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● *Clinical Original Contribution*

A RANDOMIZED TRIAL ON DOSE-RESPONSE IN RADIATION THERAPY OF LOW-GRADE CEREBRAL GLIOMA: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) STUDY 22844

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Purpose: Cerebral low-grade gliomas (LGG) in adults are mostly composed of astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. There is at present no consensus in the policy of treatment of these tumors. We sought to determine the efficacy of radiotherapy and the presence of a dose-response relationship for these tumors in two multicentric randomized trials conducted by the European Organization for Research and Treatment of Cancer (EORTC). The dose-response study is the subject of this article.

Methods and Materials: For the dose-response trial, 379 adult patients with cerebral LGGs were randomized centrally at the EORTC Data Center to receive irradiation postoperatively (or postbiopsy) with either 45 Gy in 5 weeks or 59.4 Gy in 6.6 weeks with quality-controlled radiation therapy. All known parameters with possible influences on prognosis were prospectively recorded. Conventional treatment techniques were recommended.

Results: With 343 (91%) eligible and evaluable patients followed up for at least 50 months with a median of 74 months, there is no significant difference in terms of survival (58% for the low-dose arm and 59% for the high-dose arm) or the progression free survival (47% and 50%) between the two arms of the trial. However, this prospective trial has revealed some important facets about the prognostic parameters: The T of the TNM classifications as proposed in the protocol appears to be one of the most important prognostic factors ($p < 0.0001$) on multivariate analysis. Other prognostic factors, most of which are known, have now been quantified and confirmed in this prospective study.

Conclusion: The EORTC trial 22844 has not revealed the presence of radiotherapeutic dose-response for patients with LGG for the two dose levels investigated with this conventional setup, but objective prognostic parameters are recognized. The tumor size or T parameter as used in this study appears to be a very important factor. Copyright © 1996 Elsevier Science Inc.

Low-grade glioma, Radiotherapeutic dose-response, T of the TNM staging classification, Prognostic factors.

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INTRODUCTION

There is at present no consensus on the policy of treatment for patients with low-grade gliomas (LGG). Surgery is usually attempted and either biopsy or subtotal or total excision is undertaken. In some situations, stereotactic biopsy is a possibility where eloquent areas of the brain are involved by the tumor.

After surgery or histopathologic verification different policies in general are being pursued: The wait-and-see policy is followed by some (1), and they initiate retreatment usually by surgery followed by radiotherapy on progression of the disease. The other school (4–5, 12, 15) treats the patients with planned immediate postoperative radiotherapy. Some institutions follow no definite policy, and sometimes (8) postoperative radiotherapy is used, perhaps in difficult clinical situations. In some situations radiation therapy is being advocated even without biopsy (14), particularly when any surgical intervention is fraught with the risks of unacceptable complications.

The speculative reasons for initiating early radiation therapy after histopathologic typing and grading are being recently spelled out clearly (12).

For those believing in the efficacy of early radiation therapy, the optimal dose of radiotherapy is not known, although many retrospective publications indicate the existence of a dose–response for LGG, since the classical publication by Fazekas (4) revealed steep dose–response for LGG. Better overall survival is claimed (15) when patients with LGG are irradiated with a higher dose. The existence of a dose–response for irradiated glioma, however, has never been settled with a randomized controlled clinical trial.

The lack of consensus on the efficacy of radiotherapy and the question of dose–response or the optimal dose of radiations to be chosen for LGG has been the pivotal question in the Radiotherapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) since 1983. After prolonged deliberations, two randomized controlled trials, EORTC 22844 and 22845, were initiated in 1985 and 1986, respectively, for patients with LGG. The former trial deals with the question of existence of dose–response and is composed mostly of the believers in radiation therapy. Trial 22845 questions the efficacy of radiotherapy for LGG and is composed mostly of the nonbelievers in radiation therapy. It also tries to solve the question of early vs. late postoperative radiotherapy.

The EORTC trial 22844 on dose–response started randomization in April 1985. It continued until September 1991 and had accrued 379 patients when further accrual was stopped. The Brain Tumor Cooperative Group of the EORTC joined forces early in the initiation period of the trial.

The purpose of this article is to report the results of the dose–response study with a minimum follow-up of 4.6 years, while the first group of patients was randomized

more than 10 years ago. The median follow-up is > 5 years.

