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Clinical study

Photodynamic therapy of high grade glioma – long term survival

Stanley S Stylli[1] MSc, Andrew H Kaye[1] MD MBBS FRACS, Lachlan MacGregor[2] MBBS MMEDSC, Megan Howes[1] RN, Priya Rajendra[1] MBBS

[1]Department of Neurosurgery and Department of Surgery, Royal Melbourne Hospital, University of Melbourne, Melbourne; [2]Department of Clinical Epidemiology, Royal Melbourne Hospital, University of Melbourne, Melbourne; Australia

Summary Haemetaporphyrin derivative (HpD) mediated photodynamic therapy (PDT) has been investigated as an adjuvant treatment for cerebral glioma. This study records the survival of patients at the Royal Melbourne Hospital with residences in the State of Victoria, utilizing the Victorian Cancer Registry database for patients treated with adjuvant PDT following surgical resection of the tumour. For primary (newly diagnosed) tumours, median survival from initial diagnosis was 76.5 months for anaplastic astrocytoma (AA) and 14.3 months for glioblastoma multiforme (GBM). Seventy-three percent of patients with AA and 25% with GBM survived longer than 36 months. For recurrent tumour, median survival from the time of surgery was 66.6 months for AA and 13.5 months for GBM. Fifty-seven percent of patients with recurrent AA and 41% of patients with recurrent GBM survived longer than 36 months. Older age at the time of diagnosis was associated with poorer prognosis. Laser light doses above the sample median of 230 J/cm^2 were associated with better prognosis in the 136 patients studied (primary tumour patients – (HR = 0.50[0.27,0.95],p = 0.033); recurrent tumour patients (HR = 0.75[0.42,1.31],p = 0.312). There was no mortality directly associated with the therapy, three patients had increased cerebral oedema thought to be related to photodynamic therapy that was controlled with conventional therapies.

Keywords: brain tumours, glioma, photodynamic therapy, haematoporphyrin

INTRODUCTION

Two percent of cancer deaths can be attributed to brain tumours and in the United States 18,000 new cases of primary brain tumours are estimated to occur each year.[1,2] Despite the technological advances over the years in the areas of neuroimaging, neurosurgical techniques, radiation therapy and chemotherapy, the prognosis for patients with malignant glioma remains dismal. The median survival for patients with a high grade glioma is less than one year.[3,4]

AA and GBM are generally considered to be 'high grade' tumours. The poor prognosis for cerebral glioma is due to the complex biology of the tumour and in particular the tumour cells invading adjacent normal brain tissue diffusely beyond the reach of surgical resection leading to local recurrence of the tumour. Tumours inevitably recurr as conventional treatments are unable to destroy these invading glioma cells.[5]

Many adjuvant therapies following surgical resection have been investigated but the median survival is less than 1 year for GBM and approaching 2–3 years in AA, despite the use of adjuvant radiation therapy and chemotherapy[6–9] following resection.

Photodynamic therapy (PDT) has been used as an adjuvant treatment for gliomas over the last 15–20 years.[10–12] PDT is a binary treatment consisting of two components. First, a selective uptake of a sensitizer by the tumour cell,[13] followed by the activation of the retained sensitizer by laser light of the appropriate wavelength causing a selective tumour destruction[14] mainly through oxidative reactions.[15]

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Correspondence to: Professor Andrew H. Kaye, Department of Neurosurgery, Royal Melbourne Hospital, Parkville 3052, Australia.
Tel.: +61 3 9342 7704; Fax: +61 3 9347 7695;
E-mail: a.kaye@unimelb.edu.au

We report the result of our use of PDT using haemetaporphyrin derivative (HpD) in treating patients with high grade glioma. This study is limited to patients resident in the state of Victoria whose survival data could be confirmed with the Victorian Cancer Registry located at the Cancer Council of Victoria. The Victorian Cancer Registry is a population-based registry that acts as a central repository for all hospitals and pathology laboratories for data on the presence of cancer in human tissues of patients resident in the state of Victoria. HpD was manufactured in hospital pharmacies in Adelaide and Perth, Australia.

MATERIALS AND METHODS

Patient population

A total of 358 glioma patients have been treated with PDT at the Royal Melbourne Hospital since 1986. The study sample consisted of 136 patients resident in Victoria who had surgical treatment for GBM and AA at the hospital between 1986 and 2000. The Victorian Cancer Registry data was updated during December 2003, hence for the purpose of statistical analysis, survival time data for patients known to be alive at this time were censored at 1st January 2004. All deaths were assumed to have been caused by the brain tumour.

Seventy eight patients were diagnosed with glioblastoma (GBM), while the remaining 58 were anaplastic astrocytoma (AA). The distribution is shown in Table 1. 61.8% of the patients were male, 38.2% female and the majority were recurrent tumours (55.1%).

