Angiocentric T-cell and NK/T-cell lymphoma: Analysis of local failures with special emphasis on the use of radiotherapy

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Directed by Professor Gwi Eon Kim

The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medicine

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ABSTRACT

Angiocentric T-cell and NK/T-cell lymphoma: Analysis of local failures with special emphasis on the use of radiotherapy

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(Directed by Professor Gwi Eon Kim)

Purpose: To investigate the patterns of local failure and the risk factors predictive of local failure and to establish the dose-response relationships influencing the probability of local control in patients with stage I and II angiocentric T-cell or NK/T-cell lymphoma, who were treated with radiotherapy (RT) alone.

Materials and Methods: Between 1976 and 1998, 102 patients with Ann Arbor Stage I and II angiocentric T-cell or NK/T-cell lymphoma, who underwent RT alone with a median dose of 45 Gy (range: 20-70 Gy) at the Yonsei Cancer Center, Yonsei University, College of Medicine (Seoul, South Korea), were retrospectively reviewed. Patterns of local failure, risk factors predictive of local failure, dose-response relationships, and survival data were analyzed. Because of the protean feature of local recurrences, the sites of local failure were allocated to one of three categories; (a) "True recurrence (TR)", (b) "Marginal recurrence (MR)", and (c) "Elsewhere recurrence (ER)".

Results: Despite a higher complete remission (CR) rate (72%) following RT, 60 patients experienced treatment failure, including local failure in 48 (47%), regional failure in 3 (3%), and systemic failure in 28 (27%). Patterns of local failure comprised a TR in 42, a MR in 3, and an ER in 5. Median time to recurrence for TR/MR was shorter than that for ER (1 month for TR/MR vs. 12 months for ER). Patients with TR/MR showed a more unfavorable prognosis than those experiencing an ER (2-year survival rate after salvage treatment: 6% for TR/MR vs. 80% for ER) ($p < 0.01$). The dose-response curve was sigmoid in shape within the range 20-54 Gy, which followed the plateau at doses in excess of about 54 Gy. A positive correlation was observed in the dose-response curve for the probability of local control ($p = 0.017$, logistic regression analysis). The overall 5-year actuarial survival and local recurrence-free survival rates for all patients were 42% and 53%, respectively. An achievement of CR was the most significant risk factors predictive of TR/MR and the most important prognostic factor.

Conclusions: Our data confirms that local failure remains the major obstacle for patients who received RT alone, and that achievement of CR is a particularly important determinant of treatment success in the management of these patients. Although dose escalation up to more than 54 Gy cannot entirely reduce the incidence of TR/MR, we believe that it is important to identify an appropriate subset of patients for whom additional booster dose may be beneficial. Given a high rate of local failure, an investigational approach should be conducted to supplement RT using radiosensitizers or more effective chemotherapeutic agents in future trials.

Key words: angiocentric lymphoma, dose-response relationship, local recurrence

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I. INTRODUCTION

Angiocentric T-cell and natural-killer (NK)/T-cell lymphomas, formerly known as midline malignant reticulosis, polymorphic reticulosis, or angiocentric immunoproliferative lesions, are increasingly being recognized as a distinct type of lymphoproliferative disorders[1-7]. Although encountered rarely in the United States and Europe, these lymphomas are relatively prevalent in certain parts of Central and South America and East Asia, including Korea[9-15]. A recent nationwide study of malignant lymphomas among Koreans reported that angiocentric lymphomas expressing T-cell or NK-cell markers comprise 9% of all non-Hodgkin's lymphomas and 74% of lymphomas arising in the nasal cavity and paranasal sinuses[16]. Most angiocentric T-cell or NK/T-cell lymphomas clinically present as a destructive process of the external nose or deep mid-facial structures with septal perforation, palatal destruction, orbital swelling, or obstructive symptoms related to the tumor mass[1-4, 17, 18]. Since these lymphomas often display the morphologic features of an angiocentric and angiodestructive

infiltrate, together with polymorphism of atypical cells and a zonal type of necrosis[2, 4, 5, 7, 10, 19], they were categorized as angiocentric lymphoma in the Revised European-American Lymphoma (REAL) classification[20]. However, this type of lymphoma was renamed as "extranodal NK/T-cell lymphoma, nasal type" in the new World Health Organization (WHO) classification because of a plentiful evidence that the majority of cases express the T-cell or NK-cell phenotype and genotype[7, 14, 21-25].

In addition to the confusing nomenclature, the optimum mode of therapy has not been clearly established, partly because of the rarity of the tumor and our limited understanding of its natural course. Generally, the initial response to radiotherapy (RT) is so rapid and dramatic that the use of involved-field RT has been accepted as the preferred treatment option for localized disease[12, 13, 17, 18, 26-28]. However, approximately 20-30% of patients treated with RT alone experience a systemic failure in extranodal sites[2, 15, 29-31]. Given this situation, a few investigators have advocated that systemic chemotherapy as a component of a multimodal approach is mandatory, even in the treatment of the early stage patients[6, 32, 33], but there is general agreement in the Oriental literature that neither the incidence of systemic relapse nor prognosis is significantly altered by the use of chemotherapy instead of RT or by the combined use of chemotherapy and RT in the management of these patients[34-36]. Since local failure remains the predominant pattern of failure[15, 27, 34, 37], it seems incumbent on the radiation oncologist to clarify the role of RT in each clinical setting. However, until recently, it has not been easy to find reasonable data regarding RT details and treatment outcomes. The optimal dose required to achieve appropriate local control is also in question.

