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천막 상부 저분화 성상세포종의 치료에 있어 방사선 치료의 역할

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= Abstract =

The Role of Radiotherapy in the Management of Supratentorial Low Grade Astrocytoma

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Purpose : To evaluate the role of radiotherapy in the management of incompletely resected supratentorial low grade astrocytoma with the analysis of the survival, the pattern of failure, and the prognostic variables affecting survival.

Material and methods : Between January 1990 and December 1995, fifty-one patients with supratentorial low grade astrocytoma received radiotherapy after subtotal resection(16 patients) or stereotactic biopsy(35 patients) at Asan Medical Center. External radiotherapy was done by conventional fractionation with the total dose of 4820cGy to 6000cGy(median 5580cGy) and partial brain volume. The follow-up was done from 6 to 79 months(median 48 months).

Results : Overall actuarial survival rate at 2 and 5 years were 83.4% and 54.8%, respectively. Progression free survival at 2 and 5 years were 67.4% and 48.7%, respectively. The significant prognostic factors affecting overall survival rate were the performance status, T stage, histologic subtype, radiation field and radiation response. The major pattern of failure was local failure, such as progressive disease and primary site recurrence in 23 patients (45.1%). Progression free survivors excluding 2 patients were physically and intellectually intact without major neurologic deficit.

Conclusion : Although the follow-up period of this study was relatively short, overall actuarial and progression free survival rate were encouraging. Patients with good performance status, lower T stage, pilocytic subtype, patients treated with small radiation field and radiation responder showed better survival. As the local failure was the major pattern of failure, the various efforts to decrease the local failure is necessary.

Key Words : Supratentorial low grade astrocytoma, Radiotherapy

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INTRODUCTION

Low grade astrocytomas constitute approximately 15% of brain tumors in adults and approximately 25% of brain tumors of children[1]. These tumors tend to occur in the first 4 decades of life and present insidiously, often with seizure that can predate any progressive neurologic deficit for years. Their optimum treatment and its timing remain controversial. Whether surgical intervention should be performed at time of diagnosis or at progressive neurological deterioration is still not completely elucidated. No prospective randomized study comparing adjuvant postoperative radiotherapy to the delayed radiotherapy at the time of progression or recurrence has been completed. So therapeutic recommendations are now based on the findings from a few retrospective studies which have been reported for this disease.

A number of retrospective studies have suggested a beneficial role of radiotherapy in low grade astrocytomas incompletely resected[2, 3, 4, 5]. These studies suffer from the difficulties inherent in retrospective analysis and we await the results of prospective study to determine the optimal treatment.

We have conducted a retrospective review for the patients treated with postoperative radiotherapy at Asan Medical Center from 1990 to 1995, in terms of the actuarial survival, progression free survival, pattern of failure, complication, quality of life and prognostic variables affecting the survival. This series was limited to patients with incompletely resected supratentorial low grade astrocytoma treated exclusively with uniform radiotherapy technique and megavoltage irradiation in one institution.

METHODS AND MATERIALS

1. Patients characteristics(Table 1)

Between Jan. 1990 and Dec. 1995, 51 patients with supratentorial low grade astrocytoma underwent surgery and postoperative radiotherapy at Asan Medical Center. There were 28 males and 23 females with the age range from 3 to 66 years (median age, 36 years), of whom 6 were under 18 years old. As for the Karnofsky performance status, 45 patients (88%) were≥80 and remaining 6 patients (12%) were<80. Headache was the most common presenting symptom and other symptoms were nausea and vomiting, seizure, motor or sensory deficit, visual disturbance, mentality change, cranial nerve involvement, and psychologic problem. The duration of symptom was from one to 120 months (median: 12 months). Twenty three patients (45%) had duration of symptom more than 1 year and the history of seizure was present in 33 patients (65%).

