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# Radiotherapy of the brain in elderly patients

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Despite the growing number of elderly patients currently receiving radiotherapy little is known about the side-effects and outcome of radiation in this group of population. Several retrospective studies indicate that outcome of elderly patients with cancer regarding local control and survival is comparable to younger patients, with the exception of aged patients with rectal carcinoma and high grade glioma which is perhaps caused by the less aggressive combined modality treatment given to these patients.

The incidence of primary malignant brain tumours and mortality amongst the elderly in developed countries have increased dramatically during the last 3 decades [1,2]. Some authors suggested that the gene pool of surviving 75 year old individuals in 1994 is different from the gene pool of surviving 75 year old individuals in 1900 indicating genetic factors are involved in the pathogenesis of primary brain tumours, the aggregate surviving gene pool of an ageing population cohort is important [3]. The relationship between age and outcome may, in part, reflect the greater proliferative potential of malignant glioma in older patients [4].

The role of radiotherapy, for patients with malignant gliomas, after whatever the type and extent of surgery, radical resection, partial resection or biopsy, is a recognised and unquestioned treatment, well established in randomised trials during the late 1970s [5,6]. Age, as well as histology, performance status scored by the Karnofsky performance scale (KPS) and extent of surgery, is one of the established prognostic factors [7–9].

When we evaluate the outcome of aged patients in clinical trials, we find a specific problem in relation to age; as age of 65 years often represents a cut-off point for clinical trials. Furthermore, the majority of studies regard age as a split prognostic factor for analysis at the age of 50 years. An analysis of 1578 patients accrued from three successive Radiotherapy Oncology Group (RTOG) trials, with a top age limit of eligibility of 70 years, concluded that age under or over 50 years was the most important factor that distinguished patients with malignant glioma [7]. So elderly patients are not specifically approached. Most reports available consider the value of surgery and radiotherapy to be of questionable benefit, although resection plus radiation doubles the mean length of postoperative survival [10]. Some studies have analysed the outcome of elderly patients with conventional treatment [11], pointing out that elderly patients with good performance status when treated with maximal resection and radiation have longer survival than those treated with a palliative intent with radiation therapy and biopsy, suggesting that intensive or radical treatment in this subset of population should be considered. Others reported that increasing age and poor neurological condition predict poor survival [12].

High grade gliomas are amongst the most devastating malignancies with few useful treatment options. Radiotherapy remains the most effective treatment modality in high grade glioma. Modem radiotherapy techniques to spare normal brain tissue when treating a tumour with a margin according to magnetic resonance imaging (MRI) image or computer tomography (CT) scan offers a survival benefit, and in patients without extreme functional impairment the quality of life is good. Future studies in the treatment of central nervous system (CNS) tumours should include full evaluation of the patient functional status [13]. Patients with brain tumours have multiple functional disorders affecting mobility, communication, cognitive function and per-

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sonality. Severely disabled patients with a low KPS, independently of age, have a poor prognosis. Performance status is a good prognostic indicator even in the elderly, but probably elderly patients should be analysed separately, as they seem to have worse outcome when compared with patients who can be placed in published RTOG classifications [11]. The relationship between age and outcome may in part reflect a greater proliferative potential of malignant gliomas in older patients [4].

Gross total resection is a desirable goal if it can be done safely. The indication of radical treatment in the elderly should take into account their performance status. Age *per se* is seldom a contraindication for radiotherapy and according to the available data in literature there is no indication for a total dose reduction because of age, especially in curative setting.

Brain metastases are frequent manifestations of widespread cancer disease. The development of brain metastases is associated with a considerable morbidity [14] and abrupt deterioration of quality of life. Neurological symptoms involve loss of mental and physical abilities which make it difficult for patients and families. Without treatment the course is progressive neurological impairment with a median survival of 1–2 months [15]. A vast majority of these patients receive whole-brain therapy as part of their treatment and, therefore, this patient population represent one of the largest groups of patients managed with radiotherapy. The goals of therapy have been to limit the amount of time committed to therapy to maximise the quality of life. Standard recommendation for the majority of patients is 3 Gy in 10 fractions with response rate of 50–75%, and with a median survival of 3–6 months.