The following information was recorded for the purpose of this study from the patient records stored at the hospital: gender, age at diagnosis, primary or recurrent tumour, location of the tumour, age at PDT treatment, dose of laser light administered at PDT treatment, laser device, the date of the last follow-up and whether the patient was still alive or deceased. The survival data for all

Table 1 Summary data for all treatment episodes

Grade	Primary/Recurrent tumour	Sample number (N)	Gender (F:M)	Age (years)	
				Median	Range
Astrocytoma	Primary	30	10:20	38	18-61
	Recurrent	29	16:13	35	15-52
Glioblastoma	Primary	31	11:20	47	18-72
	Recurrent	55	17:38	42	17-76
Total		145*	54:91	40	15-76

*9 recurrent tumour patients had two PDT treatments.

patients was obtained and confirmed with the Victorian Cancer Registry at the Cancer Council of Victoria. The tumour classification was made by the senior neuropathologist of the Royal Melbourne Hospital from a stained paraffin-embedded section of tumour tissue taken at the time of surgery, using the WHO 2000 classification system.[16] The date of initial radiological diagnosis was known for the majority of patients. When only the month of diagnosis was recorded, a date corresponding to the first day of that month was used in the analysis.

All patients with primary treated tumours had standard post operative radiotherapy and all those with recurrent tumour had previously been treated with radiotherapy. Chemotherapy was administered to 29% of the patients in the study.

HpD administration, operative treatment and PDT

HpD was administered intravenously at a dose of 5 mg/kg (body weight) in shielded conditions 24 hours prior to surgery over a period of 30 minutes. Laboratory studies have previously indicated this to be the optimal retention time for HpD in central nervous system tumours.[17,18] At surgery, maximal resection of the tumour was performed usually utilizing an ultrasonic aspirator leaving a tumour bed area to be irradiated. The surface area of the tumour bed was measured and the irradiation time was calculated once the fibre output was known.

Initially a dose of 70 J/cm^2 was used but this was increased to 240 J/cm^2 in a step wise fashion as preclinical studies had indicated this to be the optimal light dose (see 10 for review; 17). A total light dose of 240 J/cm^2 was administered to most patients via a sterile flat-cut 600 micron quartz fibre. The cavity left by the tumour resection was filled with 0.5% Intralipid aqueous lipid suspension (Baxter Healthcare, Australia) to allow for homogeneous distribution of the laser light and cooling of the brain tissue except when the ventricle was widely opened. During light irradiation, the Intralipid was continually refreshed within the cavity. In the initial group of ten patients it was observed that irrigation with Intralipid and saline maintained the temperature less than 37 °C. Three lasers were used during the course of this study; an Argon Ion Dye pumped laser (ARDL) (Spectra Physics, Mountain View, CA) (1986-1987), a Gold Metal Vapour laser (GMVL) (Quentron, Australia) (1987-1994) and a KTP (potassium titanyl phosphate) pumped dye laser (Laserscope, San Jose, CA) (1994-2000) with the output laser power at the fibre tip measured between 0.4 to 4.0 watts dependent on the laser used. The patients in this study were placed into two groups (AA and GBM) based on their histological tumour grading.

Statistical analysis

Survival time was defined as survival from initial radiological diagnosis for patients with primary tumour, and survival from the time of repeat surgery for patients with recurrent tumour. For patients with primary tumour, entry date was defined as the date of surgery, and survival times left-truncated. Primary and recurrent groups were analyzed separately when calculating Kaplan Meier (KM) survival estimates. The effect of tumour grade was assessed by the Wilcoxon (Breslow) test for equality of survivor functions. Other prognostic variables were tested using a Cox proportional hazard model which included both primary and recurrent tumour patients, and incorporated primary/recurrent and tumour grade (AA/GBM) as stratification variables. If patients had more than one episode of PDT treatment at RMH (9/136), only the first was included in the model. Age was assessed as a continuous variable, but was categorized by the median value (40 years) to illustrate graphically the effect of age on survival. The distribution of laser light dose was skewed, and subsequently was categorized by the median value ($\geqslant$230 J/cm^2). The effect of laser light dose differed between primary and recurrent tumour groups, hence the regression model included an appropriate interaction term. Time of censoring appeared to be independent of relevant group variables. Graphical and statistical tests were used to verify that explanatory variables satisfied the proportional hazard assumption. Hazard ratios (HRs) shown in the text are based upon the final stratified regression model which included age and laser light dose as covariates. Survival curves are truncated at 240 months. Tabulated KM survival estimates include 95% confidence intervals. Statistical analysis was performed using Stata 7.0 (StataCorp LP, College Station, TX)[19].

RESULTS

The study sample consisted of 145 treatment episodes for the 136 patients. The summary data is shown in Table 1. The median age of all patients in this study was 40 years.

Tumour grade

Primary tumour patients

Table 2 shows the estimate of survival from the time of initial radiological diagnosis for patients with primary AA and GBM, and Fig. 1 the corresponding KM survival curves. Median survival from initial diagnosis was 76.5 months for AA and 14.3 months for GBM. GBM was associated with poorer prognosis compared to AA (chi2(1) = 11.93,p = 0.001). Even though GBM was associated with a much poorer prognosis than AA initially, patients with GBM surviving at least 49 months had generally a good prognosis. Seventy-three percent of patients with AA survived beyond 36 months. Twenty-eight percent of patients with GBM survived beyond 24 months and 25% beyond 36 months. Of the 7 patients with primary GBM who survived to 60 months, none died subsequently within the observation period of each of those patients.