In the present study, we analyzed the effects of various clinical and therapeutic factors on local disease control to shed light on RT parameters, such as RT doses and fields. The aim of the study was to investigate the patterns of local failure and the risk factors predictive of local failure and to establish the dose-response relationships influencing the probability of local control in patients with stage I and II angiocentric T-cell or NK/T-cell lymphoma, who were treated with RT alone.

II. MATERIALS AND METHODS

1. Patient selection

Between 1976 and 1998, 167 patients with Ann Arbor Stage I and II angiocentric T-cell or NK/T-cell lymphoma were treated with curative intent at the Yonsei Cancer Center, Yonsei University, College of Medicine (Seoul, South Korea). Before 1987, our treatment policy for stage I or II disease was to administer involved-field RT alone, and afterwards, these patients received either chemotherapy followed by RT or RT alone by physician's preference. Reviewing their medical charts retrospectively, 62 patients who underwent either chemotherapy alone or combination chemotherapy and RT were excluded from the study in order to investigate the treatment outcome of RT alone. Of those treated with RT alone, 3 patients were excluded from the study, because they had not finished the planned RT. This study involved analysis of 102 eligible patients with localized angiocentric T-cell or NK/T-cell lymphoma treated by RT alone.

The diagnostic criteria used were strictly morphologic, based on microscopic findings, although immunohistochemical studies were performed for 54 cases in the late study period. The cardinal findings used to identify angiocentric T-cell or NK/T-cell lymphoma were the pathologic features of angiocentric infiltration or angiodestructive growth pattern and necrosis with polymorphism of individual cells and a variable percentage of atypical lymphoid cells. Pathologic slides for all patients were re-reviewed and re-classified by an experienced special pathologist (W I Yang, M.D.) who was unaware of the patients' clinical course. All patients were staged according to the Ann Arbor system. Staging evaluation consisted of a

complete history taking and physical examination, routine blood counts and serum chemistry before treatment. In all patients, a head-and-neck computed tomographic (CT) scan was performed to accurately evaluate the extent of the primary lesion. Liver ultrasound and whole-body bone scans were obtained. Lymphangiography was performed on selected patients in the earlier years, but was replaced by abdominopelvic CT for the majority of patients after 1983.

A median age of all cases at the time of initial presentation was 45 years, ranging from 14 to 76 years. The male to female ratio was about 6:4. The primary sites of involvement were classified as the nasal cavity/paranasal sinuses, nasopharynx, oral cavity/oropharynx, or larynx/hypopharynx. Although 21 patients showed involvement of two or more anatomical site, the nasal cavity was most frequently involved (64%). Twenty (20%) cases were accompanied by cervical lymphadenopathy. Sixty-eight (67%) patients were found to have stage I, and 34 (33%) patients were classified as stage II. Systemic B symptoms were present in 13 (13%) patients. Patient characteristics are listed in Table 1.

2. Radiation treatment

RT was given using a Co-60 or a 4 MV linear accelerator. The majority of patients received involved-field irradiation. All target volumes were determined using a CT scan. Generally, the planning target volume included all gross lesions and sites of potential contiguous spread with adequate margins. The commonest field arrangement was the 3-field technique, consisting of field arrangements weighted in favor of anterior field and 2-wedged lateral fields, although two lateral opposing

Table 1. Patient characteristics (n=102)

Characteristics	No. of patients (%)
Age (years)	
Median	45
Range	14-76
Sex	
Male	66 (65)
Female	36 (35)
Site of primary lesion*	
Nasal cavity/paranasal sinus	66 (64)
Nasopharynx	14 (14)
Oral cavity/oropharynx	42 (41)
Larynx/hypopharynx	5 (5)
Cervical lymphadenopathy	
No	82 (80)
Yes	20 (20)
Systemic B symptoms	
No	89 (87)
Yes	13 (13)
Ann Arbor stage	
I	68 (67)
II	34 (33)
RT dose (Gy)	
Median	45
Range	20-70
RT volume	
Primary alone	46 (45)
Primary + neck nodes	56 (55)
Response to RT	
CR	73 (72)
PR	14 (14)
NR	15 (14)

Abbreviation: RT = radiotherapy; CR = complete remission; PR = partial remission; NR = no remission.

