Ref. 104) the changes in MMSE scores over time will be summarized in the two treatment groups by the proportion of patients with significant increase (>+3 points), stable (-3 points to +3 points) or significant decrease (decrease of >3 points) of the MMSE score at the key time points of evaluation.

8.2.4 Pre-planned sensitivity or exploratory analyses

Sensitivity analyses will be performed according to the central pathology review. The efficacy endpoints will be analyzed in the populations that are defined as in 8.2.2 but considering the eligibility and the allocation to strata in the trial in function of the central pathology review assessment.

8.2.5 Prognostic factor analyses

Due to small patient numbers in each group, no prognostic factor analysis is planned.

8.2.6 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of registration – date of past event + 1) and presented using the median and range. For example, on the registration checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of registration – last administration/diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (UNL) and the degree to which it is above the UNL (for example > 2.5 x UNL, > 5 x UNL, > 10 x UNL). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

No interim analysis is planned in this study.

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment

2. The trial is mature for the analysis of the primary endpoint as defined in the protocol

3. The database has been fully cleaned and frozen for this analysis

9 Data monitoring

A Data and Safety Monitoring Board (DSMB) will monitor the recruitment, the reported adverse events and the data quality at least twice a year. Arising problems will be discussed with the Study Coordinator who will take appropriate measures. Relevant information (including relevant safety data) will be included in the study status reports serving as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating to the study.

10 Translational research

In this phase II study of 64 patients exhibiting atypical (grade WHO II) or malignant (grade WHO III) meningiomas are intended to be included. The effect of high dose irradiation on the disease will be assessed. Every patient entering the study must be asked to accord with the translational research and to sign the translational research informed consent. Participation should be highly stimulated.

10.1 Objective of the translational study

The aim of the translational study is to correlate molecular characteristics of the tumour tissue with the natural history and with response to radiotherapy. To begin with there is the general importance of make inventory of the genetic aberrations and identify the damaged genetic pathways involved in the various tumors. To this aim, for the identification of crude chromosomal changes MLPA chips including probes for 1p, 22q and chromosome 11 will be used. . Secondly, the response to therapy of the various groups defined by their genetic aberrations will recorded and groups will be compared. For aberrations at the expression level array the use of CGH is anticipated.

10.2 Methods

This study is anticipating on tissue arrays, array CGH, RNA expression arrays (and possibly arrays at the protein expression level becoming available in due course of this long-term study) to be used upon availability.

10.3 Material needed

Paraffin-embedded tumor material should be available.

Fresh-frozen tumor samples for RNA and protein extraction are highly desirable.

Also 2 samples of peripheral blood (two 5 ml tubes with EDTA) are required (one before treatment and one after treatment) and must be stored as fresh frozen leucocytes (also immediately frozen EDTA full blood is acceptable).

Fresh-frozen tumor material should not be sent in before specific request by the PI of the translational research project. The appropriate addresses will follow.

E-mail: j.m.kros@erasmusmc.nl

The EORTC rules being in force for central pathology review will apply also for the fresh frozen material.

11 Investigator authorization procedure

Investigators will be authorized to register and randomize patients in this trial only once they have returned the following documents to the EORTC Data Center:

- The updated signed and dated curriculum vitae of the Principal Investigator.
- The (updated) list of normal ranges in the investigator's institution, signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- A commitment statement / study acknowledgment form, stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

  NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the commitment form.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates for all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Data Center. **Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Data Center**.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- The accreditation letter for the laboratory (if available for a center and/or required by national law).

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to randomize patients in the trial once

- all the above mentioned documents are available at the EORTC Data Center.
- all applicable national legal and regulatory requirements are fulfilled.

Patient registration from centers not (yet) included on the authorization list will not be accepted.

12 Patient registration procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure").

A patient can be registered after verification of eligibility directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network. To access the interactive registration/randomization program, the investigator needs a username and a password (that can be interactively requested: http://www.eortc.be/random).

Alternatively registration can be done by telephone to the EORTC Data Center from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday. The phone registration is not available on the official bank holiday of Belgium. A list of these dates will be available on our web site and updated yearly.

This must be done **before the start of the protocol treatment**.

Telephone: +32 2 77416 00

Internet: http://www.eortc.be/random

A patient who has not been registered before the first treatment administration will not be accepted for the study at a later date.

