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Pulsed Dose Rate and High Dose Rate Brachytherapy in treatment of malignant glioma recurrences – preliminary assessment

Brachyterapia PDR i HDR w leczeniu wznów złośliwych glejaków – doniesienie wstępne

INTRODUCTION

Primary brain tumors are in almost 50% high-grade gliomas in adults. Even with an aggressive approach combining surgery and external beam irradiation, the median survival of patients with glioblastomas and anaplastic astrocytoma usually does not exceed 9-12 months [9, 11, 13]. Most deaths are due to persistent or recurrent tumor at the primary site. Almost 90% of the failures occur within a distance smaller than or equal to 2 cm from the initial site of the tumor [4].

A dose response relationship has been demonstrated in malignant gliomas with an increase in the median survival time when the total dose reached 60 Gy using a conventional fractionation [9, 10, 13]. Teletherapy doses above 60 Gy have not generally yielded higher survival rates, perhaps because of the significant risk of radiation-induced brain necrosis at doses above 60 to 70 Gy .The limits in the use of higher doses is represented by the potential cerebral toxicity [11].

Unfortunately, there is still a very high local failure rate with conventional radiotherapy to 60 Gy.

The rationale for brachytherapy boost is thus to escalate the dose to the main tumor mass while limiting the dose to surrounding brain tissue, using external beam radiotherapy fields to cover tumor cells that may infiltrate beyond the edge of contrast enhancement visualized by computed tomography (CT) or magnetic resonance imaging (MRI) (3). In case of recurrence brachytherapy allow to give additional dose after previous teletherapy treatment.

Indications for brachytherapy are tumors with a maximum tumor diameter of 5 cm without involvement of the corpus callosum, without brain stem involvement, not in proximity with the motor trip. Primary malignant tumors, recurrent brain tumors, metastatic brain tumors and benign brain tumors have been considered for brachytherapy [7, 9, 10].

In the early 1980s, reports appeared in the literature, describing the use of brachytherapy. The technique as well as the dosimetry have improved with higher accuracy of the implant volume. Interstitial brachytherapy is delivered with temporally (high activity) or permanent (low activity) iodine 125 or with temporary iridium 192. Intracavitary brachytherapy is delivered using colloidal P^{32} or with Rh^{106}, these being beta emmiters.

The aim of this work is to present preliminary results of brachytherapy of patients with recurrent malignant gliomas previously treated surgically and irradiated, then reoperated.

MATERIAL AND METHODS

Between April 2000 and December 2000 17 patients with malignant gliomas that had recurred after surgery and conventional radiation were treated using Pulsed Dose Rate and High Dose Rate brachytherapy in Greatpoland Cancer Center. They were disqualified from radical treatment due to advanced clinical stage, prior surgical treatment and prior teletherapy.

Most of patients had bad performance status with Karnofsky score under 50 (n = 10). The age of the patients ranged from 38 to 69 years, average – 51,2 years. There were 8 males and 9 females. Most frequent histopatological type was glioblastoma multiforme (n = 11), 3 patients had anaplastic astrocytoma, 2 – astrocytoma gemistocyticum and 1 – glioma mixtum (oligoastrocytoma).

Eleven patients underwent brachytherapy after first recurrence, 6 patients after second recurrence. Dose received from earlier teletherapy ranged from 42 Gy to 60 Gy.

Before brachytherapy all patients were initially treated surgically to obtain a histopathologic diagnosis and to resect as much of the tumor as possible. This reduced significantly mass effect and steroid dependency. During surgery a single catheter was implanted into residual mass of the tumor. Computed tomography was performed throughout the target volume, scan were made every 5 mm.

Target volume usually contained residual mass of tumor with 1 cm margin.

Imaging information was transferred to the treatment planning computer via an information network. IBU and PLATO planning system were used.

For PDR brachytherapy Nucletron unit, for HDR brachytherapy Gammamed 12i unit – were used. In first case Iridium 192 with 1 Ci activity, in second case Iridium 192 with 10 Ci activity were used.

Patients were divided into two group treated with PDR and HDR brachytherapy. It was dependent on Karnofsky score and on chances for cooperation with patient.

Fourteen patients treated with PDR brachytherapy received doses from 4000 cGy to 5000 cGy, pulse of 80 cGy to 100 cGy every hour. Because of long treatment time dose was divided into two phases with one week interval between phases. In one case treatment was interrupted after first phase due to bad cooperation with patients.

Three patients treated with HDR brachytherapy received total dose of 3000 cGy, one fraction of 300 cGy given daily.

Clinical data are summarized in Table I.

Patients underwent 6 – months observation, control CT were made after 3rd and 6th month, physical examination were made every months.

