research article

Glioblastoma in patients over 70 years of age

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Background. Glioblastoma has in last 20 years seen the steady increase of incidence, which is most prominent in the group of older patients. These older than 70 years have significantly poorer prognosis than other patients and are considered a distinct group of glioblastoma patients. Modified prognostic factors are being used in these patients and this information is lately supplemented with the genetic and epigenetic information on tumour. The therapy is now often tailored accordingly. The aim of our study was to analyse the current treatment of the glioblastoma patients over 70 years of age to determine the impact of clinical prognostic factors.

Patients and methods. Among patients treated at the Institute of Oncology Ljubljana between 1997 and 2015, we found that 207 were older than 70 years. We analysed their survival, clinical prognostic factors (age, performance status) treatment modalities (extent of surgery, radiation dose, chemotherapy).

Results. Median survival of patients older than 70 years was 5.3 months which was statistically significant inferior to the survival of younger patients ($p < 0.001$). The clinical prognostic factors that influenced survival the most were performance status ($p < 0.001$), extent of surgical resection ($p < 0.001$), addition of temozolomide ($p < 0.001$) and addition of radiotherapy ($p = 0.006$). Patients receiving concomitant radiochemotherapy with temozolomide followed by adjuvant temozolomide, had same median survival as patients receiving adjuvant temozolomide after completion of radiotherapy.

Conclusions. The increase of the number of older patients with glioblastoma corresponds to the increase in the life expectancy but in Slovenia also to the increased availability of diagnostic procedures. Clinical prognostic markers are helpful in decision on the aggressiveness of treatment. Radiotherapy and temozolomide have the biggest impact on survival, but the radiotherapy dose seems to be of secondary importance. In selected patients, chemotherapy alone might be sufficient to achieve an optimal effect. Patients that were fitter, had more aggressive surgery, and received temozolomide fared the best. The scheduling of the temozolomide seems to have limited impact on survival as in our study, there was no difference weather patients received temozolomide concomitant with radiotherapy or after the radiotherapy. Thus far, our findings corroborate the usefulness of recursive partitioning analysis (RPA) classes in clinical decisions.

Key words: glioblastoma; age group over 70 years; elderly; prognostic factors; treatment

Introduction

Glioblastoma is the most common primary brain tumour. And while it accounts in Slovenia only for around 1.5 % of all tumours, it is also responsible for 2.5 % of cancer related deaths. The incidence of glioblastoma is slowly increasing, but marked increase of the incidence in the older population; especially in the over 70 year of age has been noted.[1-7]

Unlikely many other tumours, the natural history of glioblastoma is also changing with the age of the patients. While prognosis in the patients under 50 is relatively favourable, with significant portion of the patients living past 2 years after the diagnosis, quite opposite is true for those over 70. In this

group, the median survival is well under a year, and it has not changed significantly in recent times. Along with the improved knowledge of the molecular and genetic characteristic of the glioblastoma, which show that the majority of tumours in elderly belong to the so called primary glioblastoma subgroup, with the characteristic mutation profile, and short disease history. These tumours are characterized on the genetic level by the mutation of *EGFR*, *Rb2*, and amplification of *MDM2*, gain in chromosome 7 and *LoH* of chromosome 10.[8-10]

Patients with these tumours have short history between the onset of the first symptoms and the situation leading to the diagnosis. Quite often, for some time, the patient's mental deterioration is being assigned to other conditions and only quick deterioration in the period of some weeks is the signal prompting the start of diagnostic process.[11]