An exhaustive list of questions to be answered during the registration/randomization procedure is included in the registration check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is registered.

Standard questions

- institution number ?
- protocol number ?
- step number: 1
- name of the responsible investigator ?
- patient's code (maximum 4 letters) ?
- patient's chart number (if available) ?
- patient's birth date (day/month/year) ?

Group affiliation

- primary group affiliation ?
- secondary group affiliation ?

Protocol specific questions

- eligibility criteria ?

  all eligibility criteria will be checked;

  actual values of the eligibility parameters will be requested when applicable
- date of written informed consent ?
- date foreseen for protocol treatment start ?

At the end of the procedure, a patient sequential identification number will be allocated to the patients. This number has to be recorded on the registration check-list, along with the date of registration. The completed check-list must be signed by the responsible investigator and returned

to the data center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the registration procedure identifies the patient and must be reported on all case report forms.

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the **EORTC forms** and sent to:

EORTC Radiotherapy Group Data Manager

Marianne Gallois Pierart

EORTC Data Center

Avenue Emmanuel Mounier, 83, bte 11

B-1200 Brussels, Belgium

Case report forms must be completed according to the following schedule:

A. Before the treatment starts:

- the patient must be registered at the Data Center by INTERNET or by phone
- the registration check-list should be returned to the Data Center

The optimal way to work is to complete the registration check-list first and to register/randomize the patient as soon as it is completed. The date of registration and patient sequential identification number are then completed on the check-list, and this form can be sent to the Data Center.

B. The list of forms to be completed for this study and their submission schedule is appended to the set of case report forms

C. Upon occurrence of a Serious Adverse Event (SAE)

- SAEs occurring from the time a subject is registered until 30 days after last protocol treatment must be promptly reported.
- Any SAE occurring after the 30-days period and considered to be reasonably related to the investigational product or study participation, also have to be promptly notified
- All these events must be reported **by fax** to the **EORTC Pharmacovigilance Unit** on a Serious Adverse Event Form **within 24 hours** of the initial observation.
- A completed SAE-form must be returned to the Data Center within 10 calendar days of the initial observation of the Serious Adverse Event.

ALL Forms must be dated and signed by the responsible investigator or one of his/her authorized staff members

13.2 Data Flow (Remote Data Capture)

The forms must be electronically completed according to the schedule defined in the CRF guidelines through the EORTC web based Remote Data Capture (RDC) system.

The list of staff members authorized to enter forms must be identified on the signature log and sent to the Data Center by the responsible investigator before the start of the study.

In all cases, it remains the responsibility of the investigator to check that data are entered on the database as soon as possible and that they are completely and correctly filled out.

On the data received, the EORTC Data Center will perform extensive consistency checks and issue queries in case of inconsistent data. Queries will be sent by email (PDF) or regular mail, and must be filled out on the printed paper. A copy should be kept on site, the original must be sent by regular mail to the EORTC Data Center.

The EORTC data manager will subsequently apply the corrections into the database.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been sent to the EORTC Data Center, he/she should use a Data Correction Sheet and sent it to the EORTC Data Center.

14 Reporting of Serious Adverse Events (SAE)

14.1 Definitions

AE: An **Adverse Event** is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is any untoward and unintended responses to an investigational medicinal product related to any dose administered.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

SAE: A **Serious Adverse Event** is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment.

SAR: A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Reaction**

An **Adverse Event** or **Adverse Reaction** which is considered as **serious**:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

SUSAR: Suspected Unexpected Serious Adverse Reactions

14.2 Reporting procedure

14.2.1 Non- serious adverse events and/or non-serious adverse drug reactions

Adverse Events (AE) and /or Adverse Reactions (AR) must be recorded as indicated in the protocol.

14.2.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE) occurring from the time a subject is registered until 30 days after last protocol treatment, must be reported to the EORTC Pharmacovigilance Unit within 24 hours. (Ref: http://ctep.info.nih.gov/reporting/ctc.html).

All SAEs that are simply signs and symptoms of the disease being studied do NOT need to be collected!

Examples of SAEs that do not need to be reported:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.

