Primary Radiation Therapy of Polymorhic Reticulosis

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From 1979 to 1987, 33 patients with polymorphic reticulosis (PMR) limited in the upper airway were treated with primary radiation therapy and the analysis of treatment results was undertaken. Systemic symptoms such as fever, night sweats, and weight loss were noted in 48%. The nasal cavity was most frequently involved (85%), although involvement of PNS (33%) and palate (30%) was not uncommon.

The 5 and 10 year actuarial survival rates were 47% and 40%, respectively. The difference in NSD between patients with in-field failure and those without it was significant statistically. Also, field size was significantly smaller in patients with marginal failure than those without it. During the follow-up period, systemic failure was found in 5 patients (diffuse histiocytic lymphoma in 4, histiocytic medullary reticulosis in 1). In this study, we can suggest that total radiation dose of at least 4500 cGy with generous treatment volume should be delivered to achieve better local control and that the developement of an effective systemic chemotherapeutic regimen is required to improve the survival after systemic relapse.

Key Words: Polymorphic reticulosis, Dose, Treatment volume, Radiotherapy.

INTRODUCTION

Polymorphic reticulosis, also called midline malignant reticulosis, is a localized lymphoproliferative lesion of the midface that may progress to involve practically all organ systems. First described by Eichel et al.[1] in 1966, polymorphic reticulosis (PMR) is clinically an aggressive, necrotizing lesion with a predilection for the upper respiratory tract, particularly the nose and paranasal sinuses[1~5]. Nasal lesions can be locally ulcerative and destructive, and men are more frequently afflicted with PMR than women[1,4]. Nonspecific prolonged nasal complaints are often reported prior to diagnosis and severe constitutional symptoms such as high fever, night sweats and weight loss are frequently found[1~5].

Histologically, PMR is distinguished from Wegener's granulomatosis by a polymorphous cellular infiltration of submucosa, which is usually necrotizing through mucosa and even bone or cartilage. This infiltrate frequently manifests angiocentric or angioinfiltrative growth patterns and consists of small lymphocytes with scattered immunoblastic forms, abundant plasma cells and occasional histiocytes[1,2,4~6].

PMR has been conceptualized as a lymphoproliferative disorder since its first description[1] and considered as the radiosensitive tumor[2,4,5,7~9]. When PMR is limited to the upper aerodigestive tract, radiation therapy is accepted as the treatment of choice[1~6]. But we don't have the established knowledge of proper radiation dose and treatment volume in the radiotherapy to PMR until a recent date. In an effort to address these therapeutic parameters, we have analyzed our experience of PMR cases of which extent was limited to the upper aerodigestive tract to get reasonable guidelines.

METERIALS AND METHODS

During the period from February, 1979, to April, 1987, 40 patients with pathologically proven polymorphic reticulosis limited in the upper airway were treated with primary radiation therapy in the Department of Therapeutic Radiology in Seoul National University Hospital. Of these, seven patients were excluded from this analysis because of incomplete treatment (given less than a third of

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prescribed radiation dose).

The follow-up period ranged from 53 months to 122 months (median: 68 months) of patients who were alive at the time of the analysis. There were 25 males and 8 females (male to female ratio= 3.1:1). The age ranged from 8 to 69 years with a median age of 42 years. Systemic symptoms such as night sweats, weight loss and fever were noted in 16 patients (48%) and were often severe clinically. The nasal cavity was the most frequent site of initial disease presentation and was involved in 85% of patients as component of sites. Paranasal sinus involvement was the second most common site and manifested disease in 33%. Palatal involvement was noted in 30% and each case of hypopharyngeal and laryngeal involvement was present(Table 1).