Through this prospective study a number of unanswered questions or controversial uncertainties apart from the existence of radiotherapeutic dose response were planned to be examined: (a) the T of TNM (8) staging classification, (b) the influence of the extent of surgical removal of the tumor, and (c) prognostic factors.

METHODS AND MATERIALS

From 10 countries, 27 institutions participated in selecting, randomizing, and treating 379 patients according to EORTC protocol 22844. Informed consent was obtained.

PATIENTS

All adult patients (age 16–65 years) having a definite histopathologic diagnosis of low-grade astrocytomas (G1 and G2), oligodendroglioma, and mixed oligoastrocytomas of the supratentorial areas had been included for this trial. The histopathologic typing and grading were based on the diagnosis at the study hospital. A panel of neuropathologists had previously defined the guidelines for typing and grading of the LGG in the protocol. These guidelines were based on the principles of the World Health Organization (WHO) classification (17) and were made available to the pathologist of each of the participating institutions. Grade 1 (pilocytic) astrocytoma, if totally excised, was excluded, while Grade 2 astrocytoma, even if totally excised, was included for randomization. Oligodendrogliomas and mixed oligoastrocytomas were included. The patients had to have been in reasonable to good general condition as indicated by performance score after surgery: Karnofsky index ≥ 60 and WHO score ≤ 2 . Neurologic deficit status was also recorded and defined: 1 = no deficit; 2 = some deficit but with adequate functioning for useful work; 3 = moderate functional impairment with movement difficulties, moderate dysphasia, paresis, and visual or memory impairment; 4 = major functional impairment; and 5 = lack of conscious response. The patients in Categories 4 and 5 were excluded from this trial.

Patients with pregnancy or gross hepatic, renal, or cardiovascular diseases or malignancy other than curable skin cancers were excluded. However, patients thought to be cured of cancer at least 5 years before inclusion in the protocol were eligible.

Workup, stratification, and randomization

All adult patients with the histopathologic diagnosis of LGG had to have had preoperative and postoperative routine examinations to fulfil the selection criteria of the trial. Some patients had biopsy or minimum resection of the tumor. None had stereotactic resection of the tumor as is being practiced recently in some centers (13). The clinical

data as well as preoperative CT scans were accepted as baseline investigations. The surgical procedures provided data on whether biopsy or minimal excision (<50% of the estimated volume of the tumor removed) or bulk removal (50–89%) or almost total ($\geq 90\%$) removal of the tumor had been undertaken. It was accepted after much discussion that this would be a rough but prospectively noted estimation by the neurosurgeon. Complex volumetric studies with CT scans were not undertaken in light of the complexities of a multicentric trial and the available technology and expertise in the early 1980s. However, one important parameter proposed in the protocol was to collect data prospectively on the T parameter of the TNM classification (6, 12). In view of the virtual nonexistence of the metastases (N or M) and the mandatory inclusion of only low-grade tumors, the T parameter was given importance; it was defined as early as 1983 (Table 1) based on the personal experience (12) of the study chairman and inconclusive results of a study (16) based on the UICC classification (6).

A maximal permissible interval of 8 weeks between the day of operation and initiation of radiation therapy was allowed. Usually this interval was < 4 weeks.

The present article is based on data from local neuropathologic and CT scan reports from the different participating centers.

Study design

Randomization was organized centrally at the EORTC Data Center in Brussels with stratification for each institute. This was undertaken on histologic Grade (G1 or G2) for astrocytomas. All oligodendrogliomas or mixed tumors were graded 2 for pragmatic stratification. Cerebral pilocytic astrocytoma, when totally excised, was not included in the trial.

Randomization after surgery was between two doses of radiation: For one arm a low dose of 45 Gy in 25 fractions in 5 weeks was chosen, and for the other arm a higher dose of 59.4 Gy in 33 fractions in 6.6 weeks was chosen. In both arms 1.8 Gy as daily single fraction dose was mandatory.

Follow-up with routine and neurologic examinations as well as CT scans were advised to detect progression of

the disease. End points of the study were overall survival and progression-free survival (PFS). The survival was computed from the date of randomization to the date of death. The PFS was computed from the date of randomization to the date of progression with definite regrowth or recurrence of the disease. The progression-free status of a patient was defined when clinical and radiologic (CT and, later, magnetic resonance imaging) evidence of tumor activity were not noted during follow-up. Patients who died of causes other than cancer were censored at the date of death in the progression-free survival analysis.