## 1. Late effects of radiotherapy

Three neurological syndromes are associated with radiation therapy: an increase in neurological deficit during treatment, probably caused by oedema which promptly responds to steroids, a subacute postirradiation syndrome presenting from 1 to 3 months after completion of treatment which is usually reversible; and a radiation-induced cerebral necrosis. The latter is a progressive syndrome which begins several months to several years after treatment resulting from direct damage to the brain and blood vessels that may be fatal [16]. CNS system toxicity is related to size fraction, total dose and volume, other factors that influence the expression of irradiation damage include agents such as chemotherapy, surgery and concurrent pathological processes, such as the presence of tumour [18]. Effects of radiotherapy on normal tissue are especially dependent on the size of the fraction used. De Angelis [17] reported results from 79 patients who had complete resection of a single cerebral metastasis followed by whole-brain irradiation. 38 out of 79 patients survived for 1 year or more, and 4 of them developed severe dementia with ataxia and incontinence. All had received size fractions of 5 or 6 Gy and total doses of between 30 and 39 Gy. None of the patients with fraction size of 3 Gy or less developed these problems. Although there is not definitive evidence at this time to suggest that for brain metastases the standard whole-brain radiotherapy schedule of 30 Gy in 10 fractions over 2 weeks represents an unacceptable risk for late radiation injury, some authors [18] consider it prudent to use smaller fraction sizes in elderly patients, if radiation is combined with chemotherapy and in any patient expected to be a long-term survivor. The response of malignant gliomas to radiation is limited by their extraordinary radioresistance. The sensitivity of the surrounding functional and normal brain receives the same amount of radiation as the tumour, limiting the dose that can be safely delivered to 60 Gy and when delivering total doses close to normal tissue tolerance it is recommended to avoid fractions greater than 2 Gy.

## 2. Clinical experience

All the authors agree that cerebral radiation injury is a dose-limiting complication that occurs to some degree in all irradiated patients. The clinical and radiological features are dependent on the radiation dose and schedule but also on many other factors such as previous general condition, status of the malignant disease, long-term tobacco use, paraneoplastic syndromes, micrometastases, previous surgery and neurotoxicity of anticancer drugs [16]. These factors sometimes have been erroneously attributed to irradiation [19]. Descriptions of the neurological condition of patients before radiotherapy are rarely given. So it is difficult to obtain definitive conclusions from reported retrospective studies.

In the last 10 years, a number of original papers and reviews of radiotherapy of the brain have been published. Nevertheless, there is no randomised study comparing therapeutic results and toxicity in elderly patients versus in younger patients. In general, the studies published consisted of retrospective analysis of the survival results, treatment tolerance and main toxicity in five groups of patients: brain primary tumours; postoperative whole-irradiation for metastasis; palliative whole-brain irradiation for metastases; primary cerebral lymphoma; and prophylactic cerebral irradiation in small-cell lung cancer after complete response to chemotherapy (Table 1).

In these studies, the analysis of therapeutical results and toxicity according to the age of the patients has been a coincidental observation and not the main topic studied. The cut-off in the age subgroups ranges from 40 to 81 year old patients. The radiation dose and the given

Table 1
Studies reporting survival results or toxicity following radiotherapy of the brain according to the age of patients