Table 1. Patients' Characteristics (N=33)

Characteristics	No. of Pts. (%)
Age (years)	
Range	8 – 69
Median	42
Sex	
Male	25 (76)
Female	8 (24)
Systemic Sx	
(+)	16 (48)
(–)	17 (52)
Involved sites	
Nasal cavity	28 (85)
PNS	11 (33)
Palate	10 (30)
Hypopharynx	1 (3)
Larynx	1 (3)

All patients were treated with ^{60}Co teletherapy unit. By the location of the primary tumor and the contour of external surface, one to three portals were used to cover the involved field by computer planning. Field size ranged from 30 cm^2 to 187 cm^2 and median field size was 83 cm^2. Radiation dose ranged from 3,500 cGy/19 fractions in 25 days to 6,000 cGy/30 fractions in 43 days (NSD: 1,212~1,754 ret) and median dose was 4,950 cGy (NSD: 1,496 ret).

Tumor response was determined on the physical examination and radiologic findings at one to three months after the completion of radiotherapy. For the analysis of failure patterns, failure sites were defined both for the time of initial relapse (initial failure) and for all sites manifesting disease at any time in the patient's post-relapse course. Failure sites coded include the following: (a) true in-field failure (disease recurrence within the radiation field) (b) marginal failure (disease recurrence in an immediately adjacent structure not included within the original treatment field) (c) systemic failure sites.

Salvage chemotherapy in accordance with the

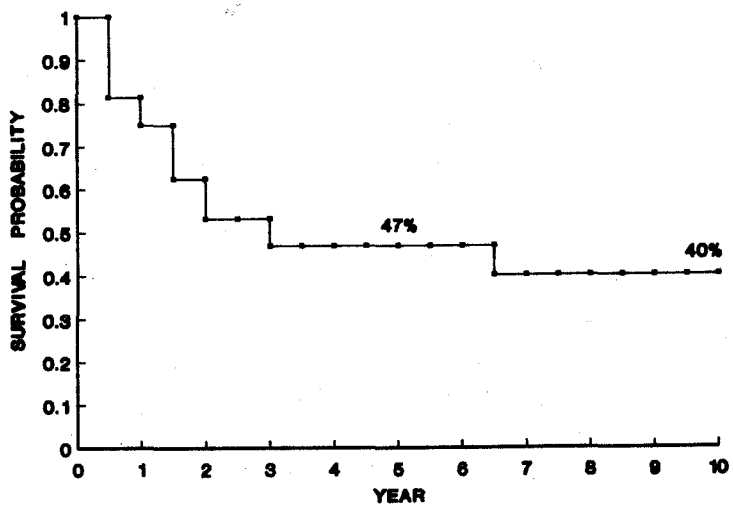

Fig. 1. Overall survival of patients.

treatment of frank malignant lymphoma was delivered at the time of systemic relapse in five patients. Survival was calculated by the life-table method[17]; the log-rank test[18] was used for the comparison.

RESULTS

The overall 5 and 10 year survival rates of 33 patients were 47% and 40%, respectively (Fig. 1). Most deaths occurred within three years. Survival difference according to response to radiotherapy was analyzed. The 20 patients with complete response and the 13 patients with partial or no response had 58% and 31% of 5 year survival rate, respectively ($0.1<p<0.25$) (Fig. 2).

The presence of systemic symptoms such as night sweats, weight loss and fever had no influence to survival (Fig. 3). The five year survival rates were 44% and 50%, respectively in patients with and without systemic symptoms. Detailed patterns of failure were analyzed in 23 patients (Table 2).

Average radiation dose in patients with in-field failure was significantly less than those without it