* Twenty-one patients had multiple primary lesion sites.

photon fields were used for patients with Waldeyer's ring or hypopharynx involvement. The radiation ports for the lymph node bearing areas also varied according to the primary sites. If the primary lesion was located in the nasal cavity/paranasal sinuses, the regional lymph node areas were not included unless they were clinically involved, whereas if the primary lesion was in the nasopharynx, oral cavity/oropharynx or hypopharynx, then elective neck irradiation was routinely performed regardless of neck node involvement. Over the period of this study, the radiation doses prescribed to clinically involved sites ranged from 20-70 Gy at a dose per fraction of 1.8-2.0 Gy. Eighty patients (78%) received RT with dose range of 40-54 Gy (median dose: 45) over 4-6 weeks. A supplemental dose in the range 10-16 Gy (up to total dose of 60-70 Gy) was administered to 11 (11%) cases of persistent tumor after delivering 54 Gy, whereas 11 patients (11%) received low-dose irradiation of less than 40 Gy, with a range of 20-38 Gy. Salvage treatments for initial relapse were individualized.

3. Analysis of treatment outcomes

After RT, all patients were regularly followed at 3-months intervals until death or relapse. Four cases were lost to follow-up within 1 or 2 years. The median follow-up period was 52 months, ranging from 1 to 136 months. Initial response to RT was assessed by both physical examination and computerized tomography (CT) scans within 8 weeks of the completion of RT. Tumor response to treatment was estimated using standard criteria. Complete remission (CR) was defined as no evidence of disease for at least 4 weeks, and partial remission (PR) as greater than 50% regression of all measurable tumor mass over the same period. Cases with less

than 50% clinical regression, stable disease, or progression were classified as no remission (NR). All sites of recurrence were recorded in patients who relapsed. Treatment failure was categorized as local failure, regional failure, or systemic failure. A systemic failure was defined as the appearance of disseminated disease at sites other than the head and neck and cervical lymph nodes. Although local recurrence or regional failure was usually documented by biopsy, systemic failure was diagnosed based on clinical and/or radiological findings. Because of the protean feature of local recurrences, the sites of local failure were arbitrary allocated to one of three categories based on their patterns of recurrences; (a) "True recurrence (TR)", occurring within RT fields; (b) "Marginal recurrence (MR)", near contiguous areas of primary site, but just outside of the border of the RT field; and (c) "Elsewhere recurrence (ER)" occurring at another extranodal site of the head and neck (Fig 1). The primary tumor persisted after initial treatment in some patients, who were regarded as having a TR.

Since one of the goals of the present study was to assess the probability of local disease control as a function of radiation dose in patients treated with RT alone, any analysis for local relapse was counted as TR/MR having a component of recurrence in the irradiated volume, excluding an ER. Dose-response relationships influencing the probability of local control were analyzed by using logistic regression. Univariate and multivariate analyses were performed for risk factors predictive of local recurrence. Overall survival rate and local recurrence-free survival rate were calculated using the Kaplan-Meier method. Overall actuarial survival was calculated from the date of diagnosis until the date of death or the last follow-up, while local recurrence-free survival was estimated from the date of