Any SAE that occurs outside of the SAE detection period (after the 30-days period), considered to be reasonably related to the investigational product or study participation, have to be promptly notified to the EORTC Pharmacovigilance Unit.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

For the causality assessment, the following definitions must be used:

Relationship to the protocol treatment	**Description**
UNRELATED	There is no evidence of any causal relationship to the protocol treatment
LIKELY RELATED	There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.

Details should be documented on the specified Serious Adverse Event Form.

PLEASE FAX THE REPORT TO:

EORTC Pharmacovigilance Unit:
Fax No. +32 2 772 8027

The EORTC Pharmacovigilance Unit will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons (**See Administrative chapter**).

To enable the EORTC Pharmacovigilance Unit to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

It should be recognized that Serious Adverse Reactions (SAR) which have not been previously documented in the Investigators' Brochure, or which occur in a more severe form than anticipated (i.e. they are 'unexpected' by nature or severity), are subject to rapid reporting to the Regulatory Authorities.

ANY QUESTION CONCERNING SAE OR SAR REPORTING CAN BE DIRECTED TO:

EORTC Pharmacovigilance Unit
Phone: +32 2 774 1676
Fax: +32 2 772 8027
e-mail: pharmacovigilance@eortc.be

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORIZED STAFF MEMBERS.

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the database of the EORTC Data Center either by a double data entry procedure or by using the RDC system. Sites will be asked to choose one of both options at the start of the study. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

15.2 Audits

To ensure quality of data, study integrity and compliance with the protocol and the various applicable regulations and guidelines, the EORTC Quality Assurance Unit regularly conducts site visits to institutions participating in EORTC protocols.

The investigator, by accepting to participate in this protocol, agrees to co-operate fully with any quality assurance visit undertaken by authorised third parties, including representatives from EORTC, national and/or foreign regulatory authorities.

The investigator will also grant direct access to documentation pertaining to the clinical trial (including CRF, source documents, hospital patient charts and other study files) to these authorized individuals.

The investigator must inform the EORTC Data Center immediately in case a regulatory authority inspection is scheduled.

15.3 External review of histology

Histological classification and grading of the meningioma must be assessed for all patients by the local pathologist prior to entry on study.

Central pathology review will be performed by the central neuropathologists after patient inclusion.

After each patient inclusion, please send immediately:

- Copy of the pathology report (anonymous, indicate patient SeqId)
  - results of progesterone and estrogen receptor immunohistochemistry (if available)
  - mitotic index (in the pathology report)
- Copy of the operative (surgery) report (anonymous, indicate patient SeqId)
- 1-2 representative H&E sections
- 15-20 unstained slides from each block suitable for immunohistochemistry
- Paraffin embedded tumor material (strongly encouraged, not mandatory)
- Notify whether fresh-frozen tumor tissue is available (strongly encouraged, not mandatory) and were it is located – to be send on request.

To be sent for central pathology review at:

Martin J. van den Bent
Attn: Johan M. Kros, Neuropathologist

ERASMUS UNIVERSITY MEDICAL CENTER
Postbus 5201 (Groene Hilledijk 301)
NL 3008 AE Rotterdam
The Netherlands

(All EORTC-trial related materials are sent to Martin J. Van Den Bent's administration prior to sending on to Johan M. Kros).

15.4 Quality assurance of radiotherapy

The quality assurance for radiotherapy in this study will be done jointly with *Advanced Technology Radiation Therapy Clinical Trials* and Advanced Technology Consortium network (ATC).

Therefore this trial has specific requirements to assess and ensure the quality of the radiotherapy delivered to every patient. The procedures will be performed via the web and will use only electronic data (DICOM-RT) and image files (format jpg, bitmap, etc).

The objectives are to check compliance with the protocol guidelines regarding PTV definition, planning technique and clinical and technical documentation. This includes image co-registration and treatment verification procedures.

The main responsible person for the QA is the Study Coordinator with the help of EORTC ROG QA team and ROG coordinating physician and in collaboration with the ATC team,

The following tree steps are mandatory:

1. All centers must fill in the Facility Questionnaire prior to the first patient entry.
2. Before the center is allowed to randomize patients, it should show that the protocol is well understood and that the center is able to treat patients according to the specified guidelines. Therefore a first patient case check is mandatory for each center and must be done prior to the randomization.