Recurrent tumour patients

Fig. 2 shows the estimated probability of survival from the time of repeat surgery for recurrent tumour by tumour grade. The corresponding data is also represented in Table 3. Median survival from

Table 2 Primary tumour: Kaplan Meier estimate of survival from initial radiological diagnosis, by tumour grade

Time t (months)	Number of patients	Number of deaths	Survivor Function	Standard Error	95% Confidence Interval	
AA						
0	0	0	1.00	–	–	–
12	28	3	0.90	0.055	0.721	0.967
24	26	2	0.83	0.068	0.645	0.927
36	23	3	0.73	0.081	0.537	0.857
48	20	3	0.63	0.088	0.437	0.778
60	20	0	0.63	0.088	0.437	0.778
72	18	2	0.57	0.091	0.373	0.721
84	15	2	0.50	0.092	0.308	0.659
96	12	1	0.46	0.092	0.277	0.626
108	12	0	0.46	0.092	0.277	0.626
120	12	0	0.46	0.092	0.277	0.626
180	4	3	0.30	0.100	0.124	0.495
300	0	0	–	–	–	–
GBM						
0	0	0	1.00	–	–	–
12	18	14	0.54	0.091	0.345	0.693
24	10	8	0.28	0.081	0.140	0.445
36	9	1	0.25	0.078	0.118	0.411
48	9	0	0.25	0.078	0.118	0.411
60	8	1	0.22	0.074	0.097	0.376
72	7	0	0.22	0.074	0.097	0.376
84	6	0	0.22	0.074	0.097	0.376
96	6	0	0.22	0.074	0.097	0.376
108	6	0	0.22	0.074	0.097	0.358
120	6	0	0.22	0.074	0.097	0.358
180	4	0	0.22	0.074	0.097	0.358
300	1	0	–	–	–	–

Note: Survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

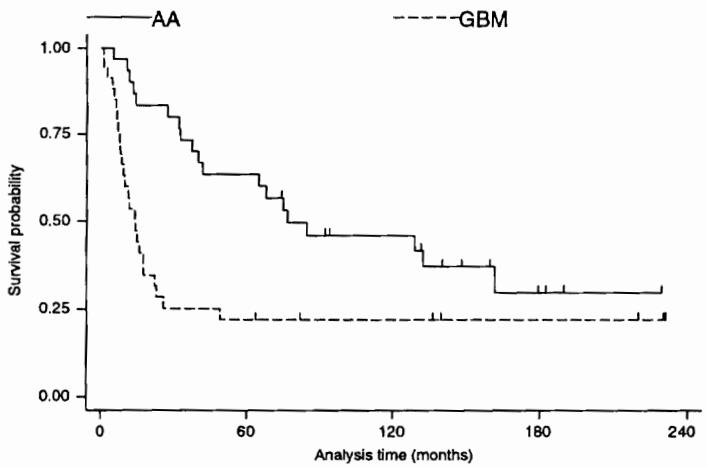

Fig. 1 Primary tumour: Kaplan Meier estimates of survival from initial radiological diagnosis, by tumour grade.

the time of repeat surgery was 66.6 months for AA and 14.9 months for GBM.

Sixty-one percent of patients with recurrent AA survived longer than 24 months and 57% beyond 36 months. Forty-one percent of patients with recurrent GBM survived beyond 24 months and 37% beyond 36 months following repeat surgery. Of 75 patients who had surgery for recurrent tumour, 18 are known to have survived for at least 10 years following surgery for recurrent tumour. The true prognosis may be better still, given that the duration of follow-up varied widely in this group. Patients with a recurrent GBM also had a poorer prognosis compared to recurrent AA patients (ie) survival from the time of repeat surgery. Although GBM patients had a poorer prognosis overall when compared to AA patients, the statistical evidence was weaker for the recurrent patients when compared to the primary tumour counterparts (GBM versus AA - chi2(1) = 2.84,$p = 0.092$). The effect of grade was not constant over time for AA and GBM tumour types and was therefore not expressed as a hazard ratio.

There were no direct serious complications from the PDT in this study, although one patient died from acute myocardial infarction 15 days post-operatively and another suffered a hemiplegia after resection of the medial temporal lobe GBM. Three patients had increasing drowsiness and hemiparesis associated with marked cerebral oedema despite conventional doses of steroid. In each of these patients, the clinical features resolved with increasing the dose of steroid therapy and use of diuretics.

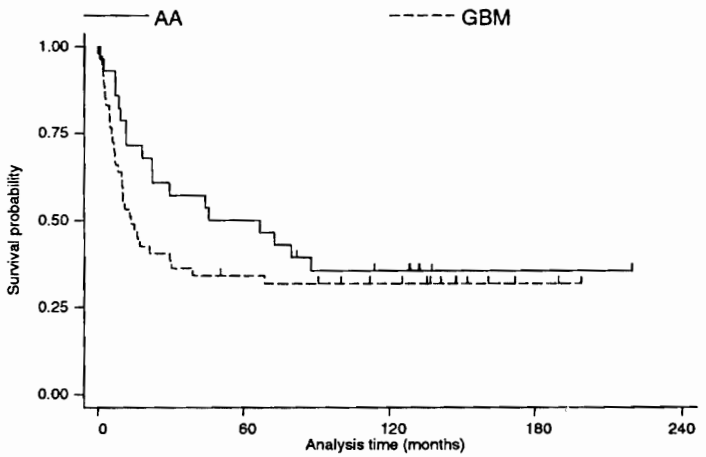

Fig. 2 Recurrent tumour: Kaplan Meier estimates of survival from repeat surgery, by tumour grade.