Location and T stage of primary tumor were determined by a review of the preoperative CT scan, MRI and operative records. The frontal and temporal lobe were most commonly involved. T stage by 1988 AJC staging system in decreasing order were T1 in 24 (48%), T3 in 14 (28%), T2 in 7 (14%), and T4 in 5 (10%). Enhancement on the preoperative CT scan or MRI after injection of intravenous contrast was present in 27 patients (53%) and cystic change was present in 11 patients (22%) and calcification was in 13 patients (25%).

2. Histopathology

All cases were histologically verified and pathology slides subsequently reviewed at Asan Medical Center. Histopathologic diagnosis was done by stereotactic biopsy alone in 35 patients (69%) and subtotal resection in 16 patients (31%). The distribution of histologic subtypes in this study population was as follows; pilocytic in 3 (6%), fibrillary in 42 (82%), protoplasmic in 3 (6%), gemistocytic in 2(4%), and unknown in 1 patient(2). Histopathologic grading basically followed the World Health Organization International Histological Classification of Tumors[6]. In this study, the distribution of the grade was as follows; grade I in 3 (6%) and grade II in 48 patients (94%) .

Table 1. Patients Characteristics with Supratentorial Low-Grade Astrocytoma(N=51)

	No. of patients(%)		No. of patients(%)
Age: 3-66 (median: 36 years)		T stage	
< 18	6(12)	T1	24(48)
18-40	31(61)	T2	7(14)
≥40	14(27)	T3	14(28)
Sex		T4	5(10)
Male	28(55)	recurrent	1(2)
Female	23(45)	Contrast enhancement	
KPS		Yes	27(53)
≥80	45(88)	No	24(47)
<80	6(12)	Cystic change	
Sx. duration		Yes	11(22)
<1 Y	28(55)	No	40(78)
≥1 Y	23(45)	Calcification	
Seizure		Yes	13(25)
Yes	33(65)	No	36(71)
No	18(35)	Unknown	2(4)
Neurologic deficit		Histologic type	
Yes	6(12)	Pilocytic	3(6)
No	45(88)	Fibrilary	42(82)
Tumor location		Protoplasmic	2(4)
Frontal lobe	24(47)	Gemistocytic	3(6)
Parietal lobe	9(17)	Unknown	1(2)
Temporal lobe	11(22)	Histologic grade	
Occipital lobe	1(2)	Grade I	3(6)
Others	6(12)	Grade II	48(94)
Operation		Radiation dose	
Subtotal resection	16(31)	<5600cGy	44(86)
Stereotactic Bx	35(69)	≥6500cGy	7(14)
		Radiation field	
		$<100cm^2$	27(53)
		$\geq 100cm^2$	24(47)

3. Postoperative radiotherapy

All 51 patients were treated with either 4, 6, and 10 MV X-ray. Radiation fields were partial brain volume in all patients and 27 patients were treated with field size $\geq 10 \times 10cm^2$. The total dose ranged from 4820 to 6000cGy (median dose 5,580 cGy) and 44 patients (86%) received a total dose of <5,600cGy.

Response evaluation was done at 1 to 3 months after completion of radiotherapy with follow-up CT scan or MRI. Complete response was defined as the disappearance of all clinical, radiologic evidence of tumor. Partial response was defined as 50% or greater decrease of tumor volume without the appearance of any new lesion. Stable disease was defined as less than 50% reduction, or no change in lesion size, or no increase in the size of any measured lesion. Progressive disease was defined as the increase in the size of lesion or the development of new lesions.

4. Survival analysis

Follow-up information was available on 49 patients (96%). The range of the follow-up time were from 6 to 79 months (median: 48 months).

Survival rate was calculated from initiation of therapy (operation or radiotherapy) to death from the tumor or time to progression (documented by operation and follow-up imaging study). The survival curves were constructed by the use of Kaplan-Meier analysis[7]. All data were analysed by Log-rank test[8] for individual prognostic factors that might influence survival. Multivariate analysis of survival was not attempted due to the limited size and number of deaths in this study.

RESULTS

1. Radiation response

The evaluation of the response was done in all 51 patients. Response was complete in 3 patients (6%), partial response in 14 patients (27%), stable disease in 28 patients (55%), and progressive disease in 6 patients (22%) (Table 2).