The treatment of the elderly patients is in many aspects identical to the treatment of other glioblastoma patients[12], with the exemption, that since many of them are co-morbid and in poorer performance status as the younger ones, there is some reluctance in offering them all treatment modalities. Accordingly, fewer patients have gross total removal of the tumour, and fewer are receiving chemotherapy. Nevertheless, they are not a single homogeneous group. Though age is being recognized as a single most important factor in survival of glioblastoma patients, the glioblastoma peak incidence in the 6th decade of life, lead for a considerable time to neglect regarding the influence of the patients age in the oldest category. So Radiation Therapy Oncology Group (RTOG) has introduced the most widely used classification of glioblastoma patients using the already recognized clinical parameters, dividing them into groups based on age under or over 50, performance status, surgery, radiotherapy dose level and mental status.[13,14] This, so called recursive partitioning analysis (RPA) classification has proved to be a useful tool in predicting prognosis of the patients and also a tool to help clinician deciding upon the treatment offered to the patient. This classification though has a major drawback, not differentiating the patients in the oldest age group. Therefore RPA analysis regarding only patients over 70 has been made. It has proved that these patients also fall into four distinct groups regarding survival.[14] In this analysis, the main focus has been given to the extent of resection, dividing the patients on the basis of surgical resection versus the biopsy into two distinct groups. The group where reception has been performed has been divided further on the basis of the patients' age (1 < 75.5; 2 >75.5) and the biopsy group regarding the performance status (3 ≥ Karnofskyperformance status [KPS] 70; 4 < KPS 70). The patient, which had a resection and were younger than 75.5 years, don't fare worse than the patients in group 5 of RTOG RPA analysis, but other fare worse, especially those biopsied and in poor performance status.

As the incidence of the glioblastoma in elderly has risen, the interest in these patients has grown and two large studies, NOA 08 in Germany and Nordic in Scandinavia, had shown that there is a chance, that the same effect on survival might be achieved with less aggressive approach.[15,16] The results of these studies had proven that in elderly, the same survival benefit might be achieved solely with the chemotherapy using temozolomide. The effect of temozolomide is primarily marked in patients, which have methylated methylguaninemethyltransferase (MGMT) promoter region, thus disabling the tumour cells to repair the alkylation of tumour DNA.

In Slovenia, we are also noting the increase of the number of elderly glioblastoma patients.[5,6] Our strategy so far has been to assign patients either to radical treatment with radiochemotherapy with adjuvant temozolomide, palliative radiotherapy or supportive care. Since the methylation status in patients over 70, is now routinely determined, and the patients are now being offered treatment also on the basis of it, we have analysed our results of the past years, with the aim of obtaining our population data, so that it could serve as a benchmark for assessment of the further treatment strategies in this group of patients.

Patients and methods

Between the 1997 and the end of 2015, 1019 patients, diagnosed with glioblastoma have been referred to the Institute of Oncology Ljubljana. They represent the majority of the patients who were diagnosed with the glioblastoma in Slovenia in this time period. The only exceptions are the patients that have died or were not fit enough for referral.

Among these patients, we have searched for those, which were older than 70 years at the time of diagnosis. For these, we calculated their survival, compared it to the survival of the younger patients and then made the analysis of the survival and patients and treatment relating factors. We also determined RPA classes for those older than 70 according to classes described by Scott *et al*.[14]

TABLE 1. Patients' and treatment characteristics

Age (median) (SD)	73 years 3.7 years
Gender Female Male	 99 (47.8%) 108 (52.2%)
Surgery	
No Biopsy	5 (2.5%) 69 (33.3%)
Reduction	96 (46.4%)
Gross total resection	37 (17.9%)
Performance status WHO	
0	3 (1.5%)
I	53 (25.6%)
II	65 (31.4%)
III	70 (33.8%)
IV	16 (7.7%)
Radiotherapy	158 (76.3%)
> 50 Gy	57 (27.5%)
40–50 Gy	33 (15.9%)
≤ 40 Gy	68 (32.8%)
Temozolomide	62 (30.0%)