| Study [Ref.] | Tumour | *n* patients | Dose (Gy)/ fractions | Age (years) analysed | Improved survival | Group of age (years) with toxicity | Neuropsychological problems |
|---|---|---|---|---|---|---|---|
| Stylopoulos [20] | Glioma | 31 | 60 | >40<br><40 | Long survivors | >40 | Leucoencephalopathy |
| DeAngelis [21] | Lymphoma | 31 | 40+1.4 | | Yes | >60 with chemotherapy | Dementia, ataxia 9.7% with chemotherapy |
| Curran [7] | Glioma | 1578 | | <50<br>⩾50 | Yes in <50 | | |
| Meckling [12] | Glioma | 103 | 49/35 | 70–74<br>75–79<br>⩾80 | Yes in <80 | ⩾80 | 15% worsened |
| Abrey [22] | Lymphoma | 31 | 36–50.4 | <50<br>⩾50 | Yes in <50 | >60 | In 1/3 of patients |
| Villá [23] | Glioma | 85 | 54–66 | 65–70<br>71–81 | Yes in <70 | | Yes, 1/2 of patients did not comply with full therapy |
| Pirzkall [24] | Metastases | 236 | 20–35 | >50<br>⩽50 | Yes in ⩽50 | | Yes, 18% of patients temporary |
| Hao [25] | Lymphoma | 50 | 42/24 | >65<br>⩽65 | Yes in ⩽65 | | |
| Fonseca [26] | Lung prophylactic | 35 | 32/16 | All | | 64 median (range: 57–69) | Leucoencephalopathy Still with small dosage |
| Brada [27] | Glioma | 211 | 55/30 | ⩾55<br><55 | Yes in <55 | | 16% of patients deterioration |
| Legerwaard [28] | Metastases | 1292 | 30/10 | 17–59<br>60–69<br>⩾70 | Yes in 17–59 | >70 less survival | |
| Aupérin [29] | Lung prophylactic Meta-analysis | 755 | 8–40 | <55<br>55–64<br>>64 | Yes, >5.4% at 3 years | | |

fractions were very different depending on the tumour being treated. The median follow-up time was different according to the prognosis of the primary tumour. The survival results were compared with others published in medical literature reports. Lymphoma patients and prophylactic cerebral irradiation in small cell lung cancer patients have longer survival. In these patients late effects of radiation could be assessed.

Aupérin and colleagues reported the results of a meta-analysis on 987 patients with small cell lung cancer in complete remission who took part in seven trials that compared prophylactic cranial irradiation with no prophylactic cranial irradiation [29]. They found a 5.4% increase in the rate of survival at 3 years (15.3% in the control group versus 20.7% in the treatment group). Prophylactic cranial irradiation also increased the rate of disease-free survival and decreased the cumulative incidence of brain metastasis. Longer doses of radiation led to a further decrease in the risk of brain metastasis, according to an analysis of four total doses (8 Gy, 24 to 25 Gy, 30 Gy and 36 to 40 Gy) ($P$ for trend = 0.02), but the effect on survival did not differ significantly according to the dose. The median age of the patients was 59 years and were subgrouped for analysis in less than 55 years, 55 to 64 years and 65 years or older. When survival was analysed in these subgroup of patients no differences were observed. The improvement in overall survival and disease-free survival was evident. A negative influence due to the age of the patients could not be observed. Whether prophylactic cranial irradiation leads to neuropsychological sequelae could not be addressed in this meta-analysis, because neuropsychological evaluation was performed in only two trials [30,31].

Concomitant treatment with cytotoxic drugs has been suggested to have a negative effect on cognitive functions in these patients [19]. These results suggest that the age of patients has no definitive effect on radiation toxicity, nevertheless for some authors, it may be prudent to consider using smaller fraction sizes in elderly patients who have already received or who are expected to receive chemotherapy [16].

Our group analysed the effect of the intention to treat with radiotherapy in the survival of elderly patients with malignant gliomas [23]. We examined 85 consecutive patients with a diagnosis of malignant glioma. Age ranged from 65 to 81 years (median 70 years). Surgical treatment, including needle biopsy, was performed in 32 patients (37.6%). Median Karnofsky performance status was 60 (range: 30–100). Median survival time was 18.1 weeks. The univariate survival analysis showed that radiotherapy ($P$ = 0.0001), extent of surgical resection

($P = 0.03$), age ($P = 0.02$) and postoperative KPS ($P = 0.0003$) were significant prognostic variables. Nevertheless, in a multivariate analysis, only radiotherapy was significant independent variable (adjusted hazard ratio 9.1, 95% confidence interval 4.5–18.7). Patients older than 70 years of age did not receive radiotherapy regularly and had poorer survival in an univariate analysis [19].