2. Survival and Prognostic Variables

Overall actuarial survival rate at 2 and 5 years were 83.4% and 54.8%, respectively. Progression free survival at 2 and 5 years were 67.4% and 48.7%, respectively(Fig 1).

Prognostic variables were examined for their possible association with actuarial survival. The following characteristics were associated with improved patient survival by univariate analysis ($P < 0.05$): KPS≥80 (Fig 2), lower T stage (Fig 3), pilocytic subtype (Fig 4), radiation field $< 10 \times 10 cm^2$

Table 2. Clinical Response after Radiotherapy (N=51)

Response	No. of patients(%)
Complete response	3 (6)
Partial response	14 (27)
Stable Disease	28 (55)
Progressive Disease	6 (12)

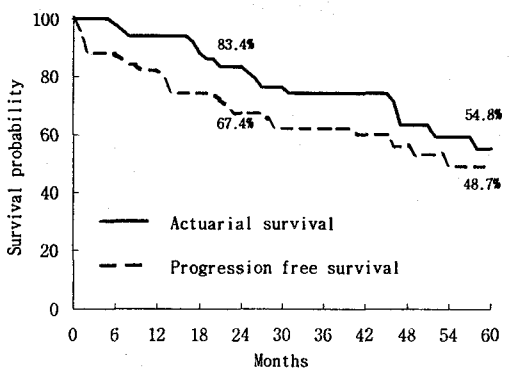

Fig. 1. The actuarial and progression free survival of all patients(N=51).

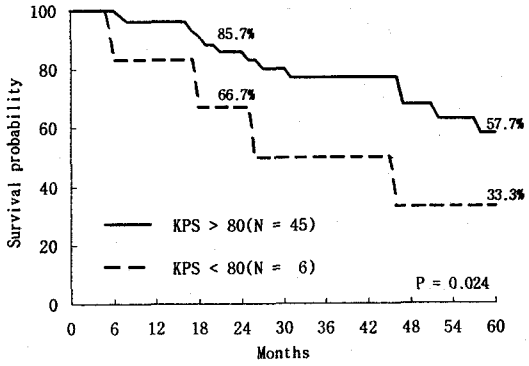

Fig. 2. The actuarial survival by Karnofsky performance status.

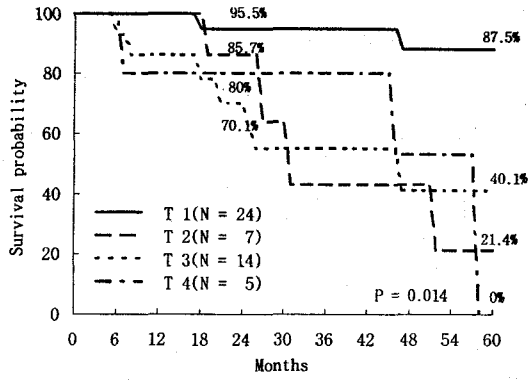

Fig. 3. The actuarial survival by T stage.

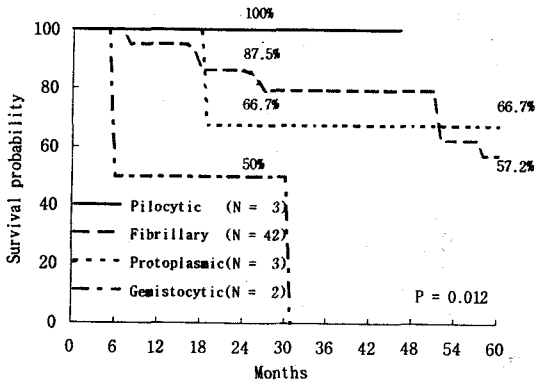

Fig. 4. The actuarial survival by histologic subtype.

(Fig 5), and better radiation response (Fig 6) (Table 3).