Table 3 Recurrent tumour: Kaplan Meier estimate of survival from repeat surgery, by tumour grade

Time t (months)	Number of patients	Number of deaths	Survivor Function	Standard Error	95% Confidence Interval	
AA						
0	0	0	1.00	–	–	–
12	28	8	0.71	0.085	0.509	0.846
24	26	3	0.61	0.092	0.404	0.760
36	23	1	0.57	0.094	0.371	0.730
48	20	2	0.50	0.095	0.306	0.666
60	20	0	0.50	0.095	0.306	0.666
72	18	1	0.46	0.094	0.276	0.633
84	15	2	0.39	0.092	0.217	0.565
96	12	1	0.35	0.091	0.185	0.527
108	12	0	0.35	0.091	0.185	0.527
120	12	0	0.35	0.091	0.185	0.527
180	4	0	0.35	0.091	0.185	0.527
300	0	0	–	–	–	–
GBM						
0	0	0	1.00	–	–	–
12	18	22	0.53	0.073	0.381	0.662
24	10	6	0.40	0.072	0.265	0.539
36	9	2	0.36	0.070	0.228	0.497
48	9	1	0.34	0.069	0.210	0.475
60	8	0	0.34	0.069	0.210	0.475
72	7	1	0.32	0.068	0.191	0.452
84	6	0	0.32	0.068	0.191	0.452
96	6	0	0.32	0.068	0.191	0.452
108	6	0	0.32	0.068	0.191	0.452
120	6	0	0.32	0.068	0.191	0.452
180	4	0	0.32	0.068	0.191	0.452
300	1	0	–	–	–	–

Note: Survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

Age at diagnosis

The distribution of the age of the patients at the time of diagnosis is shown in Fig. 3. Patients with AA were generally younger at the time of diagnosis compared to those with GBM. Median age at diagnosis for AA patients was 35 years (range 15-61 years) and 44 years for GBM (range 17-76 years) (two-sample t test: $p < 0.001$). Older age at diagnosis was associated with poorer prognosis (HR = 1.25 per 10 years of age [1.05,1.49], $p = 0.010$). This effect was independent of tumour grade and primary/recurrent tumour. Age was categorized according to the median value (40 years) in order to illustrate graphically the effect of age on survival (Fig. 4).

Laser light dose

Laser light dose values ranged from 60 to 260 J/cm^2 (Fig. 5). Approximately 62% of patients were treated with 220 J/cm^2, 27% between 150 and 220 J/cm^2 and the remaining 11% below 150 J/cm^2. Fig. 6 illustrates the effect of laser light dose relative to the median value of 230 J/cm^2 within each tumour grade. Among patients with primary tumour, light dose of 230 J/cm^2 or higher was associated with better prognosis (HR = 0.502[0.266,0.943], $p = 0.033$). In patients with recurrent tumour, there was only weak evidence for a light dose effect (HR = 0.747[0.424,1.316], $p = 0.312$) (Table 4).

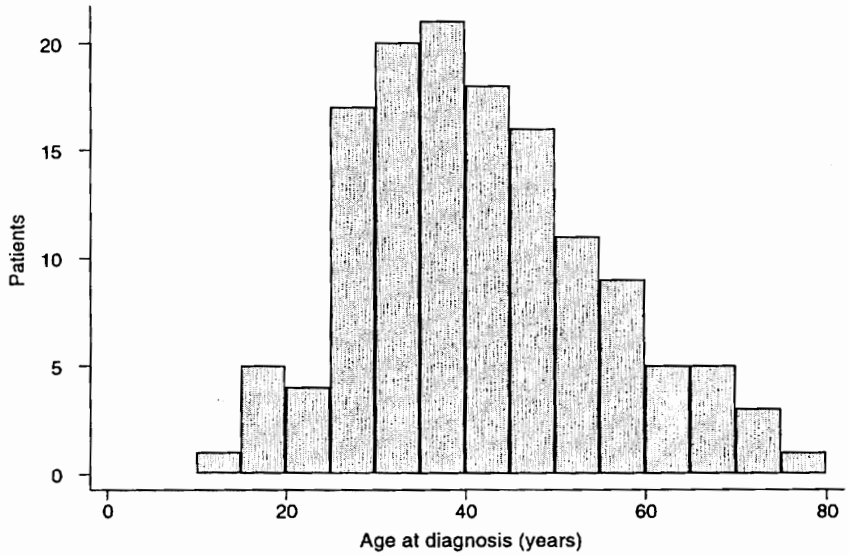

Fig. 3 Age of patients at the time of diagnosis (n = 136).