Radiation therapy and quality control

Similar modern radiation therapy with computed dosimetry was recommended for all participating institutions. They were advised to use 4–10-MV photons, with build-up where necessary (for 10-MV photons). ^{60}Co γ apparatus was allowed when a linear accelerator was not available. Only 2 institutions of 27 used ^{60}Co γ rays. Both of these institutions as well as some others were visited by the study chairman (A.B.M.F.K.) for the purpose of quality control. The institutional setup, surgical treatment, and radiotherapeutic quality of treatment, dosimetry, and techniques were found to be satisfactory in these institutions. Most other participating centers have been visited by the EORTC committee for quality control.

Technique. Parallel opposing, oblique wedge fields, or multiple crossfiring fields were used. Multiple crossfiring fields were encouraged. Shrinking fields were used for the high-dose arm (59.4 Gy), and smaller sizes of sets of fields were used at 45 Gy and, whenever possible, also at 54 Gy. The target volume had to cover the contrast-enhanced areas with a margin of 2 cm, and for the nonenhanced tumor the presumed tumor area with the hypodense zone was covered with a minimum margin of 1 cm. For the higher-dose arm, a margin of 1 cm was allowed after 45 Gy, and after 54 Gy a minimal margin was proposed. All fields should have been treated daily.

Doses were specified according to the International Commission on Radiological Units (7) Report No. 29.

Data collection

Forms for reporting the data on patients were developed for this study which had to be sent by the responsible local

Table 1. T parameter of the TNM staging classification for low-grade glioma as proposed in the protocol*

Definitions of primary tumor (T)	
T1a	Greatest diameter ≤ 3 cm, but confined to one side only.
T1b	Greatest diameter ≤ 5 cm that may be located unilaterally or smaller tumor situated relatively centrally.
T2	Greatest diameter >5 cm, <10 cm, but not encroaching on the ventricles or crossing the midline.
T3	Tumors of any size definitely encroaching on the ventricular system but not crossing the midline.
T4	Any massive tumor not conforming to the characteristics of T3 tumors, crossing the midline or the tentorium.

* The classification applies only to histopathologically verified (Grades 1 and 2) low-grade cerebral glioma of the adult, particularly for astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. T category was assessed on imaging and operative findings.

Table 2. Clinical and pathologic data on patient population in the two treatment groups [n (%)]

	Low dose (n = 171)	High dose (n = 172)
Age (median in yr)	38	39
<30 yr	41 (12%)	37 (11%) = (23%)
30–40 yr	57 (17%)	50 (15%) = (32%)
41–50 yr	39 (11%)	45 (13%) = (24%)
>50 yr	34 (10%)	40 (11%) = (21%)
Sex (M:F)	105:66	91:81
Tumor location		
Left:right:central	74:86:11	78:89:5
Tumor site		
Frontal:temporal	77:35	66:47
Parietal:occipital	19:4	34:0
Multiple or others	36	25
WHO performance scale		
0:1:2	55:90:26	45:89:38
Histopathology and grading		
Astrocytoma		
Grade 1 (pilocytic)	15	17 = (9%)
Grade 2	105	101 = (60%)
Oligodendroglioma	35	38 = (22%)
Mixed oligoastrocytoma	16	16 = (9%)

physicians of the participating centers to the EORTC Data Center in Brussels. The quality of the data was reviewed by the data manager of the EORTC (M.P.). All forms were reviewed by the study chairman. Data were analyzed with the help of the data manager and statistician (M.V.) in close cooperation with the study chairman.

Statistical analysis

The survival and the progression-free survival were estimated by the Kaplan–Meier method (9). Comparisons between the two treatment arms were performed using the log rank test. A prognostic factor analysis included an univariate and multivariate analyses. The Kaplan–Meier method and log rank test were used for the univariate analysis; the Cox regression model (3) was used for multivariate analysis.

RESULTS

The trial has accrued 379 patients from whom data on 343 patients (91%) were found to be evaluable. The minimum length of follow-up is 54 months and the median is 74 months. Altogether 36 patients were excluded owing

Table 3. Amount of tumor removed by surgery

	Low dose (45 Gy) (n = 171)	High dose (59.4 Gy) (n = 172)	Total (%)
Minimal biopsy or <50%	73	83	156 (45%)
Bulk removal 50–89%	58	45	103 (30%)
Total or 90–100%	40	44	84 (25%)

Table 4. Causes of death in 133 patients with median follow-up of 54 months

	Low-dose arm (45 Gy)	High-dose arm (59.4 Gy)
Brain tumor	64 (48%)	59 (44%)
Cardiovascular or pulmonary causes	2	2
Second primary	0	4*
Others	1	1†

* Two gastrointestinal, 1 lung, and 1 metastatic carcinoma of unknown primary.