- **For the Demonstration of Digital Data Submission Capability Test**: please contact the EORTC (QA.ROG@eortc.be) and request an ATC FTP account for digital data submission. You have to submit a complete patient digital data set to demonstrate compliance with 3D/IMRT technical requirements.
- **Timely Review by EORTC-ATC**: A timely review of the first submitted protocol case that an institution registers will be performed. The timely review will not hold up the patient treatment as it must be completed within the first 5 days after data has been received by EORTC-ATC.

3. The individual cases review will check the data for all patient(s) entered in the trial.

The following information is to be submitted for each patient:

- Digital Data Submission Information Form (DDSI Form obtain from ATC website).
- Treatment prescription and verification images
- Protocol compliant images (e.g. CT or MRI scan series);
- Protocol compliant contours using required standard names (standard structure names can be found on the ATC website) for all GTV, CTV and PTVs, and for all specified critical normal

structures. They must be contoured on all slices in which each structure exists or as defined by the protocol and include skin on ALL CT cuts;

- Color 2D isodose distribution plots for the axial, sagittal and coronal planes through the isocenter for the total dose plan must be submitted. They may be electronic files of screen dumps, such as jpg or bmp files. Volumetric 3-D dose distribution (**with** heterogeneity corrections) data in absolute dose for each fraction group used to deliver a protocol compliant dose. Note, a Fraction Group represents the beams and doses for a concurrently treated set of beams;
- DVH's computed **with** heterogeneity correction for the total dose of all dose distributions submitted for item c (summed fraction groups from item c) for all PTVs and all specified critical normal structures. A DVH of all “unspecified tissue” must also be provided.

In case some centers are unable to upload data to their server (because of software compatibility), we will provide a list of the TPS that are compatible with the ATC system.

16 Ethical considerations

16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.emea.eu.int/pdfs/human/ich/013595en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Data Center. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, the patient’s code (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

16.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data

- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician.

The template of the patient's informed consent statement is given as an appendix to this protocol.

It is the responsibility of the Coordinating Investigators for this trial (sometimes called National Coordinators) to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Data Center. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative".

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

17 Administrative responsibilities

17.1 The study coordinator

The Study Coordinator (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

Study coordinator for both EORTC Groups:

Damien WEBER

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Switzerland
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e-mail: damien.weber@hcuge.ch

17.2 The EORTC Data Center

The EORTC Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Data Center.

EORTC DATA CENTER

83, avenue E. Mounier, Bte 11
B-1200 Brussels, Belgium
Fax: +32 2 7723545

Registration of patients:

Phone: +32 2 7741600
or
http://www.eortc.be/random

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Pharmacovigilance Unit:

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Fax: +32 2 772 8027
e-mail: pharmacovigilance@eortc.be

The EORTC Pharmacovigilance Unit will forward all SAE within 24 hours of receipt to the Study Coordinator, and the Data Manager.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to the Competent Authorities whenever applicable.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary of all SAE reports which will be added in the group meeting report to which will be distributed to all participating investigators.

17.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

EORTC Radiotherapy Group

Chairperson:

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Chairman:

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18 Trial sponsorship and financing

The Sponsor of the study is the EORTC.

The contact details of the EORTC are:

EORTC Data Center
Avenue Mounier 83/11
B-1200 Brussels, Belgium
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

19 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Data Center. For details please refer to the chapter on investigator authorization.

Patients treated at **satellite institutions** are only covered by clinical trial insurance, if these satellite institutions are properly reported to the EORTC Data Center. For details please refer to the chapter on investigator authorization.

20 Publication policy

The final publication of the trial results will be written by the Study Coordinator on the basis of the final analysis performed at the EORTC Data Center. After revision by the Data Center and other co-authors (and the Sponsor, if applicable) the manuscript will be sent to a major scientific journal.

The publication will be made on behalf of the EORTC Radiotherapy and Brain Tumor Groups.

Authors of the manuscript will include at least the Study Coordinator, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and a minimum of two members of the Data Center team who have contributed to the trial.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the data center staff involved in the study, as well as supporting bodies (NCI, cancer leagues, sponsors…).

All publications (papers, abstracts, presentations…) including data from the present trial will be submitted for review to the Data Center and to all co-authors prior to submission.

The Group Chairman, the Study Coordinator and the Data Center Team must approve all publications, abstracts and presentations of data pertaining to patients included in this study.