There was an overall tendency toward higher laser light doses among patients treated within the last 15 years. This may be attributable to the higher and more stable power output from the GMVL and KTP lasers. Hence it is possible that some of the apparent effect on survival of laser light dose may be due to confounding by other prognostic factors (eg: surgical technique, post-operative care) which changed over the period of this study.

Laser devices

There were three laser devices used over the study period; ARDL (15 treatments), GMVL (67 treatments) and KTP (63 treatments). The KTP laser was used almost exclusively after 1994. Controlling for light dose, there was no evidence to indicate that any particular device was associated with better prognosis (HR = 0.69[0.38,1.27], $p = 0.234$).

Tumour location

Tumour were classified as 'frontal' or 'other' for the purpose of exploring any potential relationship between tumour location and prognosis. Based upon this classification, frontal tumour location did not appear to be prognostic (HR = 1.14[0.75,1.75], $p = 0.540$).

Gender

There was no evidence of a relationship between gender and prognosis (male vs female: HR = 0.99[0.65,1.52], $p = 0.963$).

Chemotherapy

Twenty-nine percent of all patients received chemotherapy. There was no association between the use of chemotherapy and prognosis following PDT (primary tumour patients: chi2(1) = 0.04, $p = 0.852$); recurrent tumour patients: chi2(1)2.58, $p = 0.108$).

DISCUSSION

Malignant gliomas are invasive tumours and are difficult to control with conventional treatments. The poor prognosis is due to the complex biology of the tumour and in particular, the widespread invasion of the tumour cells into the adjacent brain. Over 80% of the tumours are known to recur locally despite conventional treatments and consequently, any improvement in local control may result in improved survival.

PDT is a form of local treatment which can be used as an adjuvant therapy to conventional methods in the treatment of malignant glioma. It is based upon the selective accumulation of photosensitizer in tumour tissue followed by the subsequent activation of the photosensitizer by laser light of a specific wavelength causing the destruction of the tumour cells by the production of by-products such as singlet oxygen. The combination of a selective photosensitizer and tissue penetrating laser light provides for considerable potential in the treatment of the cancer cells that invade through the brain. Maximal surgical resection, radiotherapy or chemotherapy have been the standard of care, but the majority of malignant gliomas recur generally within 2 cm of the original tumour location[20] and only a very small minority of patients achieve long term survival.[21]

In 1978, Walker et al. published the landmark study showing that the median survival time for high grade glioma was less than 12 months for treatment with surgery, radiotherapy and chemotherapy.[22] Neoadjuvant applications including the use of post-operative chemotherapy before radiation therapy have been investigated as a multi-modal approach to brain tumours (Table 5). Phase I-II and randomised phase III studies investigating the role of chemotherapeutic drugs in treating malignant glioblastomas have yielded survival times similar to the results originally reported by Walker.[22]

The reported 5-year survival rate with standard therapies for patients with GBM has remained at best 4-5% for the last 25-30 years[23–27] and tumour registries in Canada and Sweden have suggested that the long-term survival rate may in fact be lower at less than 3%.[28,29] The Neuro-Oncology Service at the University of San Francisco has reported their results using radiation therapy and chemotherapy in the treatment of high grade gliomas[6–8] with a 1 year survival of 44% reduced to 6% for 3 years and 0% for 5 years for surgery with radiation therapy. They reported improved survival when adjuvant chemotherapy was added to the treatment regime. In the European Organisation for Research and Treatment