Table I. Patients treated in Greatpoland Cancer Center (recurrence after surgical treatment)

Clinical data	Survival time < 6 months	Survival time > 6 months
1. Median age (51,2)		
< 51,2	4	3
> 51,2	3	7
2. Sex:		
Male (8)	3	5
Female (9)	4	5
3. Histopathology:		
glioblastoma multiforme (11)	5	6
anaplastic astrocytoma (3)	2	1
astrocytoma gemistocyticum (2)		2
glioma mixtum (oligodendrioglioma) (1)		1
4. Karnofsky score:		
< 50 (10)	6	4
60 (2)	1	1
70 (3)		3
90 (2)		2
5. Prior treatment:		
surgical + teletherapy (11)	3	8
surgical + teletherapy + surgical (6)	4	2
6. Brachytherapy:		
PDR (14)	6	8
HDR (3)	1	2

* - 2 patients died in 2nd months after brachytherapy because of staphylococcal leptomeningitis

RESULTS

In whole group of patients 10 survived longer then 6 months. 5 patient died in 2, 3, 4, 4, and 5th months of observation, all from group with bad performance status (Karnofsky score under 50). Two patients died in second months after brachytherapy because of staphylococcal leptomeningitis. In survived group 5 patients live in good performance status, the others have neurological disfunctions in different stadium. In CT and clinical examination we observe no recurrence of tumor after 6

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months of observation. Two patients live without recurrence longer then 12 months. Due to small group of patients we can"t conclude any statistically important correlations between clinical data.

DISCUSSION

Brachytherapy for recurrent malignant gliomas represents an increasing part of indications for brachytherapy in central nervous system tumors. Some studies have shown the efficacy of interstitial brachytherapy for selected patients. One of the largest experience has been reported by the University of San Francisco with 307 patients implanted for brain tumors, 43% of them being treated for a recurrence [11]. This included 66 adults with recurrent glioblastoma multiforme and 45 adults with recurrent high-grade astrocytoma. The median Karnofsky score at the time of brachytherapy was 90 (range 70 – 100) and the median patient age was 50 years in patients with recurrent glioblastoma and 38 years in those with recurrent anaplastic astrocytoma. The median brachytherapy dose was 64 Gy (range 46 – 129 Gy). The median survival time calculated from the date of the implant was 51 weeks for patients with glioblastoma and 53 weeks for patients with anaplastic astrocytoma, with 1- and 3-year survival probabilities of 48% and 14%, respectively, for glioblastoma and 54% and 23%, respectively, for astrocytoma. The reoperation rate was almost 56% in the two groups at a median interval of 36 weeks after brachytherapy. Survival was significantly prolonged in patients who underwent reoperation in comparison with those who did not. Table II summarized series reporting results of brachytherapy in the treatment of recurrent malignant gliomas, showing median survival times ranging from 7 to 18 months. Our 17 patients were treated with palliative aim. Six of them underwent three times surgical treatment, the rest two times, what should have influence on their survival chance.

Table II. Brachytherapy. Results for recurrent high-grade gliomas

Authors	Isotope	Patients, tumors	Karnofsky score (median)	Median survival (months)
1/ Bernstein et al.	I^{125}	18 MG	80	10
2/ Kumar et al.	Co^{60}	19 GM	ND	7
3/ Larson et al.	Au^{198}	13 GM/20 AA	„good"	9/17
4/ Lucas et al.	Ir^{192}	7 GM/13 AA	ND	10/11
5/ Malkin	I^{125}	24 GM/12 AA	73	10/10
6/ Matsumoto et al.	Ir^{192}	9 GM/14 AA	80	18/18
7/ Sneed et al.	I^{125}	66 GM/ 45 GM	90	12/12
8/ Willis et al.	I^{125}	4 GM/ 8 AA	80	18
9/ Zamorano et al.	I^{125}	23 MG	ND	10

MG – malignant glioma; GM – glioblastoma multiforme; AA – anaplastic astrocytoma; NGM – nonglioblastoma multiforme malignant glioma; ND – no data

It seems that patients treated surgically three times had worse prognosis for survival then others, but they tolerate brachytherapy relatively good. Ten patients (66,7%) survive for longer then 6 months after brachytherapy, some of them in good performance status.

Short time of observation doesn't allow to draw any radical conclusions. We think that after prior teletherapy brachytherapy is an important and only accessible (in some cases) treatment possibility for patient with recurrent malignant glioma.

CONCLUSIONS

1. Brachytherapy is applicable in patients with malignant glioma recurrence with good Karnofsky scores and well-circumscribed residual lesion after preceding reoperation.
2. Both (HDR and PDR) brachytherapy methods are good tolerated.
3. Brachytherapy could improve the survival and quality of life of patients with recurrent malignant gliomas.