3. Patterns of failure and Quality of life

Thirty-three of 51 patients remained alive at the time of review, 5 with progressive disease (15 to 54 months, median 46 months), 28 without progression of disease (11 to 79 months, median 46 months). Eighteen patients died of disease (6 to 66 months, median 26 months).

Overall, 23 patient (45.1%) had treatment failure at primary tumor sites, based on both neurologic deterioration and progression of disease on CT or MRI or with subsequent tissue confirmation of recurrent tumor. Six patients showed progression of disease right after radiotherapy and remaining 17 patients showed local recurrence after 6 months of completion of radiotherapy. The median actuarial survival and progression free survival of these 23 patients were 31 and 14 months, respectively. The additional tissue was obtained from six patients due to suspected progression of disease based on the worsening of the neurologic sign and radiologic image between 7 and 49 months after treatment (4 with reoperation, 2 with stereotactic biopsy). Of whom, 4 patients showed a malignant transformation of tumors (2 Glioblastoma multiforme, 2 anaplastic astrocytoma) and 2 patients had a low grade tumor.

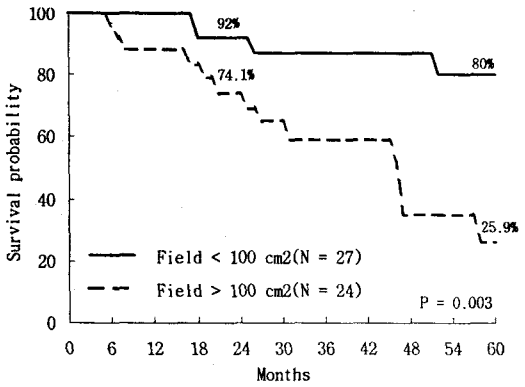

Fig. 5. The actuarial survival by radiation field.

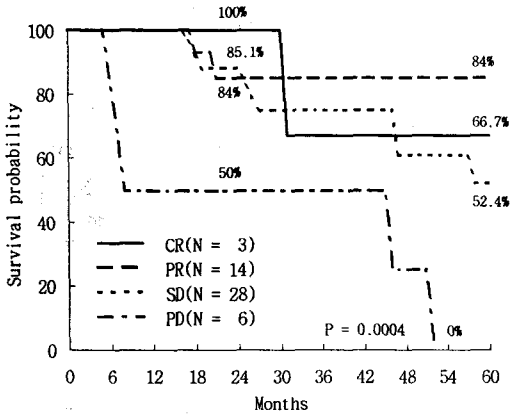

Fig. 6. The actuarial survival by radiation response.

Twenty-eight progression free survivors excluding 2 patients were all physically and intellectually intact without neurologic deficit. However one patient was in status of hemiplegia due to sequale of neurocysticercosis and another patient had right arm hemiparesis due to Moyamoya phenomenon with cerebral infarction. Half of progression free survivors were under anticonvulsants control. Seven patients had petit mal seizure. Three patients showed radiation induced complication; radiation necrosis in 1, white mater demyelination in 1, and Moyamoya phenomenon due to great vessel disease in 1. One patient with radiation necrosis at 4 months after completion of radiotherapy had been improved with conservative management.

DISCUSSION

The progressive increase in survival of patients with low grade astrocytoma over the past 60 years has been noted since initial reports documented median survival of 2 to 3 years[9]. Later series reported modest improvements of survival[2, 10]. The 5- year survival rate for low-grade astrocytomas, as determined from 1,366 patients included within 10 major studies performed between 1956 and 1985, was 48%[11]. The most recent studies have demonstrated improved survival. Vertosick et al[12] reported 68% of 5-year survival in 25 well-differentiated cerebral astrocytomas in adults treated between 1978 and