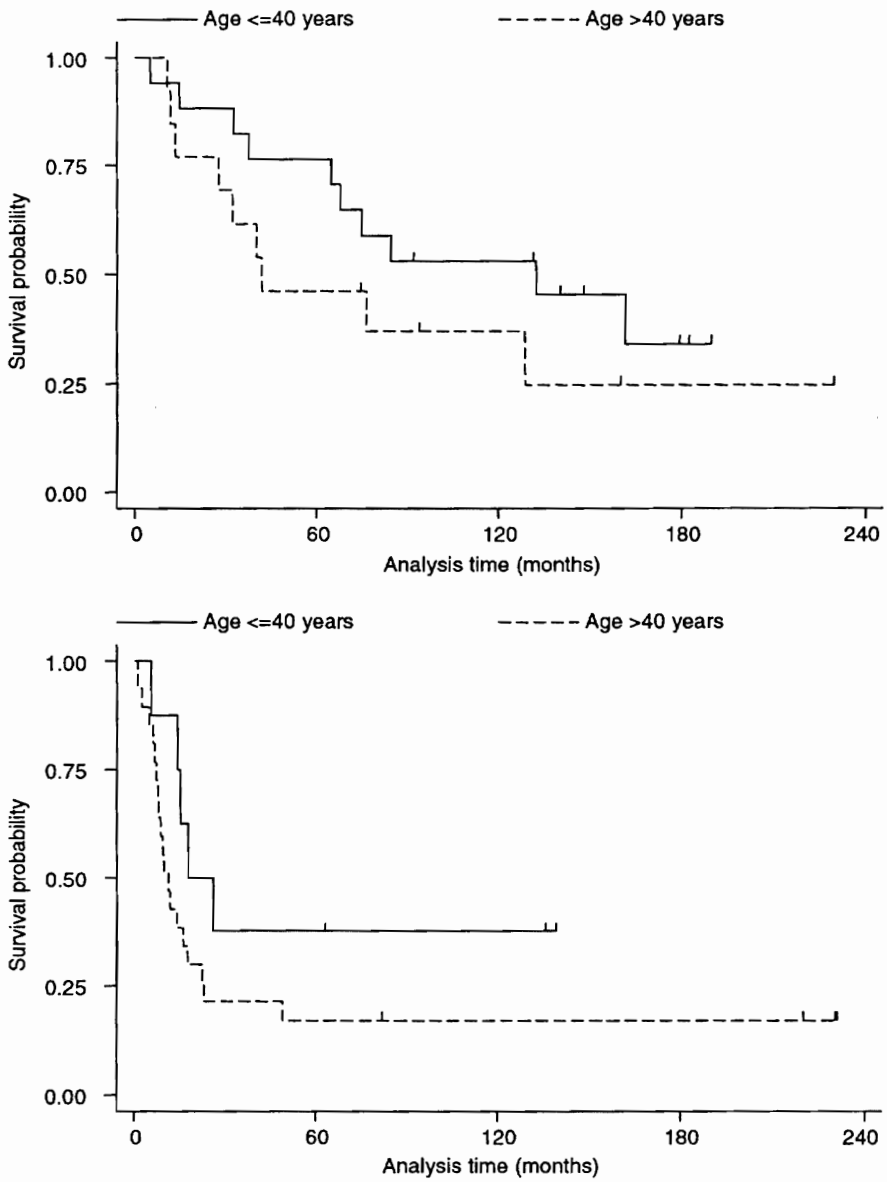

Fig. 4 Primary tumour: Kaplan Meier estimates of survival from initial radiological diagnosis, by age group (AA – upper panel; GBM – lower panel).

of Cancer Brain Tumour randomised trial for patients with malignant gliomas, the median survival of patients receiving radiation therapy and/or dibromodulcitol and BCNU was 13.0 months versus 10.4 months for radiation therapy alone.[9]

Our study demonstrates that previous or subsequent chemotherapy did not appear to be a significant prognostic factor when combined with PDT. This was also demonstrated by Wong et al.[30] who reported 322 patients with recurrent GBM using a 'salvage' treatment dichotomy when patients with fewer than three prior surgeries or chemotherapies had a similar response regardless of the actual number of treatment sessions. In general, the use of adjuvant treatments such as chemotherapy and immunotherapy have been very disappointing with only modest increases in median survival time or undesirable side effects.[31–38]

There are two potentially useful measures of survival. These are: (i) survival from the time of initial radiological diagnosis and (ii) survival from the time of surgery. Most of the patients in this study with primary (newly diagnosed) tumour had surgery within a few weeks of initial radiological diagnosis. Consequently, when measured from the time of surgery (rather than from initial diagnosis), median survival for patients with primary tumour was correspondingly shorter, although HR estimates were almost identical for each definition of survival. For primary AA, median survival from the time of surgery was 76.5 months and for primary GBM 14.3 months. For primary patients, we have presented KM survival curves showing survival from the time of diagnosis. Among patients with recurrent tumour, the interval between initial diagnosis and repeat surgery varied widely (median 20.9 months). Survival was calculated from the time of repeat surgery in this group. Survival estimates are likely to be more accurate when obtained separately for primary and recurrent tumour patients.

In an earlier study, we reported on the median survival of 120 patients that had undergone PDT at the Royal Melbourne Hospital.[10] Using a historical control group of 100 patients with GBM

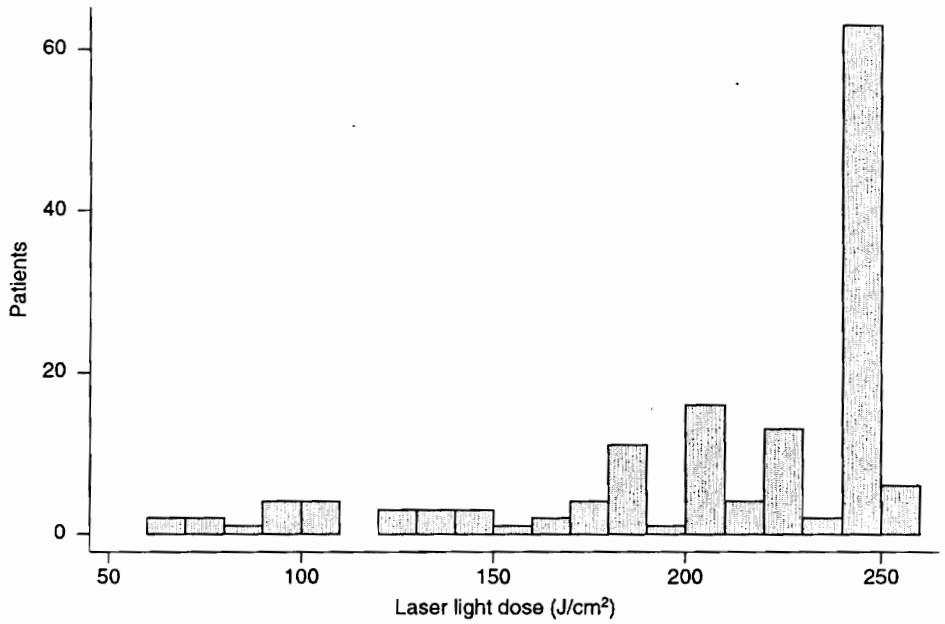

Fig. 5 Laser light dose distribution of patients enrolled in study.