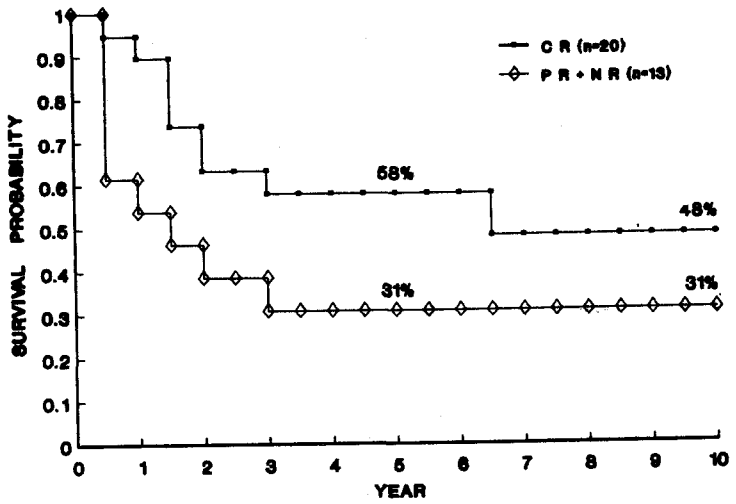

Fig. 2. Survival by response.

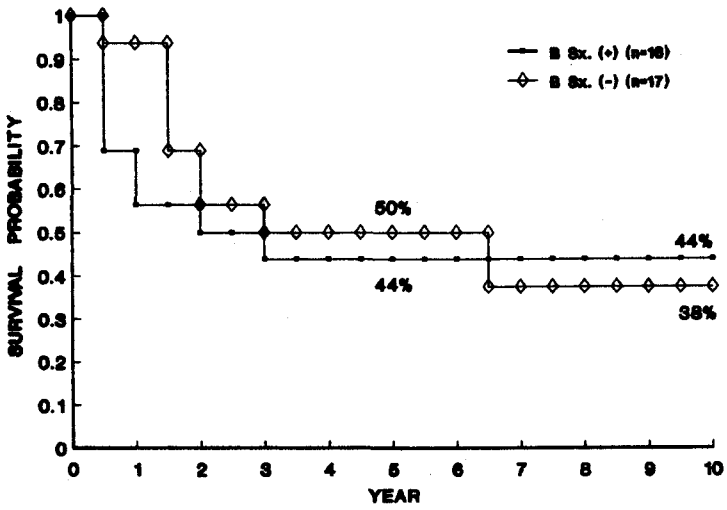

Fig. 3. Survival by systemic symptom.

Table 2. Patterns of Failure

Failure site	Initial failure (n=9)	Eventual failure (n=8)
In-field	2	3
Marginal#	3	0
Systemic	4	5
DHL* — 4 cases		
HMR** — 1 case		

— Analyzed with 23 eligible patients
1 patient with marginal failure was salvaged after reirradiation.
* Diffuse histiocytic lymphoma
** Histiocytic medullary reticulosis

Table 3. Dose and In-field Failure

In-field failure	NSD* (ret)	P-value
Yes	1287 ± 184.0	
		< 0.025
No	1482 ± 91.4	

* NSD : Nominal standard dose

Table 4. Field Size and Marginal Failure

Marginal failure	Field size (cm^2)	P-value
Yes	50.5 ± 15.3	
		< 0.05
No	83.5 ± 26.7	

(Table 3). Although field size was variable according to the location and size of tumor, field size was significantly smaller in patients with marginal failure than those without it (Table 4). Of the five patients with systemic relapse subsequently, four patients developed diffuse histiocytic lymphoma and one patient did histiocytic medullary reticulosis. In spite of salvage chemotherapy, they succumbed to disease in 1 to 14 months after the initiation of chemotherapy.

DISCUSSION

It is now accepted that PMR is a disease entity distinct from Wegener's granulomatosis and other clinically similar conditions. A substantial amount of confusion, however, seems to persist regarding the proper classification of these entities. Progressive destruction of the upper aerodigestive tract is seen in a variety of conditions including a variety of infections, environmental intoxications, immunological disorders and various neoplasms. The chief area of difficulty in differential diagnosis seems to arise in the separation of Wegener's granulomatosis, lethal midline granuloma and PMR. Wegener's granulomatosis is typified by epithelioid necrotizing granulomas and vasculitis involving small arteries and veins. Renal and pulmonary involvement is common and no associations exist with the subsequent development of malignant lymphoma[2,4~6]. The treatment of choice is cytotoxic chemotherapy and corticosteroid.