† One suicide and 1 cause of death unknown.

to ineligibility. The reasons for ineligibility were incomplete data in 16 patients, wrong localization of the tumor and/or incorrect histopathology in 11 patients, low performance score in 4 patients, and prior treatment or delay in initiating radiation therapy in 5 patients. The ineligible patients were equally distributed in the two arms of the trial. The characteristics of the patients and the tumor in both arms of the trial are listed in Table 2. The estimated amount of the tumor removed by the surgical procedure is listed in Table 3. During this period, 149 patients developed progression of the brain tumor: 79 in the low-dose arm and 70 in the high-dose arm. Some died of the tumor or of other causes. The causes of death in 133 patients are detailed in Table 4.

Figure 1a and b shows the overall survival and proportion of PFS for both arms of the trial. It appears that neither the survival nor the PFS revealed significant differences between the two groups of patients treated with higher or lower doses. The number of survivors with PFS at 5 years is 47% for the patients treated with the lower dose and 50% for the other group treated with a higher dose. However, the number of patients with a minimum of 5 years follow-up is rather small: 37 and 35, respectively.

Prognostic values on survival and PFS

In analyzing prognostic factors, age alone was considered to be a discrete variable in the univariate analysis, and for multivariate analysis all cofactors such as T classification, performance, or neurologic deficit status, age, and so forth were entered as continuous variables. Table 5 shows the univariate and multivariate analyses on prognostic factors for both survivors and progression-free survivors. Age had a significant prognostic influence ($p < 0.04$) on survival but not on PFS ($p = 0.054$). Sex was not a prognostic factor for LGG ($p > 0.66$) in this study. The site of the tumor had a significant prognostic influence for survival only on univariate analysis. The histopathologic type had a significantly worse prognostic influence on survival for astrocytoma Grade 2 tumors than for any other histologic types or grading in this study. The worse influence was much higher for PFS on multivariate analysis ($p = 0.0001$). Patients with Grade 1 pilocytic astro-