This is applicable to any individual patient registered in the trial, or any subgroup of these. Such publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy”. Therefore, such a publication cannot include the analysis of any of the study end-points unless the final results of the trial have already been published by the Study Coordinator.

It is the EORTC's policy not to release trial results before data maturity has been reached for the primary endpoint(s) of the trial unless the publication is authorized by an Independent Data Monitoring Committee. If the group wishes to publish or present study data before the publication of the primary trial endpoint, this may be authorized under the conditions specified in the EORTC Policy 009 "Release of Results and Authorship Policy" available from http:\\www.eortc.be, or authorized by an Independent Data Monitoring Committee.

Appendix A: References

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for

those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17 Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of

funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix D: Patient Information Sheet and Informed Consent document for clinical trials

INFORMATION FOR INVESTIGATORS:

This document is an English version of the Patient information sheet & informed consent for clinical trials (PIS & IC). The translation and national regulatory submission process of this document is the responsibility of the National Coordinator for this trial. He/she will keep you aware and informed and will send the translated and approved document as soon as available.

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- this document represents an English version of PIS & IC to be used in the present study
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  - send a copy of the approved translated document to EORTC Data Center who will than distribute the document to other national participating investigators
- bold parts, appearing in the English template, **must** appear also in the translated version of the PIS & IC
- final translated and approved PIS & IC must have version number and date

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European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

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1. Title of the research protocol:

Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase-II and observation study (EORTC 22042-26042)

2. Invitation to participate in the study

"The EORTC Radiotherapy and Brain Tumour Groups are initiating a research study on patients that have a disease similar to yours. The study will be conducted at the European level under the supervision of physicians recognized as experts in this field of medicine. Today, you will be invited to take part in this research project after you have been given full information about the study".

3. Introduction

A few weeks ago you have been operated for a brain tumour, which proved to be an atypical or malignant meningioma.

The postoperative radiotherapy is recommended in general when a subtotal or a total resection is performed in order to prevent the local recurrence. However this is a general consensus but no prospective controlled studies have been done to investigate the optimal amount of radiation needed to insure the local control.

In many cases of remnant atypical or malignant meningioma, the tumour may progress within 1-3 years of surgery and may lead to local disease progression within 5 years of surgery. Such recurrent or progressive tumour decreases life expectancy. Life expectancy for the long-term can hopefully be increased by administering higher dose radiotherapy.

It is known from several retrospective studies that increasing the radiation dose may result in a better local control of the disease especially in the incomplete surgical resection. Therefore in this study the participating patients will all receive a certain radiation dose as a function of the amount of residual tumour left by the surgeon. More specific, a higher dose of radiotherapy may prevent the tumour relapse in the cases in which the complete excision was not achieved. For this reason, if the removal of your tumor was complete you will be treated with a standard radiation dose and with a higher dose in case of incomplete tumor removal. Meanwhile, an increased dose of radiation can lead to more treatment-related complications. Therefore, the main question in this study will assess if an increased dose of radiation for patients with incomplete surgery will benefit to atypical and malignant meningioma patients in terms of tumour control and treatment complications.

4. Description of the research

Only patients with atypical or malignant meningioma can take part in the study. The form of irradiation chosen depends on the volume and location of the tumour remnant and to the specific condition of the meningioma. This preference will be thoroughly discussed with you. Usually the radiation therapy doesn't involve hospital stay. A brain-protective drug (corticosteroids) during radiation treatment may be prescribed for you by your physician.

You will receive the treatment according with the surgery report and especially according to the resection margins status:

1. If you have had a complete tumour removal the radiotherapy will involve a total of 30 radiation treatments, five working days a week for a period of six weeks.

2. If you have had an incomplete surgery, radiotherapy will consist of 35 treatment days, five working days a week for a period of seven weeks.

In all cases, a thermo plastic mask or a (relocatable) stereotactical mask will be used to guarantee accurate delivery of the irradiation.

Regular 3 and 6 months after enter in the study and then yearly follow-up visits. Imaging studies (MRI) will be performed at each follow-up visit, except at the 3 months follow-up visit where no MRI is needed. During the pre-treatment and follow-up visits a medical history will be taken, and physical and neurological examinations will be done routinely. No blood samples need to be taken. Both before taking part in the study and during the follow-up visits, specific questions will be asked and registered by the physician. Those questions concern your memory and graphical capabilities among other factors and are an essential part of the study, because it intends to get information from you about your neurological condition.