Recently, we published a study on 400 patients to analyse age as a critical factor for complied oncological therapies [32]. 200 patients were aged over 70 years old and 200 aged under 70 years old. We observed that the percentage of patients who underwent oncological treatment was higher in the younger patients than in the older patients (87.5% versus 56%, $P < 0.001$). The main cause of therapeutic exclusion in both groups was poor performance status. Nevertheless, in the older group, other variables such as the presence of chronic disease and patient or relatives' wishes or doctors' opinions, influenced the decision for not giving specific treatment.

To conclude, we think that an upper age limit should not be used solely as a discriminatory factor for a reduction or a suppression of radiotherapy of the brain. The expected increase of cancer patients amongst older people in the coming decades means that age should not be considered independently as a factor for oncological management. Nevertheless, it is important to determine which subset of older patients will or will not benefit from brain irradiation.

## 3. Conclusions

The elderly population is continually increasing and thus, the need for cancer care and oncological treatment for the elderly is likely to grow. Radiotherapy on the brain is a standard therapy for patients with cerebral primary lymphoma, glioma or brain metastases as well as for prevention of brain metastasis after complete response to chemotherapy in small cell lung cancer. Injury to normal brain as a complication of cerebral radiation therapy is related to total dose, dose fraction and volume. Long-term survival in patients treated with radiation, and the use of new non-invasive imaging technology, has increased the diagnostic rate of late radiation effects. In elderly patients the decision to treat may be influenced by the belief that tolerance might be compromised. Nevertheless, the results reported in the last decade do not support an age limit to avoid this type of therapy. In general, they are retrospective studies, where age is analysed as a coincidental factor. Other factors such as performance status, chemotherapy or other concomitant chronic diseases are involved in survival and tolerance to radiation. We feel that the increase in the life expectancy of population has to induce the oncologist to determine possible sub-sets of elderly cancer patients that can benefit from potentially toxic therapies such as radiation of the brain.

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## 1. Introduction

Although brain radiotherapy is a necessary treatment to prolong life expectancy in patients with primary or metastatic brain tumours, it has damaging effects that are poorly understood, especially in elderly patients, and mostly detrimental to the patients' quality of life. Whilst several reports adequately document brain injury from brain radiation therapy, the full impact of the problem is still not completely clear because the quality of life and mental status of the survivors have received less attention than the actual survival. If the treatment of patients with glioblastoma is palliative, concern about the effects of radiotherapy for anaplastic astrocytoma or brain metastasis of a well stabilised extracranial tumour in elderly patients becomes meaningful and every effort must be made to understand and prevent the potentially devastating long-term sequelae of such treatment.

## 2. Adverse effects of radiotherapy of the brain

The standard treatment of patients with high grade gliomas is radiotherapy at the dosage of 1.8–2.0 Gy/day given 5 days a week up to 59.4–60 Gy [1]; this treatment, however, is not free of damaging effects, especially when administered on the whole brain.

According to the time of appearance, the adverse effects of radiation can be divided [2,3] into: (a) Acute reactions, which occur during radiotherapy, and are correlated with time-dose fractions. 200 rad fractions with a total dose of 60 Gy are usually tolerated, even if cortiocosteroids are often required. These acute effects are considered reversible. (b) Early delayed reactions, which can appear a few weeks to several months after radiotherapy; these are characterised by somnolence and lethargy which can persist up to 14 days, but these signs generally improve after 4 weeks and disappear in 6–8 weeks. The predominant pathological finding is a loss of myelin probably due to a lack of replacement of mature oligodendrocytes with their slow turnover [2]. This causes long-term memory processing deficits because hippocampal, thalamic and neocortical connections are very sensitive to white matter damage due to subacute demyelination [4]. Eldor and colleagues [5] found that early delayed radiation injury is characterised by vascular damage; the initial site of damage appears to be the endothelial cell lining of the vessel wall, with nuclear and cytoplasmic swelling and formation of mural thrombi; these changes later evolve into thickening of the basement membrane and tunica media, uncontrolled proliferation of endothelial cells, and formation of platelet and fibrin thrombi [6]. This can lead to a total obliteration of the lumen of small blood vessels. In larger blood vessels, radiation has been

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