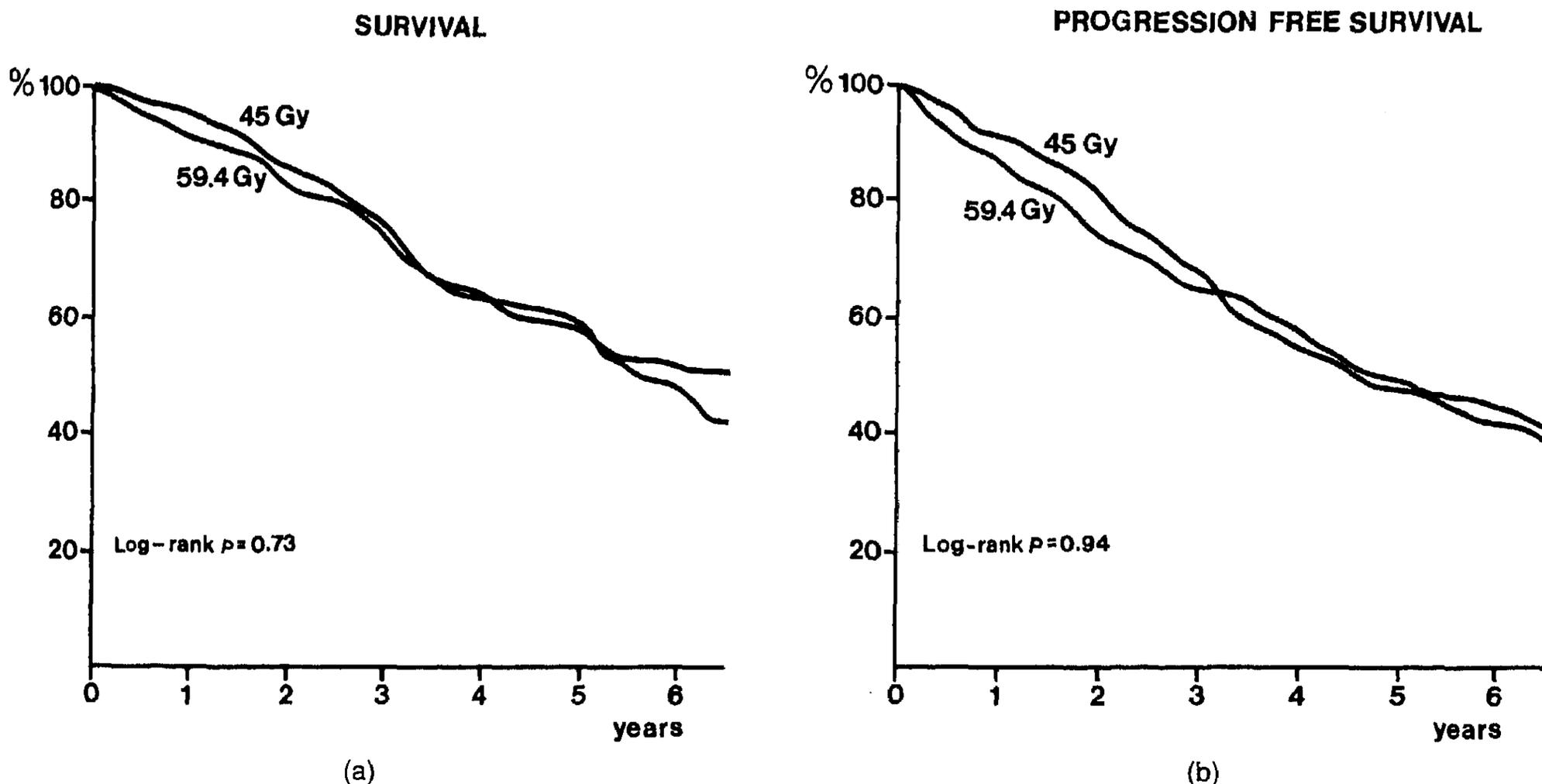


Fig. 1. (a) Survival and (b) progression-free survival (PFS) of patients treated with a low dose (45 Gy) and high dose (59.4 Gy).

cytoma had better survival but their number was small (32). In this study the neurologic deficit status appears to be a better predictor than the WHO performance status.

In view of known improved results with surgical removal of the tumor (2), further analysis was undertaken with the parameter being the amount of tumor removed by surgery. Three subgroups were analyzed as detailed in Table 3.

While dose-response was not found to be present in these different subgroups of patients with different amount of tumor rests after surgery, the survival and PFS for each of these three subgroups revealed significant differences as shown in Fig. 2a and b and Table 5.

The T parameter of the TNM staging classification as proposed in the protocol (Table 1) was analyzed for 300 patients for whom the data were available. The T parameters as proposed in this study are significantly discriminant (Figs. 3a and b and Table 5) for prognosis for overall survival ($p < 0.0001$) as well as PFS ($p < 0.0001$). The log rank test for trend was used for comparison of all ordered categorical data including the T classification.

Complications

Acute minor complications of short duration were noted in both arms of the trial as are usually seen during and after radiation (e.g., skin reactions, vomiting, headache, otitis). These were not significantly higher in the

Table 5. Prognostic factors: EORTC 22844

	Survival			
	Overall		Progression free	
	Univariate	Multivariate	Univariate	Multivariate
Age	*	†		
T classification	‡	‡	‡	‡
Site of the tumor	†			
performance status	‡		‡	*
neurologic status	‡	‡	‡	*
Surgery (amount of tumor removed)	†	*	‡	*
Histologic type (astro., oligo, or mixed types)	*		‡	‡

* $p < 0.05$.
 † $p < 0.01$.
 ‡ $p < 0.001$.

high-dose arm. However, radiotherapy had to be interrupted for more than 1 week in 13 patients treated with a low dose and in 26 patients treated with a high dose. In the latter group treatment was discontinued for nine patients. Long-term sequelae, as far as was retrievable from follow-up CT scans, were rare, perhaps owing to the low daily doses used in this protocol. Virtually no definite necrosis of brain has been reported so far. The sequelae and the quality of life do not appear to be different in the two arms but will be reported separately later in another report.