Over 70 patients will take part in this study.

5. Description of foreseeable risks and discomforts

Side effects due to the treatment may occur. Depending on the technique used, radiation therapy may cause symptoms, like redness and soreness of the skin of the irradiated area, hair loss, fatigue, and difficulty with concentration. Some headache could occur although it is unsual. With the use of present modern, sophisticated techniques these side effects mostly are mild and temporary. There is a clear relationship between the occurrence of side effects and the location and the volume of the irradiated tumour, because the larger this volume, the larger the adjacent volume of healthy tissue getting a certain amount of radiation.

Sometimes the effect of the radiation on the tumour tissue is so strong that so-called radio-necrosis occurs, which might behave like an expanding tumour. In most cases symptoms and signs of radio-necrosis can be controlled with corticosteroids. In some cases, additional surgery may be needed for this complication. Radiation-induced complications may be negligible for favorably shaped and located meningiomas.

The irradiation techniques used in this trial are standard ones.

6. Description of the ultimate goal of the clinical research project

The question that this study addresses is whether an increased dose of irradiation, for an atypical or malignant meningioma, which has been incompletely resected, results in improved disease contro**l**. A secondary objective of the study is to assess the eventual risk for complication of the treatment**.** Finally, the neurological status of the treated patients will be evaluated.

7. Expected benefits (description of possible expected benefits)

The possible benefit of this treatment is an improved disease control and no need for further treatment.

8. Voluntary participation

"Your participation in this clinical trial is entirely voluntary and you will be given sufficient time to decide whether or not you wishing to participate. You are free to decide at any time without giving any reason that you no longer wish to participate in the trial. Such decision will not affect your subsequent treatment or relationship with your treating doctor or the hospital staff in any way. Medical data collected during your participation to the clinical trial as well as follow up data which will still be prospectively collected will be kept for research and analysis unless you specify otherwise."

9. Data protection

"Your consent for participation in this Protocol also includes your consent to allow the use of the data in your medical/clinical record to be used for research purposes. Your consent also includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical records,…).

All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and national applicable laws.

The trial involves the collection of information contained in your medical records, which relates to your disease. It is very important that the information collected is accurate and from time to time it may be checked against medical records. Recorded medical information may be checked by authorized persons under strict confidentiality (health authorities, pharmaceutical industry representatives...). Duly authorized persons (EORTC research staff, national and/or foreign health authority representatives) may have access to your medical records. With the exception of access by the duly authorized persons to your personal data on your medical record, all information will be strictly confidential and your identity will never be divulged, you have the right to access this information according to the laws applicable in your country.

To verify the initial diagnosis, as was accomplished by the pathologist in your hospital, another dedicated pathologist will using the microscope review glass slides of your tumour biopsy(s), which were taken at the time of surgery. Very often the expert will not be working in the hospital where you will have your study treatment, or even in your country. In all cases a (frozen) sample of your tumour biopsy and a sample of your blood (also taken at the time of surgery) is asked for in this study. This material might be used to prepare new slides for additional diagnostic tests or to perform extra laboratory investigations to learn more about possible differences on a molecular level in the behavior of various meningiomas."

10. Sponsorship

"This clinical trial is conducted under the legal framework of EORTC without any other financial contribution.

The EORTC as sponsor, is responsible for the conduct of this trial, has asked your treating doctor to disclose any existing conflict of interest he/she may have as a result of his/her activities related to this trial. The EORTC has set up procedures to ensure the integrity of this process."

11. Insurance

"The sponsor of the Study has obtained clinical trial insurance in accordance with the applicable legislation of your country to cover risks related to your participation in this study.

If you need to undergo another medical treatment, we advise you to inform the study doctor to ensure this will not have any effect on your participation to the trial.

Everything has been done and will continue to be done to prevent health problems occurring as a result of your taking part in this trial".

12. Ethics Committee

"This research protocol has been submitted to the ethics committee whose mission is to verify that all conditions with respect to your safety and rights are respected. Approval to this research has been given by the Ethics Committee of _____ on _____"

13. Contact persons

"In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: _____

Hospital: _____

Telephone: _____

If you consent to join this trial, you will be given a telephone number of the hospital that you can contact at any time if you feel unwell or have further questions. With your agreement, your family doctor will also be informed about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is unclear. You are entitled to keep a copy of this document after you and your doctor have signed it."