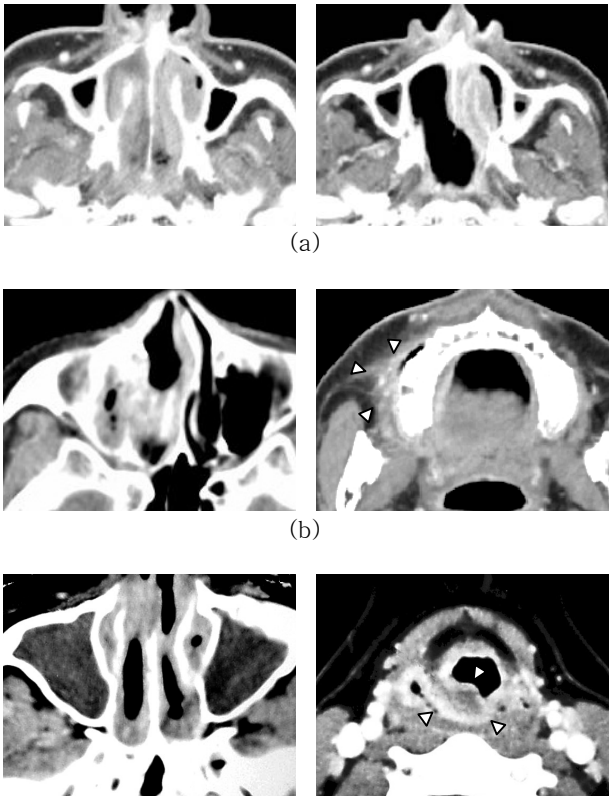


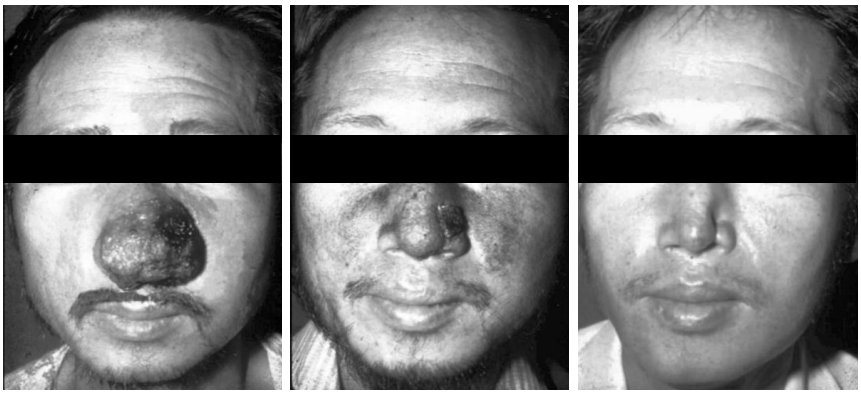
Figure 1. The patterns of local failure were arbitrary divided into the three categories based on their sites of local recurrences. Pretreatment CT scans (left column) and CT scans at the time of local failures (right column) show the different patterns of local recurrence; (a) “True recurrence (TR)”, (b) “Marginal recurrence (MR)”, and (c) “Elsewhere recurrence (ER)”.

treatment to the date of detection of the initial TR/MR. Univariate analysis was performed to define the prognostic factors influencing overall survival and local recurrence-free survival. The relative importance of the covariates in determining prognostic factors was also assessed by using multivariate Cox's proportional hazard model.

III. RESULTS

1. Initial response to RT and patterns of treatment failure

As shown in Fig. 2, initial response to RT was rapid and dramatic in many cases. Seventy-three (72%) of the 102 patients achieved CR, and 14 patients (13%) PR immediately after RT (overall response rate; 85%). Although most patients responded favorably to RT, 15 (15%) patients showed stable disease or disease progression. None of the patients who received less than 30 Gy achieved CR. Conversely, 7 of the 11 patients with residual disease after receiving the planned RT dose (45-54 Gy) attained CR with dose-escalations up to more than 60-70 Gy, whereas the remaining 4 patients resulted in a higher level of complications without achieving CR.



(a) (b) (c)

Figure 2. A destructive mass of the external nose at the time of initial presentation (a) had disappeared immediately after involved field RT with 50 Gy (b). Patient survived over 5 years (c).

The patterns of treatment failure for all patients are illustrated in Fig. 3. Despite a higher CR rate following RT, there were 60 treatment failures, including local failure in 48 (47%), regional failure in 3 (3%), and systemic failure in 27 (26%) at the time of analysis. Of the patients with treatment failure, 41 (40%) had a single site of failure, and 19 (18%) had one or more relapsed sites. Two (2%) and 17 (16%) patients with local failure had simultaneous regional relapse and systemic relapse, respectively. In contrast with the relatively high rate of local failure, regional failure was much uncommon. Only 3 (3%) patients experienced a regional failure at the untreated or treated neck during the follow-up periods. Although none of the 36 N0 patients who received an elective neck irradiation experienced a regional failure, only one (1%) of the 46 node-negative (N0) patients who did not receive an elective neck irradiation developed a regional recurrence. Conversely, 2 (10%) of the 20 node-positive (N+) patients subsequently suffered neck node recurrences, apparently within the RT field. Of particular interest was the finding that systemic failure showed a unique pattern with a variety of clinicopathologic feature. Most patients with widespread dissemination showed site predilection, such as the brain/orbit (2 cases), lungs/mediastinum (3 cases), breast/axilla (5 cases), liver/ spleen (10 cases), kidney/adrenal gland (2 cases), gastrointestinal tract (2 cases), skin and testes (8 cases), or bone/soft tissue (4 cases). More interestingly, 5 cases were accompanied by a number of medical complications or aberrant immunologic disorders, such as sepsis, intractable hemorrhage, or an increased propensity for the evolution of secondary non-lymphoid malignancies. Three patients developed a hemophagocytic syndrome, which quickly pursued a fatal course.

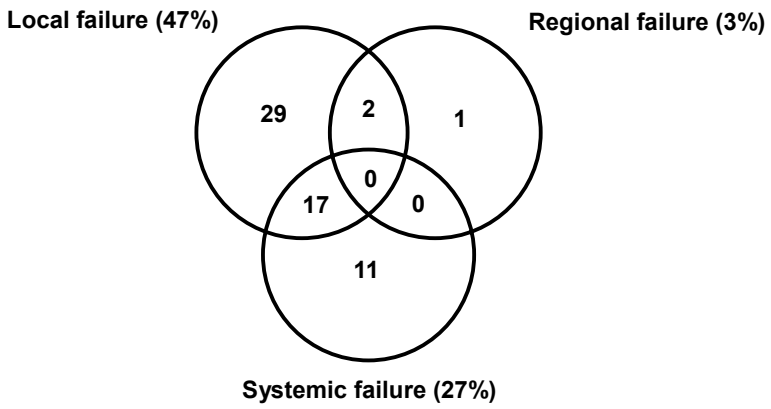


Figure 3. Patterns of treatment failure following definite radiotherapy for stage I and stage II angiocentric T-cell and NK/T-cell lymphomas of the head and neck.