The term of lethal midline granuloma describes a clinical entity with nonspecific histologic findings characterized by progressive destruction of the midfacial area, which, if untreated is uniformly fatal. This clinical picture can result from any of the specific clinicopathologic entities previously discussed, including PMR. If, therefore, a patient manifests evidence of a specific clinicopathologic entity, the disease process is then classified and treated according to its more precise nosologic entity. Lethal midline granuloma remains a clinical diagnosis of exclusion with nonspecific histopathologic findings[2,4~6]. Lymphomatoid granulomatosis has histologic features which appear to be identical to PMR[2,9]. It is well known that lymphomatoid granulmatosis is a type of peripheral T-cell lymphoma by immunohistologic findings[9]. After Liebow et al[10] first described it in 1972, it was accompanied by pulmonary involvement in all cases. Although some debate still exists, most authors agree that PMR is also a type of peripheral T-cell lymphoma[11,12]. The appearance of four diffuse histiocytic lumphoma cases in our study cannot be regarded as a synchronous existence of PMR and lymphoma at the time of diagnosis but as a supporting finding of what PMR could be considered as a low grade lymphoproliferative disorder, as asserted by Smalley et al.[13].

Since M' Arthur and Dew first used radiotherapy in the treatment of midline granuloma in 1925, varying degrees of favorable response have been reported by several authors[3,14]. However, precise evaluation of the efficacy of radiotherapy in midline granuloma in previous several studies is difficult because they failed to distinguish various causes of midline granuloma.

Although several early studies recommended low dose radiotherapy and discouraged the use of

radical radiotherapy[16,17], it is established firmly that high dose localized radiation therapy is needed to control the PMR limited in the upper airway[3,11~14]. Several authors confirm that generally the dose needed ranges from 4,000 cGy to 5,000 cGy. Table 3 shows clearly the relationship between the dose and in-field failure. Smalley et al.[13] reported that dose of 4,200 cGy or greater (TDF of 70 or more) was associated with improved in-field control. Halperin et al.[3] reported that they favored doses equivalent to the 4,000~5,000 cGy at 180 cGy/fraction used in other lymphoproliferative disorder. So it might be said that patients with PMR should receive minimum dose of 4,500 cGy or more. In Table 4, we can see that field size and marginal failure is correlated significantly. In fact, every case was so variable in size and location of tumor that our result should be cautiously interpretated.

But it is evident that the wider field size is, the less marginal failure occurs. Smalley et al[13] also suggested that generous treatment volume should be used to include clinically uninvolved adjacent structures at risk. Smalley et al.[13] reported that eight of the 32 patients manifested systemic failure as a component of eventual failure. Others reported that the proportion of progression to malignant lymphoma in PMR ranged from 10% to 27% and patients with systemic relapse had poor prognosis in spite of systemic chemotherapy[2,10,11]. This fact is well in line with our results that five patients with systemic relapse were not salvaged by chemotherapy.

In conclusion, we can recognize in this study the following facts; 1) PMR limited in the upper airway should be treated with proper radiation dose (minimum 4500 cGy or more) and more generous treatment volume than in other malignant tumor. 2) Systemic relapse (mainly malignant lymphoma) constitutes about 20% of eventual failure. 3) Ultimately effective systemic chemotherapy is required to substantially improve the survival after systemic relapse.