Table 3. Significance (P value) for the Prognostic Variable by Long-rank test

Variables	5YSR(%)	P value	Variables	5YSR(%)	P value
Age		0.379	Contrast enhancement		0.184
<18	83.3		Yes	42.3	
18-40	56.1		No	65.0	
≥40	30.6		Cystic change		0.772
Sex		0.846	Yes	51.1	
Male	49.3		No	56.1	
Female	74.9		Calcification		0.387
KPS		0.024	Yes	60.0	
≥80	57.7		No	54.3	
<80	33.3		Histologic type		0.012
Symptom duration		0.206	Pilocytic	100	
<1Y	42.6		Fibrillary	57.2	
≥1Y	66.7		Protoplasmic	66.7	
Neurologic deficit		0.262	Gemistocytic	0	
Yes	55.6		Histologic grade		0.314
No	60.4		Grade I	100	
Seizure		0.061	Grade II	53.3	
Yes	61.7		Extent of surgery		0.582
No	42.3		Subtotal resection	52.6	
Tumor location		0.742	Stereotactic Bx	67.1	
Frontal	37.6		Radiation dose		0.602
Parietal	61.0		<5600cGy	52.9	
Temporal	65.6		≥5600cGy	57.1	
Occipital	100		Radiation field		0.003
Others	66.7		$<100cm^2$	80.1	
T stage		0.014	$\geq 100cm^2$	25.9	
T1	87.5		Radiation response		0.004
T2	21.4		CR	66.7	
T3	40.9		PR	85.1	
T4	0		SD	52.4	
			PD	0	

5YSR: 5 year survival rate

1988. McCormack et al[13] reported 64% of 5-year survival in a study of 53 patients with adult low-grade astrocytoma treated between 1977 and 1988. The progressive increase in survival of patients with low grade astrocytoma could be attributed to better therapy (i.e., the advent of megavoltage radiotherapy, the introduction of oral corticosteroids, the development of better anesthesia, improved asepsis, the refinement of surgical techniques, general postoperative care, and availability of more effective anticonvulsant drugs). Also improvement in diagnostic accuracy by imaging studies has allowed earlier detection of lesion and management of lesion at neurologically more intact status.

The role of radiotherapy in the treatment of low grade supratentorial astrocytoma remains under considerable debate. Several retrospective series have reported a survival advantage to irradiation following incomplete resection[2, 3, 10, 18, 21]. The 5 year survival of patients with supratentorial low grade astrocytoma who underwent surgery alone was about 20%, and for with incompletely resected tumor patients who received postoperative radiotherapy, 5-year survival appeared to be about 50%. The 5-year survival rate of 54.8% in our institution was encouraging. However this result was poorer than that reported by the most recent series. It may be due to the fact that the more radically resected cases were not referred for radiotherapy and patients only treated with postoperative radiotherapy after subtotal resection or biopsy were included in our studies.

Several important prognostic variables have been identified. Favorable prognostic features include the following: young age, complete resec-

tion, lower histologic grade, low proliferative potential, and good performance status. Other features, such as long duration of symptom, history of seizure, lack of neurologic deficit, and cystic component of the tumor, have been suggested but not universally accepted as favorable prognostic factors[2, 3, 10, 13, 14, 15]. In our study, performance status, T stage, histologic subtype, radiation field, and radiation response were correlated with an increased survival.

Age is generally considered as a significant factor in predicting surviva[3, 15, 16]. However it did not seem to be prognostically important in our series; this could be partially explained by the absence of patients younger than 18 years (6 cases only), to whom the best prognosis is generally attributed[3]. The patients with good performance status showed better survival chance in our studies, which was similar to other studies[17]. History of seizure had been associated with higher survival, which may be related to earlier presentation and diagnosis. Law et al[3] also found seizures to be positively correlated with survival.

Patients with low T stage according to AJC staging had the better survival than those with high T stage in this study. North et al[18] reported that patients with involvement of more than one lobe had a significant short survival than patients with involvement of only one lobe. Our studies did show survival difference by histologic subtype. Three patients with pilocytic astrocytoma are all alive at 31, 36, 48 months. Generally pilocytic astrocytoma appears to have an excellent prognosis no matter how radical the surgical resection or what type of postoperative adjuvant therapy had been[19]. Gemistocytic subtype showed poorer survival than other subtype and all died of disease at 6 and 31 months. The clinical behavior of gemistocytic astrocytomas seems to have a high incidence of conversion into more malignant forms and thus worse prognosis than other low-grade astrocytomas[20]. This studies, in which the grade one tumors were few, did not show survival difference by histologic grade. Law et al[3] found no survival difference between grade I and grade II tumors. Leibel and associates[4], however, found a marked survival advantage for grade I over grade II tumors.