2. Patterns of local failure

The patterns of local failure were protean, comprising TR in 42 patients, MR in 3 patients, and ER in 5 patients. Ninety percent of local failures were either TR or MR. Since CT-assisted RT plans were unavailable for patients treated before 1983, the assessment of MR was not easy to identify, but only 3 patients were considered as having MR by the location of recurrent sites on the basis of contiguity. Interestingly, 5 patients had an ER with local failure removed from the site of initial involvement and from adjacent areas. Patterns of local failure are summarized in Table 2. Although 80% of treatment failures were found within 2 years after the completion of RT, the median time to evolve local failure was variable depending on the pattern of local recurrence; an ER tended to occur later than a TR or a MR The median time to recurrence of 12 months

for ER was comparable to that of 1 months for TR/MR (Fig. 4). The actuarial rate of freedom from local recurrence at 5 years was 53% for patients with TR/MR, and 93% for patients with ER. Although salvage treatments for local recurrence depended on the patient's general condition, recurrent sites and extent, and previous treatment, patients experiencing an ER showed a higher salvage rate than those experiencing TR/MR. The 2-years survival rate after salvage treatment in ER was much superior to that of TR/MR (80% vs. 6%, $p < 0.01$).

Table 2. Patterns of local recurrence

Characteristics	Local recurrence*		
	True recurrence	Marginal recurrence	Elsewhere recurrence
Total No. of patient	42	3	5
Failure site			
Nasal cavity/Paranasal sinus	22	1	0
Nasopharynx	4	0	0
Oral cavity/Oropharynx	23	2	2
Larynx/Hypopharynx	2	1	4
Associated regional failure	2	0	0
Associated systemic failure	15	1	1
Initial response to RT			
CR	13	3	5
Non-CR	29	0	0
Salvage treatment			
Radiotherapy	5	1	3
Chemotherapy	6	2	0
Surgery	1	0	0

Abbreviation: RT = radiotherapy; CR = complete remission.
* One patients had true recurrence and elsewhere recurrence. The other had marginal recurrence and elsewhere recurrence.

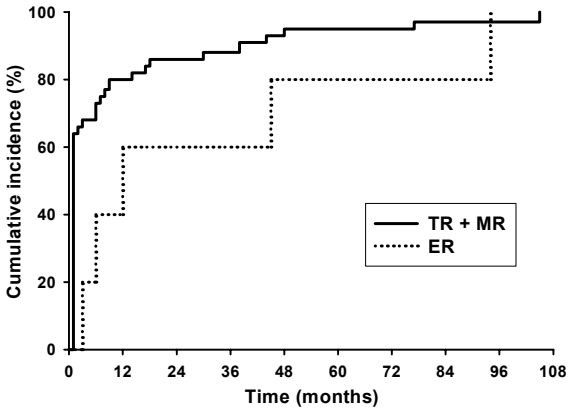


Figure 4. Cumulative incidence of true recurrence (TR) and marginal recurrence (MR) (solid line) and elsewhere recurrence (ER) (dashed line).

3. Risk factors predictive of local failure

Clinical and treatment variables with potential predictive value of local recurrences were investigated for 45 patients with TR/MR, excluding 5 patients who developed ER, because of concerns that local tumor control in an irradiated site might be independent of tumor control at other unirradiated sites in the same patient. Clinical factors included age, gender, primary site, lymph node involvement, systemic B symptoms, and Ann Arbor stage, while treatment factors included RT dose, RT fields, and initial response to RT. As shown in Table 3, neither cervical lymphadenopathy nor the presence of systemic B symptoms was predictive of TR/MR. Although Ann Arbor stage and the primary site were identified as significant and as marginally significant predictors of TR/MR, both were found unreliable by multivariate analysis. Of the treatment factors, an initial response to RT was found to be the most potent predictor of TR/MR ($p < 0.01$). Since response to RT would tend to strongly weight the analysis of risk factors predictive of local

failure, the primary site, Ann Arbor stage, and RT dose were subjected to multivariate analysis. RT dose less than 45 Gy was found to be a significant predictor of local recurrences in multivariate analysis, eliminating a factor of the initial response to RT (p = 0.03).

Table 3. Risk factor predictive of local failure excluding elsewhere recurrence

Factor	Local failure		P value	
	No. of patients/ Total No. of Patients	%	Univari-ate	Multivaria-te
Age			0.30	
< 45 years	29/60	48		
≥ 45 years	16/42	38		
Sex			0.71	
Male	30/66	45		
Female	15/36	42		
Primary site			0.08	0.23
Sinonasal	25/66	38		
Non-sinonasal	20/36	56		
Lymph node involvement			0.27	
No	34/82	41		
Yes	11/20	55		
Systemic B symptoms			0.87	
No	39/89	43		
Yes	6/13	46		
Ann Arbor stage			0.03	0.12
I	25/68	37		
II	20/34	59		
RT dose			0.02	0.03
< 45 Gy	16/25	64		
≥ 45 Gy	29/77	38		
RT volume			0.12	
Primary alone	17/46	36		
Primary + neck nodes	28/56	50		
Response to RT			< 0.01	
CR	16/73	22		
Non-CR	29/29	100		

Abbreviation: RT = radiotherapy; CR = complete remission.