DISCUSSION

The EORTC study 22844 with a large number of patients has revealed some aspects on LGG previously unknown from a prospective multicentric study, but the study denies the presence of a dose-response in the studied dose range. This may change with a longer follow-up. New developments such as newer imaging methods with volumetric considerations, computer-assisted stereotactic resection of tumors (13), three-dimensional conformal radiotherapeutic treatment techniques, as well as other sophisticated developments (e.g., cell kinetic parameters) are not yet universally available. These are the new frontiers for advances (11) in the treatment of LGG as well as other tumors or lesions of the brain. Future dose-response studies should incorporate all of these and other developments with probably much higher doses. For the present, in the many institutions not participating in trials on LGG,

patients may be spared from the inconveniences of more treatment sessions if they are treated with the present conventional techniques. In this way valuable megavoltage space may be spared.

The T parameter as was defined in the protocol appears to be a good prognostic discriminator. While the myth of heterogeneity of the LGG should be further studied, the neurooncologists may start to use the T of the TNM staging system to separate the apples from the oranges or the pears in all prospective studies from now on. It is perhaps possible to modify and simplify further definitions of the T parameter. It is important to realize that the T parameter as defined in this study differs slightly from that of the UICC/AJC classification (16). The important deviation proposed (12) for staging LGGs is the size of tumor, and we are now looking for the clinical validity of staging LGGs only on size. This will be soon reported.

The influence of the age of patients on overall survival in many retrospective studies has been recognized and is also confirmed in this prospective study. However, the influence of age on the PFS was not significant in this study. The parameters of neurologic and performance status showed prognostic influence on survival as well as PFS, but the influence of neurologic status appears to be more than that of the performance status.

It is noted that LGGs are slow-growing tumors, and the survival may be observed to be different from the disease-free survival only after years of follow-up (10).