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ABSTRACT

Purpose: The aim of this work was to analyze feasibility and preliminary results obtained with Pulsed Dose Rate and High Dose Rate brachytherapy of recurrent malignant gliomas.

Material and methods: Seventeen patients with recurrent brain tumor were treated using Pulsed Dose Rate and High Dose Rate brachytherapy from April 2000 to December 2000 in Greatpoland Cancer Center. They were qualified for brachytherapy due to advanced clinical stage, prior surgical treatment and prior teletherapy. The age of the patients ranged from 38 to 69 years, average – 51,2 years. There were 8 males and 9 females. Most frequent histopatological type was glioblastoma multiforme (n = 11). Eleven patients were underwent brachytherapy after first recurrence, 6 patients - after second recurrence. Fourteen patients treated with PDR brachytherapy received doses from 4000 cGy to 5000 cGy, pulse 80 cGy to 100 cGy every hour. Because of long treatment time dose was divided into two phase with one week interval between phases. Three patients treated with HDR brachytherapy received total dose of 3000 cGy, one fraction of 300 cGy was given daily.

Results: From whole group of patients 10 survived longer then 6 months. 5 patient died in 2,3,4,4, and 5 months of observation, all from group with bad performance status (Karnofsky score under 50). Two patients died in second months after brachytherapy because of staphylococcal leptomeningitis. In survived group 5 patients live in good performance status, the others have neurological disfunctions in different stadium. In CT and clinical examination we observe no recurrence of tumor after 6 months of observation. Two patients live without recurrence longer then 12 months. Due to small group of patients we can"t conclude any statistically important correlations between clinical data.

Conclusions: 1. Brachytherapy is applicable in patients with malignant glioma recurrence with good Karnofsky scores and well-circumscribed residual lesion after preceding reoperation.

2. Both (HDR and PDR) brachytherapy methods are good tolerated.

STRESZCZENIE

Cel pracy: analiza tolerancji leczenia oraz wstępnych wyników brachyterapii PDR (pulsacyjnej) i HDR (wysoką mocą dawki) wznów złośliwych glejaków mózgu.

Materiał i metody: siedemnastu chorych ze wznową złośliwego glejaka mózgu było leczenych metodą brachyterapii PDR i HDR w okresie od kwietnia 2000 do grudnia 2000 w Wielkopolskim Centrum Onkologii. Zostali zakwalifikowani do brachyterapii ze względu na przebyte poprzednio leczenie napromienianiem z zewnątrz oraz stan kliniczny. Wiek pacjentów sięgał od 38 do 69 lat, średnio – 51, 2 lata. Grupa obejmowała 8 mężczyzn i 9 kobiet. Najbardziej częstym typem histologicznym był glejak wielopostaciowy (n = 11). Jedenastu chorych zakwalifikowano do brachyterapii po pierwszym usunięciu wznowy, 6 – po drugim usunięciu wznowy. Czternastu chorych leczonych metodą PDR otrzymało dawkę łączną od 4000 cGy do 5000 cGy, wielkość impulsu - 80 cGy do 100 cGy co godzinę.

Z powodu długiego okresu leczenia dawkę podzielono na dwie fazy co tydzień. Trzech chorych leczonych metodą HDR otrzymało całkowitą dawkę 3000 cGy, dawka frakcyjna podawana raz dziennie wynosiła 300 cGy.

Wyniki: Dziesięciu chorych (66,7%) przeżyło ponad 6 miesięcy. Pięciu zmarło w 2, 3, 4, 4 i 5 miesiącu obserwacji, wszyscy z grupy w złym stanie ogólnym (wg skali Karnofsky'ego - poniżej 50). Dwaj pacjenci zmarli w drugim miesiącu po zakończeniu brachyterapii z powodu gronkowcowego zapalenie opon miękkich. Wśród żyjących chorych 5 żyje w dobrym stanie ogólnym, pozostali mają różnego stopnia neurologiczne zaburzenia. W badaniach tomografii komputerowej oraz klinicznych nie stwierdza się cech nawrotu choroby. Dwaj pacjenci żyją w dobrym stanie ponad 12 miesięcy. Niewielka grupa chorych oraz krótki czas obserwacji nie

pozwala na analizę statystycznie istotnych zależności pomiędzy danymi klinicznymi leczonych pacjentów.

Wnioski: 1. Brachyterapia może być alternatywną metodą leczenia chorych ze wznową złośliwego glejaka mózgu wcześniej leczonych napromienianiem z zewnątrz oraz z umiejscowioną pozostałością guza po resekcji

2. Obie metody brachyterapii (HDR i PDR) są dobre tolerowane przez chorych .