REFERENCES

1. **Eichel BS, Harrison EG, Jr Devine KD, et al:** Primary lymphoma of the nose including a relationship to lethal midline granuloma. Am J Surg 112:597-605, 1966
2. **DeRemee RA, Weiland LH, McDonald JJ:** Polymorphic reticulosis, lymphomatoid ganulomatosis-two diseases or one? Mayo Clin Proc 53:634-640, 1978
3. **Halperin EC, Dosoretz DE, Goodman M, et al:** Radiotherapy of polymorphic reticulosis. Br J Radiol 55:645-649, 1982
4. **McDonald TJ, DeRemee RA, Harrison EG, et al:** The protean clinical features of polymorphic reticulosis (lethal midline granuloma). Laryngoscope 86:936-945, 1976
5. **McDonald TJ, DeRemee RA, Weiland LH:** Wegener's granulomatosis and polymorphic reticulosis-Two diseases or one? Arch Otolaryngol 107:141-144, 1981
6. **Kassel SH, Echevarria RA, Guzzo FP:** Midline malignant reticulosis (so-called lethal midline granuloma). Cancer 23:920-935, 1969
7. **Ishii Y, Yamanaka N, Okawa K, et al:** Nasal T-cell lymphoma as a type of so-called "lethal midline granuloma". Cancer 50:2336-2344, 1982
8. **Neiman RS:** The peripheral T-cell lymphomas come of age. Mayo Clin Proc 61:504-506, 1986
9. **Weis JW, Winter MW, Phyliki RL, et al:** Peripheral T-cell lyumphomas; histologic, immunohistologic and clinical characterization. Mayo Clin Proc 61: 411-426, 1986
10. **Katzenstein AA, Carrington CB, Leibow AA:** Lymphomatoid granulomatosis, a clinicopathologic study of 152 cases. Cancer 43:360-373, 1979
11. **Harrison DFN:** Midline destructive granuloma; fact or fiction. Laryngoscope 97:1049-1053, 1987
12. **Pickens JP, Modica L:** Current concepts of the lethal midline granuloma syndrome. Otolaryngology-Head and Neck Surgery 100:623-630, 1989
13. **Smalley SR, Cupps RE, Anderson JA, et al:** Polymorphic reticulosis limited to the upper aerodigestive tract-natural history and radiotherapeutic considerations. Int J Radiation Oncology Biol Phys 15:599-605, 1988
14. **Fauci AS, Johnson RE, Wolff SM:** Radiation therapy of midline granulma. Annals of Internal Medicine 84:140-147, 1975
15. **Feder BH, Shramek JH, Ikeda TS:** Large field radiotherapy in lethal midline granuloma. Radiology 81: 293-299, 1963
16. **Dickson RJ:** Radiotherapy of lethal midline granuloma. J Chronic Dis 12:417-427, 1960
17. **American Joint Committee on Cancer:** Reporting of cancer survival and end results. In Manual for Staging of Cancer. JB Lipppincott Co, Philadelphia, 1988, pp 11-24
18. **Peto R, Pike MC , Armitage P, et al:** Design and analysis of randomized clinical trials requiring prolonged observation of each patients, II. analysis and examples. Br J Cancer 35:1-39, 1977

= 국문초록 =

다형성 세망증의 방사선 치료성적

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1979년부터 1987년까지 서울대학교 병원에서 상기도에 국한된 다형성 세망증으로 근치적 방사선 치료를 받은 33명의 환자의 치료성적을 분석하였다. 발열, 체중감소, 도한등의 전신적 증상은 대상 환자중 48%에서 나타났으며 침윤병소로는 비강이 85%로 가장 많았고 부비동 및 구개부가 각각 33%와 30%이었다. 전체 환자의 5년 및 10년 생존율은 각각 47%와 40%이었다. 방사선 조사야 내에서 재발한 경우와 그렇지 않은 경우간의 방사선 선량 차이는 통계학적으로 유의하였으며 조사야 경계부위에서 재발한 경우는 그렇지 않은 경우에 비해서 조사야 면적이 작았다. 추적 관찰 기간중 악성 임파종 4예, 골수 세망증 1예 등의 전신적 전이가 확인되었다.

따라서 방사선 치료를 시행하여 다형성 세망증의 국소 치료율은 향상시키기 위해서는 최소 4,500 cGy의 선량과 병소주위의 조직을 충분히 포함하는 조사야를 사용해야 하며 전신적 전이를 효과적으로 치료할 화학요법 면에서의 개선이 필요하다고 판단된다.