4. Dose-response relationships for local control

Although the numbers of patients who treated with doses greater than 54 Gy or less than 40 Gy were too few to draw definite conclusions, the local control rates steadily increased as the RT dose increased in the range 20-54 Gy. The overall local control rates varied according to dose delivered as follows: 20-39 Gy, 9% (1 of 11 patients); 40-44 Gy, 57% (8 of 14 patients); 45-50 Gy, 64% (34 of 53 patients); 51-54 Gy, 53% (7 of 13 patients); and 55-70 Gy, 63% (7 of 11 patients). A positive correlation was observed between the RT dose and the probability of local control (p=0.017, logistic regression analysis). The dose-response curve for the probability of local control had sigmoidal shape within the dose range 20-54 Gy, which followed the plateau at doses in excess of about 54 Gy, indicating little enhancement of local control rate was obtained at these dose levels. Fig. 5 illustrates the dose-response relationship as a function of the RT dose delivered.

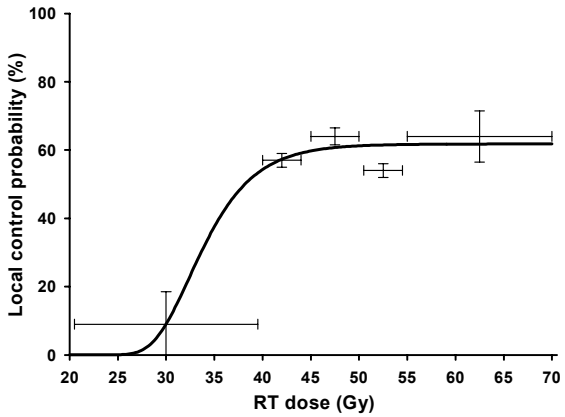


Figure 5. Local control probability as a function of radiation dose in patients treated with RT alone. Horizontal lines are the range of RT doses delivered. Vertical lines are 95% confidence interval of local control probability.

5. Survival and prognostic factors

The 5-year overall actuarial and local recurrence-free survival rates for all 102 patients were 42% (95% CI, 32-52%) and 53% (95% CI, 43-63%), respectively (Fig. 6). The 5-year survival actuarial rates for Ann Arbor stages I and II were 53% (95% CI, 41-65%) and 20 % (95% CI, 6-34%), respectively ($p < 0.01$), while the 5-year local recurrence-free survival rates for Ann Arbor stages I and II were 62% (95% CI, 50-74%) and 32 % (95% CI, 10-54%), respectively ($p < 0.01$). On the other hand, 50 patients who evolved local failure had a grave prognosis. The majority of patients experienced re-recurrence or systemic relapse despite salvage treatments. For the entire group of local failures, the 2-year actuarial survival rate following local recurrence was 20%.

The clinical and treatment factors assessed for potential prognostic impact included (a) patient-related factors, age and gender; (b) tumor-related factors, primary site (nasal cavity and paranasal sinuses vs. others), lymph node involvement (no vs. yes), and the presence of B symptoms, and Ann Arbor stage (stage I vs. stage II); and (c) treatment-related factors, RT dose (< 45 Gy vs. ≥ 45 Gy), RT volume (primary alone vs. primary and neck node irradiation), and response to RT (CR vs. non-CR). Among the various prognostic factors, patients with an Ann Arbor stage I, an RT dose of more than 45 Gy and those who achieved a CR after RT had a more favorable survival rate and a better local recurrence-free survival rate than their counterparts. However, achieving a CR was found to be the most potent prognostic factor affecting overall survival and the local recurrence-free survival of patients. Because of strong weighting of an initial response to RT in analysis of prognostic factors, the primary site, Ann Arbor stage, and RT dose were

subjected to multivariate analysis. Although Ann Arbor stage and RT dose appeared to be a prognostic determinant for 5-year overall actuarial survival rate, eliminating a factor of the initial response to RT. However, none of these variables was an independent prognostic factor of 5-year local recurrence-free survival rate in multivariate analysis (Table 4).

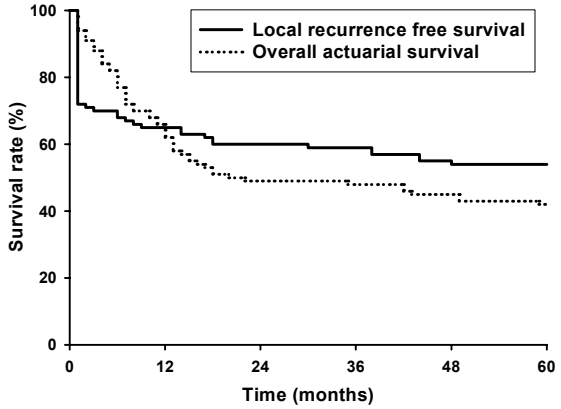


Figure 6. Overall actuarial survival and local recurrence free survival rates.