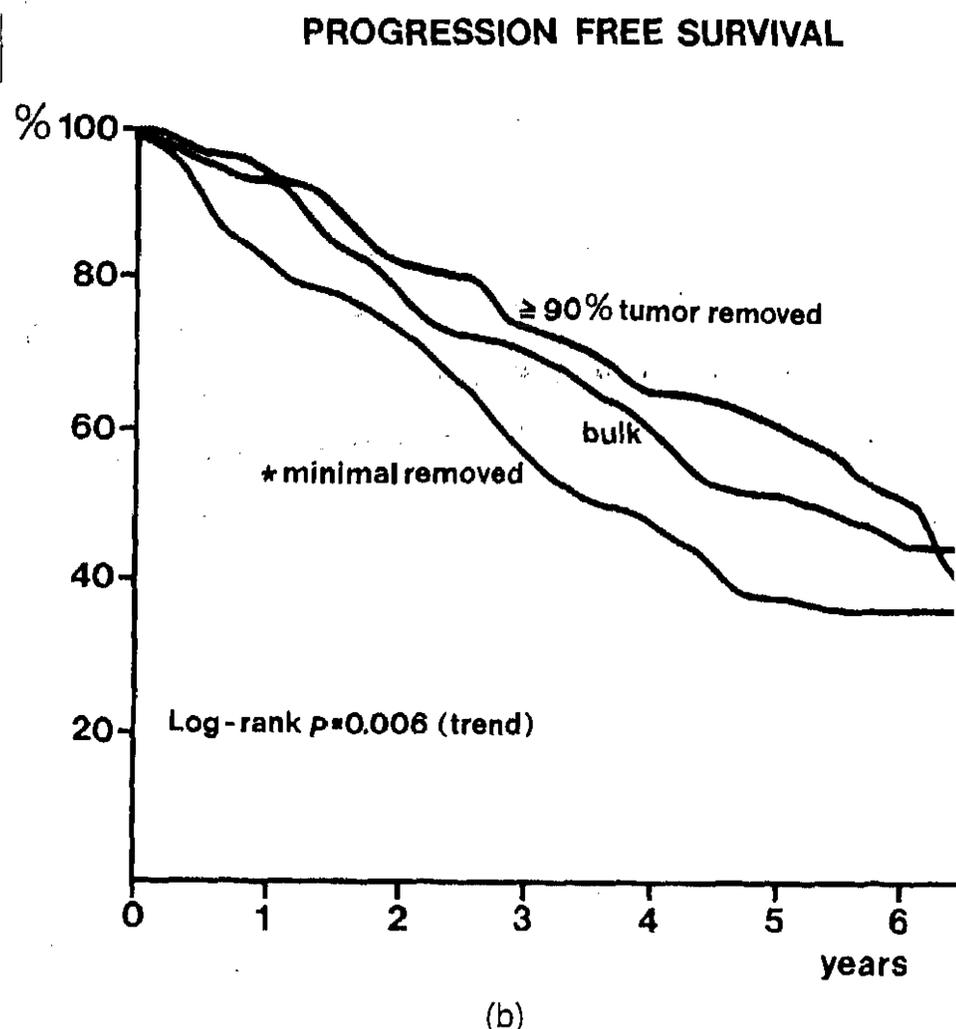
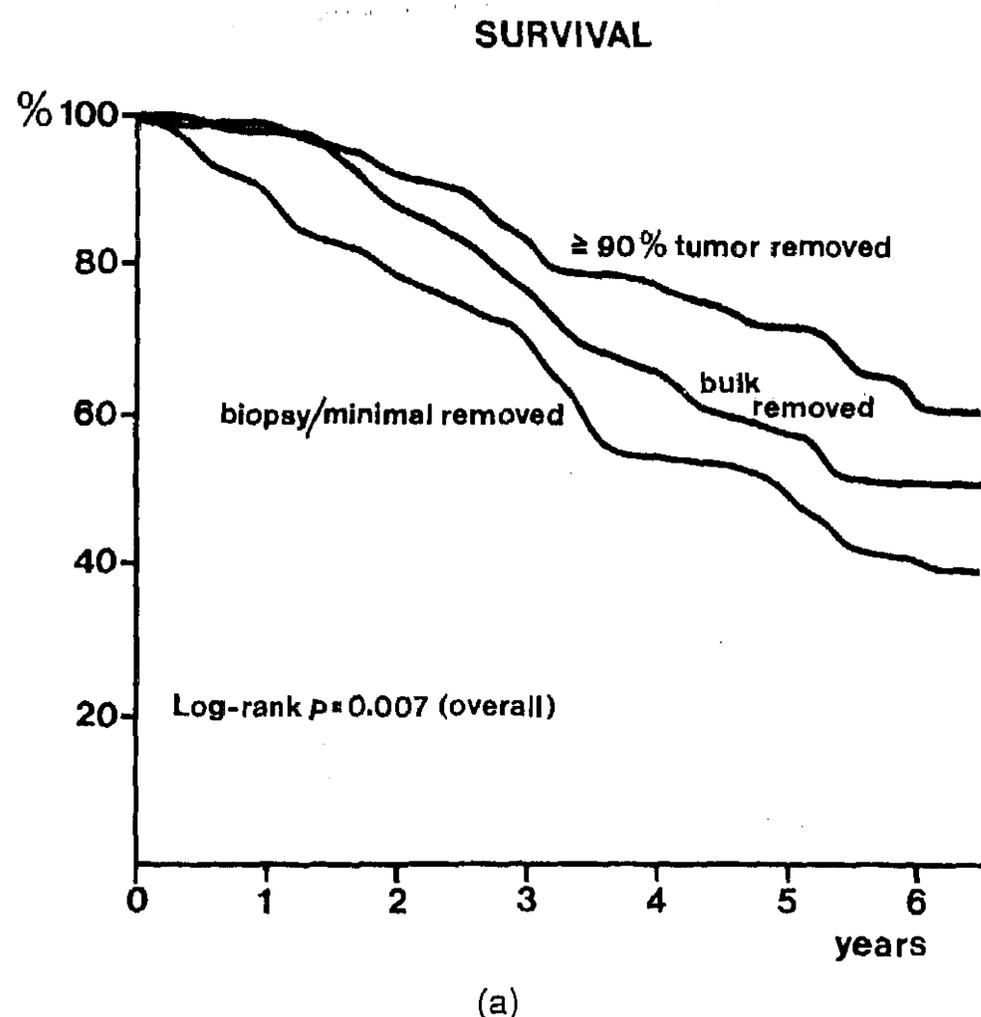


Fig. 2. (a) Survival and (b) progression-free survival (PFS) of patients whose LGGs were removed minimally (<50%), in bulk (50–89%) or almost totally (90–100%).