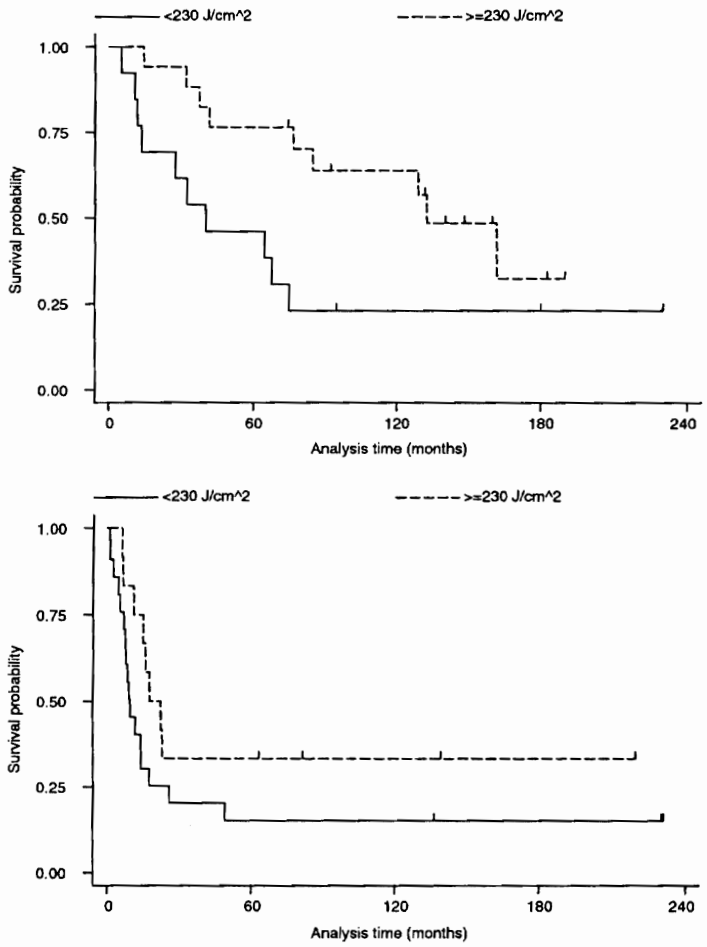

Fig. 6 Primary tumour: Kaplan Meier estimates of survival from initial radiological diagnosis, by laser light dose. AA – upper panel; GBM – lower panel.

Table 4 Prognostic variables tested using a Cox Proportional Hazard model

	Hazard Ratio	95% Confidence Interval		P value
Age at Diagnosis	1.25	1.055	1.484	0.010
Light dose >= 230 J/cm^2(Primary Patients)	0.50	0.266	0.947	0.033
Light Dose >= 230 J/cm^2(Recurrent Patients)	0.75	0.424	1.316	0.312
Male Gender	0.99	0.645	1.520	0.963
Tumour Location (Frontal versus others)	1.14	0.746	1.751	0.540
Laser Type (KTP Laserscope versus others)	0.69	0.380	1.267	0.234

Note: Primary/Recurrent tumours and grade (AA/GBM) were included as stratification variables.

Table 5 Phase I/II and randomised Phase III chemotherapy/radiotherapy trials – GBM survival times

	Trial Stage	Number of patients	Therapy	Median Survival time (months)
DeAngelis et al, 1998[49]	Phase III	203	Radiotherapy alone	8.5
		185	Radiotherapy + chemotherapy	11.5
Levin et al, 2000[50]	Phase III	134	Radiotherapy + chemotherapy	13.3
		138	Radiotherapy + chemotherapy	14.2
Prados et al, 2001[51]	Phase III	57	Radiotherapy fractionated alone	10
		58	Radiotherapy	9.2
		57	Radiotherapy fractionated + chemotherapy	10.5
		59	Radiotherapy + chemotherapy	11
Fisher et al, 2001[52]	Phase I/II	47	Radiotherapy + chemotherapy	9.7
Jeremic et al, 2001[53]	Phase I/II	61	Radiotherapy + chemotherapy	11
Gilbert et al, 2000[54]	Phase I/II	47	Radiotherapy + chemotherapy	9.3
Coughlin et al, 2000[55]	Phase I/II	107	Radiotherapy + chemotherapy	10
Groves et al, 1999[56]	Phase I/II	88	Radiotherapy + chemotherapy	12.5
Fountzilas et al, 1999[57]	Phase I/II	39	Radiotherapy + chemotherapy	10.7
Lassen et al, 1999[58]	Phase II	29	Radiotherapy + chemotherapy	11.4

from the Royal Melbourne Hospital, the median survival time was 8 months with no survivors beyond 3 years.[10] The data in the current study shows a median survival of approximately 14.3 months for the 31 primary GBM patients. It is encouraging that 22% of primary GBM patients survived beyond 60 months given that the Central Brain Tumour Registry of the United States showed that greater than 90% of GBM patients are deceased at 2 years after initial diagnosis.[39]