Table 4. Prognostic factors influencing 5 year overall survival and local recurrence free survival

Factor	5-yr OS		5-yr LRFS	
	Univari-ate	Multiva-riate	Univari-ate	Multiva-riate
Patient related				
Age (≥ 45 years)	NS	–	NS	–
Sex	NS	–	NS	–
Tumor related				
Primary site (sinonasal vs. others)	NS	–	0.09	NS
Lymph node involvement	NS	–	NS	–
Systemic B symptoms	NS	–	NS	–
Ann Arbor stage (I vs. II)	< 0.01	< 0.01	< 0.01	0.09
Treatment related				
RT dose (< 45 Gy vs. ≥ 45 Gy)	< 0.01	0.02	0.02	0.10
RT volume (neck node RT)	NS	–	NS	–
Response to RT	< 0.01	–	< 0.01	–

Abbreviation: OS = overall survival; LRFS = local recurrence free survival.

IV. DISCUSSION

Because of the overwhelming problems of frequent local recurrence and the ineffectiveness of systemic chemotherapy[12, 13, 15, 17, 18, 27, 34-36, 38-40], several authors have advocated that RT is the logical modality for angiocentric T-cell and NK/T-cell lymphoma patients[28, 34, 36, 37, 40]. Until recently, however, the majority of previous papers have not fully addressed the RT technique and its outcome in these patients. Furthermore, most studies have been based on grouping of inhomogeneous patient cohorts, mixed with those receiving RT alone, chemotherapy alone, or a combination of systemic chemotherapy and RT[28, 37, 41]. Hence, such data is unlikely to provide valid information upon the patterns of local failure or optimal radiotherapy parameters, concerning the RT doses or RT fields. Although the present study also contains the potential biases associated with the retrospective analysis of patients treated over several decades without a constant protocol, our results indicate that the patterns of local failure represent the protean features, comprising TR/MR or ER, and that an achievement of CR is the most important parameter for treatment success in patients who have received RT alone. In addition, we observed that local control rate was not enhanced with RT doses in excess of 54 Gy, although the dose-response curve for local control is sigmoidal shape within the range of RT doses from 20 Gy to 54 Gy. Our data also shows an important finding that the omission of elective nodal irradiation does not result in an increase in regional recurrence.

The patterns of treatment failure after definite RT presented here provide information regarding the biologic behavior as well as therapeutic considerations for Ann Arbor Stage I and II patients. In agreement with previous data[15], our

study outlines that a high incidence of local failure remains the most serious problem, which is contrast to the relatively low rate of regional failure. Even though it is not easy to determine whether a local recurrence following RT is attributable to a recurrence of the original tumor or the appearance of a new separated tumor, we arbitrary classified the diverse features of local relapse as TR, MR, or ER according to the sites of recurrences in relation to the vicinity of the original tumor. Although TR or MR occurring in or near the site of the primary tumor was the most predominant pattern of local relapse, ER also posed another interesting clinical problem in our study. We observed that 5 patients experienced an ER, which evolved at other non-contiguous extranodal sites of the head and neck, far beyond the initial RT field. However, it seems reasonable to consider TR or MR as a failure to control the primary tumor due to the geographic proximity of the primary and recurrent lesions, while an ER occurring at other sites of the head and neck might be considered as a failure to eradicate multi-centric foci of tumors. Additionally, we found that median time to recurrence for TR/MR was much shorter than that for ER. Simultaneously, patients experiencing an ER showed a higher salvage rate and a more favorable prognosis than those with TR/MR. Substantial differences in the temporal relationships of local relapses and their prognoses in cases of TR/MR and ER provided supplementary evidence that the biologic mechanisms of these types of local recurrences are dissimilar. With regard to RT volume, earlier reports have claimed the importance of wide-field RT that the margins of apparently normal tissue should be sufficiently included enough to avoid a MR or an ER. Our experience with 3 cases of MR supports the importance of generous margins of clinical target volume to minimize marginal miss, but experience with 5 cases of ER did not reflect such an

approach, because the likelihood of an ER appears to be unrelated to the RT volume. Although it is still uncertain whether elective node irradiation is necessary, we observed that omitting nodal irradiation did not result in an increase in the frequency of regional recurrence, particularly in patients whose primary sites were the nasal cavity and/or paranasal sinuses.