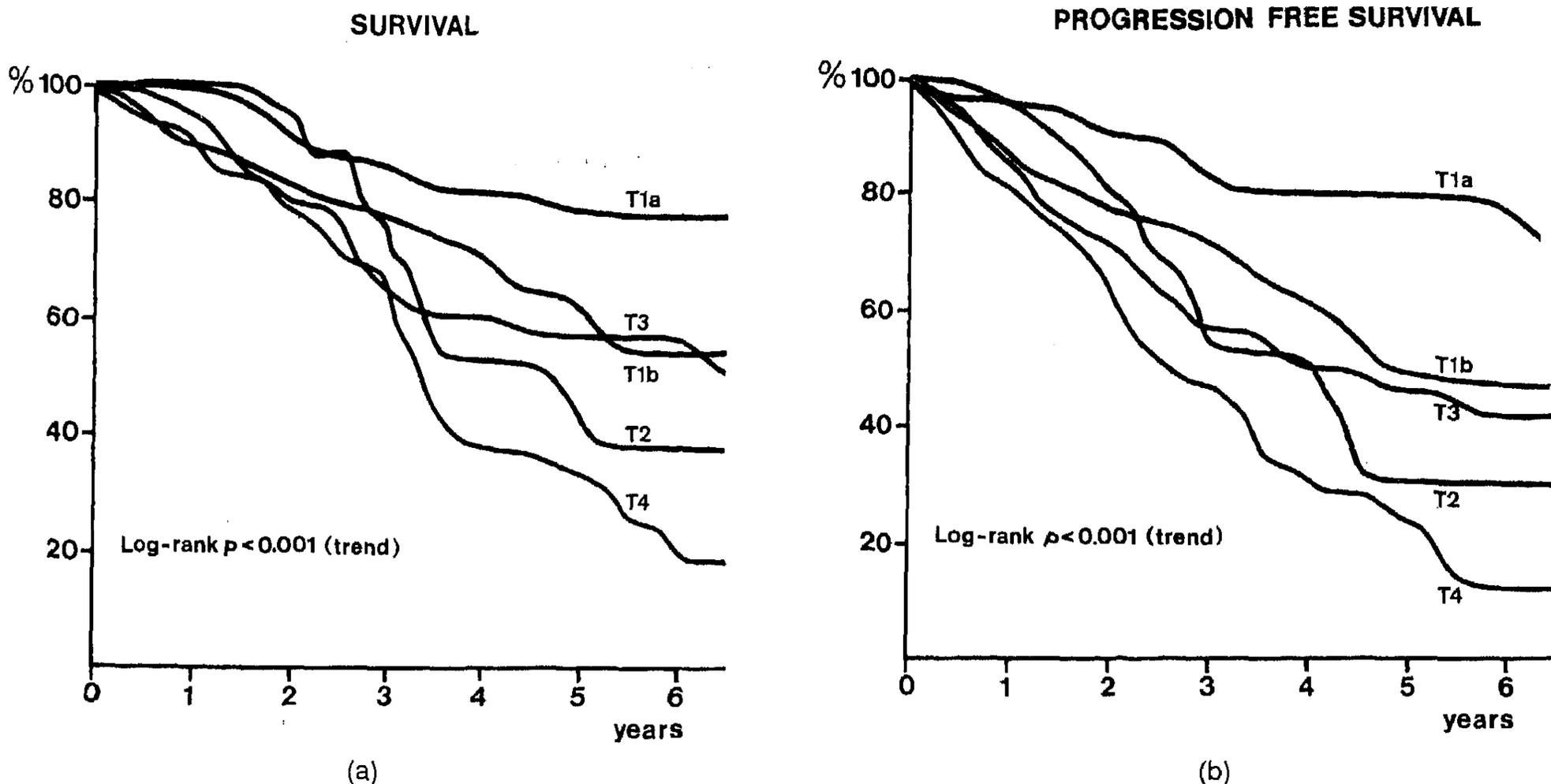


Fig. 3. (a) Survival and (b) progression-free survival of patients according to the T parameter of the TNM staging classification as proposed in the protocol.

CONCLUSION

There is no evidence of a dose-response for the LGGs for the two doses in a conventional setup as studied in this protocol. It is, however, rewarding to invest in the efforts of various participating centers for such a relatively rare tumor. The responsible neurooncologists, including the neuropathologists and neuroradiologists, have worked together to the success of the trial with

answers to some controversial issues including the prognostic factors from a prospective study. Of these factors, the proposed T staging classification demonstrated a very significant prognostic value both for progression-free and overall survival in a multivariate analysis. The important question of efficacy of radiotherapy must now be awaited from the results of the other "non-believer" EORTC trial 22845.

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