SD = standard deviation

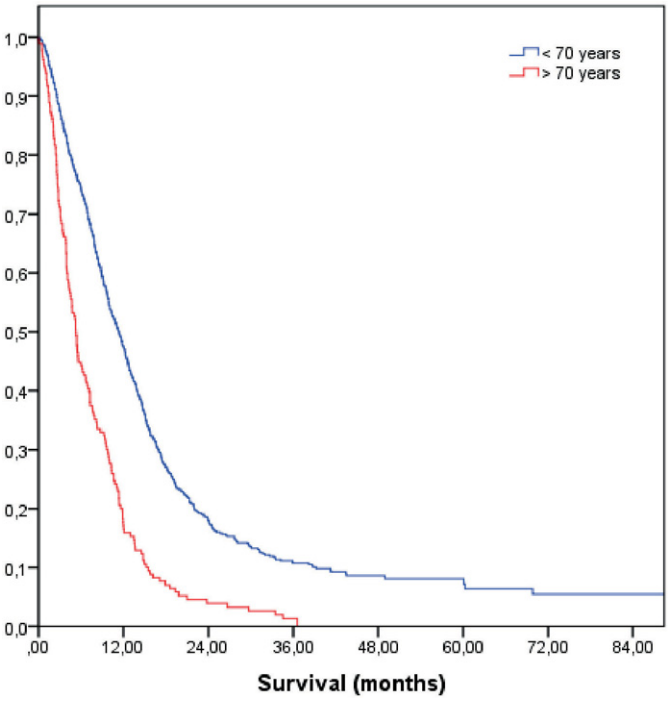

FIGURE 1. Survival of patients with glioblastoma according to the age below and over 70).

For the statistical analysis we used SPSS software package. We calculated demographic characteristics, frequencies of patients in the corresponding RPA groups, changes of frequencies during the analysed period and the frequencies of treatment characteristics. We used Kaplan-Maier analysis and Cox regression for survival analysis. We also performed a multivariate analysis using R. The significance level was at 0.05 for all statistics.

Ethical considerations

The study is retrospective analysis. It is a spinoff of an earlier analysis, which was approved by the Commission for Medical Ethics of the Republic of Slovenia.

Results

The median age of 1019 patients, treated for glioblastoma at the Institute of the Oncology Ljubljana between 1997 and 2015, was 60 years (standard deviation [SD] 11.8 years; min. 18 years, max. 86 years) (Table 1). Their overall survival was 10 months (SD 0.4 months). Of these patients, 207 were older than 70 years, and their median survival was 5.3 months

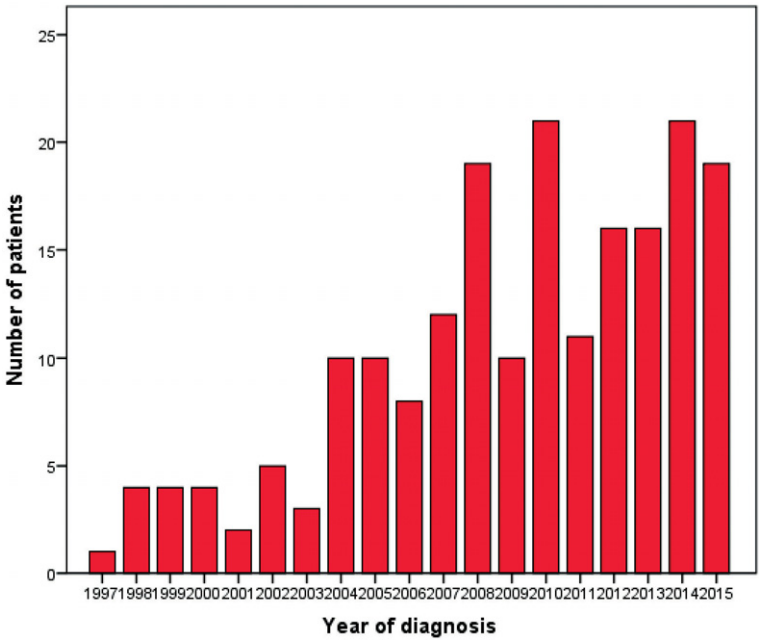

FIGURE 2. The number of patients older than 70 from 1997 to 2015).

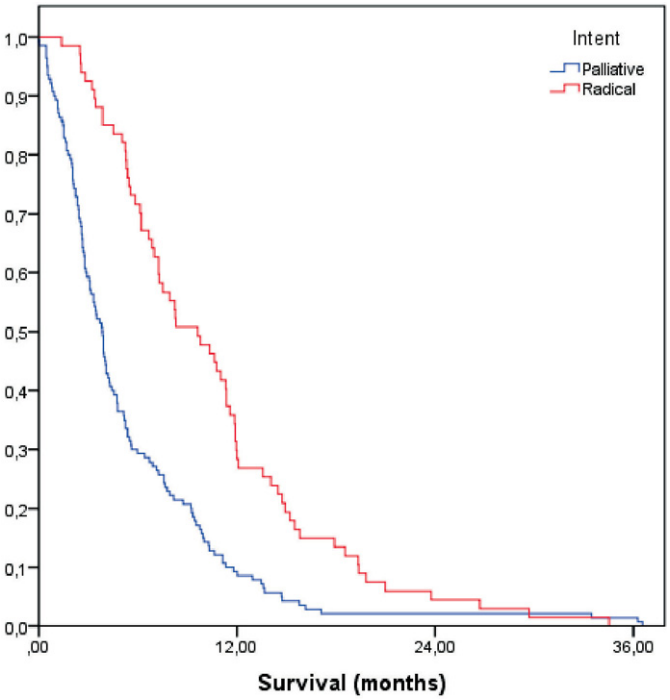

FIGURE 3. Survival of glioblastoma patients older than 70 according to intent of treatment.