Age was observed to be a prognostic factor in this study as in many others, with older age at diagnosis generally associated with a poorer prognosis. Fig. 4 shows the effect of age on estimated survival time that was categorized according to the median value of 40 years. For patients with an AA, there is approximately a 90 month difference in the median survival of patients when categorized above or below the median value of 40 years. This is also evident for GBM patients although the difference has been reduced to 5 months for this group of patients. The effect of age on survival has also been shown in a large number of cooperative trials carried out in the United States.[40–46]

An analysis has been conducted by Kostron et al.[47] of 12 primary GBM patients who were treated with a variety of first generation porphyrin based photosensitizers (HpD, Photosan-3 and Photofrin). The same series also treated 39 recurrent GBM patients (25 of which were first recurrences). The median survival time for these patients was 9 months. It must also be noted that the median time from initial surgery to first recurrence in these patients (without any other adjuvant treatment) was 7 months. Our current results show that the median survival for a recurrent GBM patient is approximately 14.9 months from the time of the PDT treatment at repeat surgery with 37% of recurrent GBM patients surviving beyond 36 months.

Muller and Wilson[48] also investigated the effect of PDT on the survival of a series of 50 patients with newly diagnosed GBM. The median survival of the patients was 6.6 months. When the patients were categorized according to a total light dose of 1700 J, the patients that underwent PDT treatment at doses greater than 1700 J had an overall increased median survival of 9.2 months when compared to patients who received below 1700 J. A similar trend was observed in our current study where there was a better prognosis associated with an increase in the total light dose greater than or equal to the median of 230 J/cm^2 for all primary tumours (Fig. 6).

The potential complications of PDT include cerebral oedema and skin photosensitization. Two patients in our series had excessive sunburn related to sensitization, and in both cases, the patients disobeyed the written instructions to avoid excessive exposure to harsh sunlight. The standard instructions include gradual exposure to sun three weeks following the treatment, the use of protective clothing and protective sunscreens.

Cerebral oedema has been reported as a clinical complication of photodynamic therapy despite the use of pre-operative steroids,[48] although in our experience, it can be readily controlled with steroid therapy. Although the patients in our series received higher doses of light exposure compared to other reports, the incidence of serious cerebral oedema seems to be less than in other series. This could be due to a more radical resection of the tumour mass that not only leaves more space for cerebral oedema but also might result in a smaller number of residual tumour cells that will be affected by the PDT treatment. It is presumably the necrosis of the residual tumour cells that is responsible at least in part, for the development of oedema following the therapy.

The basic aspect of brain tumour biology that continues to hamper therapies is the process of tumour cell invasion into surrounding normal brain well away from the main tumour mass. Photosensitizers have been shown to localize in these infiltrating cells as well as the main tumour mass. Therefore strategies must be developed to create photosensitizers that are actively taken up by tumour cells, but activated by light of a longer wavelength that will result in greater tissue penetration and consequently

destruction of the infiltrating tumour cell further from the main tumour mass. Alternatively, photosensitizers that can possibly be utilized in a 'dual-mode' approach such as PDT and boron neutron capture therapy might be advantageous. It has been shown that porphyrin based photosensitizers containing boron cages can localize to tumour cells[59] and therefore an adjuvant combination treatment of PDT followed by boron neutron capture therapy may assist in the eradication of tumour cells that have migrated into surrounding normal brain away from the surgical resection margin.

The prognosis of the patients treated with PDT is encouraging given that the median survival for GBM patients is usually less than one year and long term survival is rare. We have previously reported a reasonable survival outcome for GBM patients when examining the effect of HpD uptake on survival.[60] The primary aim of this study was to assess survival of all patients who had PDT at RMH during the period 1986-2000. The study sample includes a smaller sub-group of patients for whom HpD tissue uptake data was available and which we described in the previous paper.[60]

We have estimated survival separately for patients with primary and recurrent tumour and defined survival in terms of survival from repeat surgery in the recurrent group, on the assumption that selection for repeat surgery is conditional upon a variety of complex factors. Therefore survival estimates in this group of patients with recurrent tumour apply to a specific reference population (ie) patients with recurrent tumour deemed suitable for repeat surgery, which may differ between sites and over time.

The investigation of other prognostic factors other than HpD uptake as presented in the current study still show promising results, even though they are limited to a study from one institution. As this is an evolving adjuvant therapy, it is difficult to amalgamate results from various institutions due to variations in protocols and the photosensitizer used. Nonetheless, it could be surmised from the data in this study that PDT of primary and recurrent gliomas can, in general, result in an increase in the median survival for the patient. It is encouraging that 24% of primary GBM patients survived beyond 60 months from the initial radiological diagnosis. In the future, laboratory and clinical studies should be devoted to the development of new photosensitizers, possibly in conjunction with the use of molecular biological analysis of the tumor or other therapies with a view to utilizing multiple adjuvant therapies that will have the maximal effect on the residual tumour following resection.

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