Informed consent

☐ ***I have been properly informed about the clinical trial and have been given sufficient time to consider my participation.***

☐ ***I have received a copy of the patient information sheet.***

☐ ***All my rights have been clearly explained to me.***

☐ ***I agree to participate in the clinical research study entitled _____ and to be registered in EORTC study number _____. I accept that any data resulting from this clinical research study can be linked with other resources for cancer research purposes. My participation is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my relationship with my treating doctor. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws.***

☐ ***I have been informed that the data (personal, clinical and biological material) collected may be used in the future for cancer scientific research purposes while confidentiality will be ensured.***

All data (personal, clinical and research on biological material) collected on my behalf will be treated in compliance with the European and national applicable laws.

My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law.

Patient's name: _____

Patient's signature: _____ Date: _____

Person designated by the investigator to participate in the informed consent process:

Name: _____

Signature: _____ Date: _____

Investigator's name: _____

Title/Position: _____

Investigator's Signature: _____ Date: _____

This document has been prepared taking the following documents into account:

- World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland June 1964. Revised 1975, 1983, 1989, 1996 and on October 6, 2000 in Edinburgh, Scotland (www.wma.net).
- ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997.
- International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
- WHO: Operating Guidelines for Ethics Committee that Review Biomedical Research, Geneva, 2000.
- European Union Directive on the protection of individuals with regard to the processing of personal data (Dir/95/46/EC)

Appendix E: Patient Information Sheet and Informed Consent document for optional research on biological material.

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Research on biological material includes only patients who choose to take part without compromising their possibility to participate to the proposed clinical trial.

1. Title of the research protocol:

EORTC 22042-26042: Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase-II and observation study

2. Research on biological material - objectives and description

You have just consented to participate to the above mentioned trial. In addition to this we are also asking patients if they would consider taking part in the translational study described in this information sheet. This research is "optional", your denial of this research will not affect your participation to the therapeutic study.

Beyond the review by a pathologist of a tumor sample, this trial includes specific research on a specimen of your tumor and chromosomal analysis in blood and tumor sample. These studies will look for any changes in different proteins and genes, which could have affected the cancer evolution or the way in which your cancer respond to the radiotherapy. Specific genes that are known to be related to cancer evolution will be studied, as well as genes that may be related to how your body responds to treatment. The further molecular analysis of tumor samples in relation to the outcome of treatment may provide a better understanding of brain tumors and may lead to improvement of treatment and patient selection for treatments. The EORTC considers this type of research very important. At present the protein and genes cannot be specified, because ongoing research results may influence the optional research. However, for this type of future and unspecified research we need your specific consent. At some point in the future the involved investigators and the EORTC will decide which further research shall be carried out. ***This biological material will not be used to investigate any hereditary tests***.

Therefore we ask your permission to use available biological material for future research.

1. Previous tumor samples for specialised genetic and protein tests.
2. Two samples of peripheral blood (two 5 ml tubes)

The participation on this research study will not affect your hospital visit schedule during the follow up. If you participate in this study, only two additional blood tests will be performed at the start of the treatment and at the first follow-up visit.

"Part(s) of biological material taken during diagnostic process or surgical procedure that you undergo or have undergone, may be used for research under the EORTC legal and scientific responsibility to better understand and improve cancer care. Any research project conducted with this biological material will begin only if it has been approved by an Ethics/Scientific Committee according to all applicable laws. "

"If you consent for research on biological material, this also implies you agree to the storage of your biological material. This material can be stored for several years, as long as there is sufficient material to produce reliable analysis (also for future cancer research). The biological material will be handled and stored at the institution where you are/were treated, or at the institution where the tests are/were being performed, or at the EORTC Data Center in Brussels in accordance with all existing applicable laws. Your doctor should be able to inform you where the biological material(s) is (are) stored.

The mission of EORTC, being a non-profit research organization, is to do everything it can in the best interests of cancer patients. Collaboration with third parties, including private companies, may be necessary for the EORTC to develop more effective treatments. It cannot be excluded that results from use of biological material could lead to acquisition of exclusive rights, which are based on research discoveries. You will not receive any financial return. Should there be any financial return for the EORTC, it will be reinvested in cancer research only to improve cancer care".