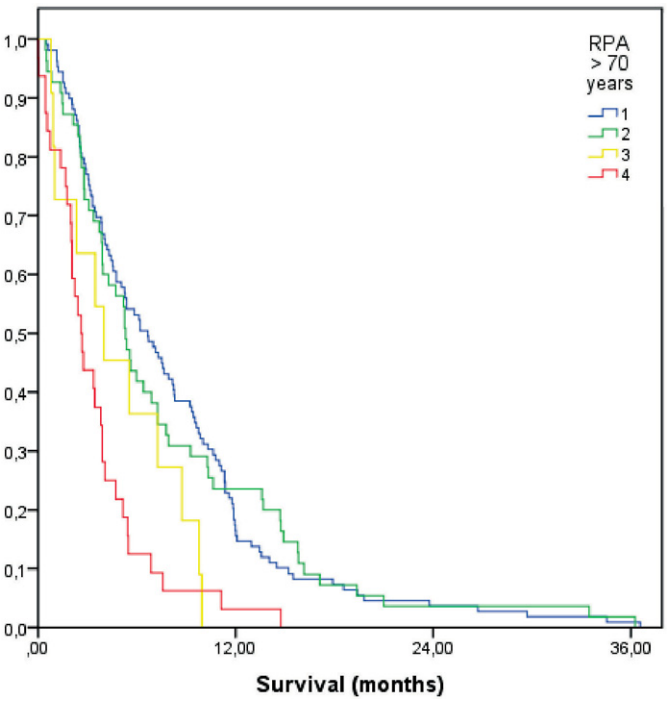

FIGURE 4. Survival of glioblastoma patients older than 70 according to prognostic recursive partitioning analysis (RPA) classes.

(SD 0.4 months). When comparing the groups of the patients younger than 70 with those older, the difference in median survival between groups was statistically significant at $p < 0.001$, with median survival of those younger than 70 years 12 months (SD 0.5 months) (Figure 1).

The number of patients older than 70 has increased over the observed years (Figure 2). The percent has risen from less than 10% in 1997 to more than 20% since the middle of 2000s.

Of the 207 patients older than 70 years, 99 were females and 108 males (1 : 1.1). The majority of whom had a surgical resection (69 gross total resections and 96 reductions), while less had biopsy only. For 5 patients, multidisciplinary team (MDT) decided, that any kind of surgical intervention would be too risky, so the diagnosis was decided upon radiological criteria. Except for this group, in which patients were somewhat older, the groups were identical regarding age and performance status.

The usual treatment following surgery was radiotherapy, 158 (76.3%) of patients were irradiated. Of those, who were not, majority were in poor performance status (WHO 3 and 4), some refused any further treatment and couple of them deteriorated rapidly. Only 2 of them received chemotherapy with temozolomide instead of radiotherapy.

Of the 207 patients, 67 were deemed suitable for "radical" treatment, and they proceeded with conventional radiochemotherapy 60 Gy in 30 fractions in 6 weeks with concomitant temozolomide, followed by adjuvant temozolomide. Others received either radiotherapy alone, radiotherapy followed by temozolomide, lower dose radiotherapy (45 Gy) with temozolomide or supportive care.

While overall survival for the group was 5 months, the median survival of those treated with radical intent was significantly higher (9.6 months, SD 1.5; $p < 0.001$) (Figure 3).

Also, the patients in good performance status fared better, from 8 months for the patients in WHO performance status 1 to 1.5 months for patients in performance status of 4 ($p < 0.001$).

Extent of surgical resection also proved to have a significant impact on survival. When neurosurgeon described a gross total resection, median survival was 7.1 months, in reduction 5.2 and in patients with the biopsy only 2.8 months ($p < 0.001$).