Gross total resection has been associated with improved patient survival[2, 3], but this has not been confirmed by others[15, 16, 21]. Shaw et al[25] reported that survival difference by the degree of surgical removal in ordinary astrocytoma was not significant. North et al[10] reported that patients who received radical or subtotal surgery had significantly better survival than those receiving biopsy only. Eyre et al[22] reported no significant survival difference between patients with partial resection, and those with biopsy only. In our study, there is no survival difference between subtotal resection group and biopsy only group in which the risk to malignant transformation of residual tumor cells still remains.

The optimal radiation dose and dose-response relationship for treating low-grade astrocytoma has yet to be defined. Rutten et al[24] reported that none of 9 patients with subtotally removed grade 2 astrocytomas who received >5,000cGy were long term survivors compared to 11 of 16 patients who received <5,000cGy. In contrast, in the 90 patients studied by Fazekas[2], a gradual improvement in local control was found at 20%, 56%, 69%, with equivalent doses of>850 ret, >1150 ret, >1450 ret, respectively. In a retrospective analysis of patients with low-grade ordinary astrocytomas and mixed oligoastrocytomas treated between 1960 and 1982 at Mayo Clinic[25], postoperative radiotherapy for patients receiving doses>5,300 cGy was significantly associated with higher survival rate than those receiving<5,300cGy or surgery alone. We found no dose response within this study group: however, the dose delivered fell into a relatively small range, with all but one patient receiving between 5000 and 6000cGy. Trials to define the optimal dose is currently being studied in three ongoing prospectively randomized studies (Mayo-NCCTG, EORTC, BTSG-RTOG). These studies compare moderate and high-dose localized radiation, with the hypothesis that higher doses will lead to better local control and survival.

Irradiation of whole brain was proposed in the era before computed tomography was available, on the basis of the impossibility of defining the tumor volume[26], but the result were similar[10] to or even poorer[16] than those after focal irradiation. Shaw et al[10] reported absence of survival difference between patients receiving partial brain and those receiving whole brain (with or without a partial brain boost) irradiation. The analysis of failure patterns in 20 of the 27 patients with treatment failures revealed all recurrences to be within the radiation portals. For these reasons, plus the potentially negative effect of whole brain radiation on intellectual function in glioma patients, localized brain irradiation is recommended. Radiation field larger than $100cm^2$ was related with poor survival in this study. It was probably due to that larger tumor had been treated with larger radiation field. Recently, Anthony et al[29] reported 11 local failure within primary site in 46 patients who were treated with 3D conformal external radiotherapy. They suggested the use of 3D conformal field that might be associated with reduced toxicity, and thereby allow delivery of higher total dose to central tumor.

The major pattern of failure of low grade astrocytomas is almost local progression. At the time of local recurrence or death, whether tumors remained still low-grade or underwent malignant dedifferentiation had not been known in the available literature. The rate of malignant dedifferentiation reported in many literature was variable with the range from 13% to 80%[3, 15, 17]. In a review of more than 130 low-grade astrocytomas of patients who had a second operation because of recurrence, Muller et al.[23] found that only 14% of the tumors were still low grade, 55% were anaplastic astrocytomas and 31% were glioblastomas multiforme. In our study, additional tissue were obtained from 6 of 23 patients with suspected progression. These patients had tumors at the time of reoperation, 4 of which appeared to have undergone transformation to high grade malignancy. Since astrocytic gliomas are heterogeneous tumors, the histologic modification at recurrence can be attributed to two reasons: 1) a sampling error in the first biopsy (i.e., the presence of anaplastic areas in parts of the tumor that were not removed), and 2) the occurrence of a malignant dedifferentiation in the time interval between the two biopsies[17]. The rationale for treating incompletely resected low-grade astrocytomas with radiotherapy may be to destroy the undetected anaplastic foci, which has already been suggested in a pathologic study, and/or to retard the occurrence and decrease the incidence of malignant dedifferentiation[27].