3. Expected benefits

"The results of the research studies on biological material are unlikely to be available in the foreseeable future. This is because research can take a long time and tissue samples and data must be taken from many patients before results are known.
New relevant information, that directly concerns your future health, may well be available from your treating doctor at the institution where you have been treated following the present protocol."

4. Voluntary participation

"Your participation in the research project on biological material is entirely voluntary and you will be given sufficient time to decide whether or not you are wishing to participate. You are free to decide at anytime without giving any reason that you no longer wish to participate in the research project on biological material. Withdrawal from this part will not affect your participation into the clinical research study or relationship with your treating doctor or the hospital staff in any way. In case of withdrawal, your data will not (no longer) be used in any analysis, unless it has already been completed prior to your withdrawal. All unused material will be returned to your treating institution, if requested."

5. Data protection

"Your consent for participation in the research on biological material also includes your consent to allow the use of the data in your medical/clinical record or data resulting from research on tissue to be used for research purposes. Your consent also includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical records). Handling of biological material will be done in such a way, that scientists, analyzing it for research purposes, will not be able to find out your identity.

All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and national applicable laws.

It is very important that the information collected is accurate and therefore from time to time, this collected information may be checked against your medical records. Duly authorized persons (EORTC research staff, national and/or foreign health authority representatives) may have access to your medical records. With the exception of access by the duly authorized persons to your personal data on your medical record, all information will be strictly confidential."

6. Ethics Committee

"In addition to the Ethical Committee review for your participation in the clinical trial, further ethical and scientific review will be conducted prior to any research with biological material. This is to verify that all conditions with respect to your safety and rights are respected. "

7. Contact persons

"In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: _____

Hospital: _____

Telephone: _____

If you consent to give your biological material for cancer research, you will be given a telephone number of the hospital that you can contact at any time if you feel unwell or have further questions. With your agreement, your family doctor will also be informed about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your study doctor if anything is unclear. You are entitled to keep a copy of this document after you and your study doctor have signed it."

Informed consent

Title of the research protocol:

EORTC 22042-26042: Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase-II and registration study

☐ **I have been properly informed about the research on biological material and have been given sufficient time to consider my participation.**

☐ **I have received a copy of the patient information sheet.**

☐ **All my rights have been clearly explained to me.**

☐ **I have been properly informed and accept collection, storage and research on biological material that I provide. I was given sufficient time to consider my participation. I accept that any data resulting from the research study on biological material can be linked with other resources for cancer research purposes. My participation is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my participation into the clinical research study or relationship with my treating doctor or the hospital staff in any way. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws".**

In case of EORTC collaboration with a third party, I agree that my biological material can be used by:

☐ **Another academic institution/organization**

☐ **Pharmaceutical company**

☐ **I accept that future cancer research studies may be conducted on the biological material that I provide and that any data resulting from these studies can in the future be linked with other resources for research purposes. My participation to this is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my participation in the clinical study nor my relationship with my treating doctor or the hospital staff in any way. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws.**

In case of EORTC collaboration with a third party, I agree that my biological material can be used for future cancer research by:

☐ **Another academic institution/organization**

☐ **Pharmaceutical company**

All data (personal, clinical and research on biological material) collected on my behalf will be treated in compliance with the European and national applicable laws.

My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law.

Patient's name: _____

Patient's signature: _____ Date: _____

Person designated by the investigator to participate in the informed consent process:

Name: _____

Signature: _____ Date: _____

Investigator's name: _____

Title/Position: _____

Investigator's Signature: _____ Date: _____

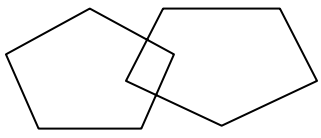
This document has been prepared taking the following documents into account:

- World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland June 1964. Revised 1975, 1983, 1989, 1996 and on October 6, 2000 in Edinburgh, Scotland (www.wma.net).
- ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997.
- International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
- WHO: Operating Guidelines for Ethics Committee that Review Biomedical Research, Geneva, 2000.
- European Union Directive on the protection of individuals with regard to the processing of personal data (Dir/95/46/EC)

Appendix F: Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date:_____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor."(The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Source:

Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975;12:189-198.