While patients over 70 fare worse than younger, the age does not seem to have such an impact in this group.

RPA classes were calculated, based on age, performance status and extent of surgical resection.

The survival was as predicted best in those with resection and younger than 75.5 years and worst for patients with biopsy in poor performance status ($p < 0.001$) (Figure 4).

We also looked in the impact treatment modalities have on survival. Patients receiving radiotherapy had a better survival, 6.1 months with radiotherapy and 3 months without ($p = 0.006$). And so is true for the addition of temozolomide with 10.4 months with the temozolomide and 3.8 without ($p < 0.001$). However, it seems, that concomitant temozolomide is no better than other schedules, as the survival remains the same, (10.3 and 10.6 months respectively, $p = 0.64$) in patients receiving concomitant temozolomide followed by adjuvant and adjuvant only.

In multivariate analysis, the significant impact on survival is retained by extent of operation ($p < 0.001$, HR 1.5 for biopsy), performance status ($p < 0.006$, hazard ratio [HR] 1.2 for WHO performance status > 1), and temozolomide ($p < 0.001$ HR 0.6 for temozolomide).

Discussion

In the last decade, we are observing a surge in the number of glioblastomas in the elderly population. This is being observed worldwide, and we demonstrated it for Slovenia. In our analysis, the rise is seemingly greater than in other reports. The rise is surely coming from the fact that the lifespan has extended considerably from the old threescore and ten. In Slovenia in the observed period, the life expectancy was 74.6 years in 1997, but in the 2015 it was 81.1 years.[17] The other thing, we can assume could be responsible for the increase we are observing is the availability of diagnostic procedures for instance according to Organisation for Economic Cooperation and Development (OECD) data, the number of CT scanners in Slovenia has risen from 18 in 2004 to 28 in 2016, and this can be seen also in the number of MRI scanners (2004–2010; 2016–2017)[18], thus diagnosis has become much more affordable. Admittedly, the direct proof of the later is lacking, but it is a plausible hypothesis.

In the analysis, we have shown that the median survival is worse for the elderly patients. But the therapeutic nihilism is ill warranted[19], as with the appropriate treatment we can at least approach the median survival of some patients to the median survival of those in more favourable groups. The impact of good surgery in elderly is marked[20], so it is the impact of radiotherapy and chemotherapy, the key is probably to tailor the postoperative therapy to individual patients. After surgery, all patients deserve a good radiotherapy if they are fit to receive it; more questionable is this approach in those which were only biopsied, or even had a diagnosis of malignant glioma established only by radiology. But even in those, some kind of palliative radiotherapy might result in better symptom control.[21] Data, which has been published has shown, that there has been no significant detrimental effect of radiotherapy on cognitive status[22], but the tests used have only limited sensitivity for more subtle changes. In the period we are describing, routine MGMT methylation testing haven't been performed in Slovenia[23], so the impact of alkylating agents is harder to determine, but the inclusion of temozolomide in treatment schedule, has resulted in improved median survival even in unknown methylation status.

Interesting find was that the patients receiving concomitant chemoradiotherapy and adjuvant chemotherapy had identical survival to those receiving radiotherapy followed by adjuvant temozolomide. This may be due to the fact, that more fragile patients haven't been exposed to such aggressive treatment, which might produce detrimental effect, but had benefited from systemic therapy as the performance improved. Of course, with the routine MGMT methylation assessment, with which we have started in 2016, group benefiting the most from temozolomide might be singled out, so we will not be giving the potentially non effective therapy to frail, while we will be able to avoid radiotherapy in those, where chemotherapy alone would suffice for the best palliative effect.

Conclusions

Glioblastoma is becoming ever more important problem in the population of patients aged over 70 years. While we are not able to cure these patients, we are able at least in the portion of them to prolong the survival and ameliorate the symptoms. The means we have at disposal towards this goal are essentially the same as the means we are utilising in the younger patients, the poorer performance status, arising not only due to the tumour related factors, but also due to the patients' comorbidity in elderly patients is forcing us to use them right. Up until now, the clinical prognostic factors have been our sole tool, with which we have accomplished our goals with a measure of success. The epigenetic and possibly even genetic

markers will hopefully improve our decision making capabilities and maybe improve the lot of some of these patients.

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