Radiotherapy is not possible without its potential toxicity. Patients with low-grade astrocytoma may survive long enough to develope late, delayed complications that may not be apparent in patients with malignant astrocytoma in whom the survival duration is often shorter. On reviews of 139 patients with primary brain tumors receiving 4500cGy or more, Marks and co-workers[28] found no cases of radionecrosis below dose equivalent to 5400 in 30 fractions over 42 days. The incidence of brain necrosis increased above this dose level. The white matter demyelination and Moyamoya phenomenon were developed in this study. Radiation therapy in these patients was done at very young age (3 - and 4 - years old) and radiation dose was 5040cGy in two patients. The radiation therapy should be carefully administered in young patients with a long and useful life.

In conclusion, although the follow-up of this study was relatively short, overall actuarial survival and progression free survival of patients with incompleted resected supratentorial low-grade astrocytoma after radiotherapy were encouraging. Patients with good performance status, lower T stage, pilocytic subtype, patients with small radiation field and radiation responder showed better survival. As the local failure was major pattern of failure, the various efforts to decrease the local failure is necessary.

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= 국문 초록 =

천막 상부 저분화 성상세포종의 치료에 있어 방사선 치료의 역할

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목 적: 저분화 성상세포종 치료에 있어서 방사선 치료 역할을 생존율과 치료 실패 양상으로 평가하고 생존율에 영향을 미치는 예후인자를 분석한다.

대상 및 방법: 1990년 1월부터 1995년 12월까지 서울 중앙 병원에서 아전절제술과 조직생검으로 확진된 저분화 성상세포종 환자 중 천막 하부를 제외한 총 51(남:여=28:23)예를 대상으로 하여 후향적으로 방사선 치료 성적을 분석하였다. 방사선 치료는 최저 4820cGy, 최고 6000cGy를 분할 치료하였고 치료 부위는 종양에 2-3cm 여유를 두고 국소조사하였다. 추적률은 96%이었으며 추적 관찰 기간의 중앙값은 48개월이었다. 생존율은 Kaplan-Meier법으로 분석하였다.

결 과: 총 51예의 2년 및 5년 전체 생존율은 83.4% 및 54.8%이었고 2년 및 5년 무진행 생존율은 67.4% 및 48.7%이었다. 전체 생존율에 영향을 주는 예후인자는 Karnofsky 수행도(p=0.024), T 병기(p=0.014), 조직학적 유형(p=0.012), 방사선 조사야(p=0.003), 방사선 반응도(p=0.0004)이었다. 그러나 절제 정도(아전 절제술 대 생검) 및 방사선 선량(5600cGy 이상 대 이하)은 생존율에 영향을 주지 못했다. 방사선치료후에 진행을 보이지 않은 45예중 17예 (37.8%)에서 국소 재발을 보였으며, 6예에서는 방사선 치료 직후 진행을 보여 총 23예 (45.1%)에서 국소실패를 보였다. 2예를 제외한 28예의 무진행 생존자들은 모두 신체적으로 지능적으로 정상이었다.

결 론: 본 연구에서는 비교적 추적 기간이 짧지만 저분화 성상세포종에 대한 방사선치료후 5년 생존율과 무진행 생존율은 54.8%와 48.7%로 우수하였다. Karnofsky 수행도가 높을수록, T 병기가 낮을수록, Pilocytic 유형인 경우, 방사선 치료에 반응할수록 양호한 예후를 보였다. 그러나 주 치료 실패 요인인 국소실패율을 감소시키기 위한 다각도의 연구가 필요하리라 사료된다.