Even though several studies have shed light on the relationships between tumor control and RT doses in angiocentric T-cell and NK/T-cell lymphomas, it is not yet determined whether local control rates are enhanced by increasing total doses of RT. Smally *et al.*[27] reported the first convincing data that a minimum tumor dose of 42 Gy or time-dose fractionation (TDF) of 70 is required to achieve long-term local control, based on their findings that RT doses of less than 40 Gy are often associated with a high rate of local recurrence. Shikama *et al.*[37] reported that the 5-year local control rate was significantly higher, when the total dose was greater than 50 Gy (100% vs. 67%, $p = 0.013$). However, we failed to demonstrate a definite dose-response above dose levels of 54 Gy in our patients. The dose-response curve was sigmoid in shape within the range 20-54 Gy, which followed the steep part of the curve, reflecting little enhancement of additional local control was obtained at dose levels in excess of 54 Gy. The lack of a statistically significant impact of radiation dose on tumor control at higher dose levels may be explained by patient selection or the lack of an apparent dose-effect in bulky tumors or radioresistant tumors. Nevertheless, it seems necessary to identify an appropriate subset of patients for whom an additional booster dose may be beneficial, because approximately half of the patients with residual disease after receiving the planned RT dose attained CR with dose

escalations of up to 60-70 Gy. Recently, ^{18}F-deoxyglucose positron emission tomography (FDG-PET) scanning has been suggested to be helpful for documenting such candidates[36]. Conversely, some authors have favored a combined chemotherapy and RT despite the ineffectiveness of chemotherapy. Sakada *et al.*[41] recommended that it is desirable to deliver 60 Gy with sequential chemotherapy to maximize in-field disease control, and Cheung *et al.*[36], reviewing data from several series, also suggested that concurrent chemoradiotherapy should be employed with a tumor dose of at least 50 Gy to intensify local treatment, given the extremely poor local control rate found in their previous analysis. To further improve the local control rate, we believe that RT should be incorporated with other interventions using radiosensitizers or more effective chemotherapeutic agents.

An assessment of reliable risk factors predictive of local recurrence would probably provide a clue as to how to select patients at risk who either did or did not benefit from RT. The current study indicates that neither cervical lymphadenopathy nor the presence of systemic B symptoms was the principal risk factor for local recurrence. Although Ann Arbor staging at the time of the initial diagnosis correlated with the probability of TR/MR by univariate analysis, it became less important in multivariate analysis. No significant difference in recurrence rates was observed between stages I and II patients. Of the various treatment-related factors, achieving a CR after definite RT was found to be the major treatment parameter in determining treatment success. As expectedly, a dose lower than 45 Gy was a potential predictor of an increased risk of TR/MR, but RT volume was not found to be an independent predictive risk factor in our analyses. However, this analysis does not point out certain clinical parameters. These

problematic aspects included the RT plans and techniques, i.e., inhomogeneous dose distribution within the tumor, insufficient treatment volume, and the difficulty in reproducing the daily setup. In order to improve the local control rate, optimal RT planning should be considered as important contributors to local failure. A better treatment outcome will ensure with advances in medical imaging techniques and potential benefits from 3-dimensional treatment planning or IMRT planning.

In summary, it is apparent from our observation as well as by previous studies[6, 15, 18, 27, 28, 34, 37] that despite a relatively higher radiosensitivity, angiocentric T-cell and NK/T-cell lymphoma patients who received RT alone appear to carry a relatively unfavorable prognosis. In addition, our data documents that local failure is still a major obstacle in the management of these patients and that an achievement of CR is a particularly important determinant of treatment success. Although dose escalation up to more than 54 Gy cannot entirely reduce the incidence of TR/MR, we believe that it is important to identify an appropriate subset of patients for whom an additional booster dose is beneficial. Given a high rate of local failure, an investigational approach should be conducted to supplement RT using radiosensitizers or more effective chemotherapeutic agents in future trials.

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ABSTRACT (IN KOREAN)

국한성 두경부 혈관 중심위 림프종에서 방사선 조사선량에 따른 반응율 및 국소 제어율 관계

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목 적: 1기, 2기 혈관 중심위 T 세포성 및 NK/T 세포성 림프종의 방사선 단독 치료 시 국소 실패 양상 및 위험인자를 조사하고 국소 제어율에 영향을 미치는 방사선 선량-반응 관계를 알아보고자 하였다.

재료 및 방법: 1976년부터 1998년까지 1기, 2기 혈관 중심위 T-세포성 및 NK/T-세포성 림프종으로 중앙값 45 Gy (20 Gy에서 70 Gy까지)의 방사선 조사 선량으로 치료를 받은 102명을 대상으로 하였다. 국소 실패 양상, 국소 실패 위험인자, 방사선 조사선량-반응 관계 및 생존율을 분석하였다. 다양한 국소 재발의 형태로 인하여, 방사선 조사영역에 따라 조사영역 내 재발 (true recurrence, TR), 경계부위 재발 (marginal recurrence, MR), 그리고 조사영역 밖에서의 재발 (elsewhere recurrence, ER)로 구분하였다.

결 과: 방사선치료 후 72%의 높은 완전관해율에도 불구하고 60명이 재발하였고 국소 재발, 지역 재발, 전신 재발이 각각 48명(47%), 3명(3%), 28명(27%)이었다. 국소 재발 양상은 방사선 조사영역 내 재발이 42명, 경계부위 재발이 3명, 조사영역 밖에서의 재발이 5명이었다. 조사영역 내 및 경계부위 재발까지 중앙 기간(1개월)은 조사영역 밖의 재발(12개월)보다 짧았다. 또한 구제술 후 2년 생존율이 각각 6%, 80%로 조사영역 내 및 경계부위 재발 시 불량한 예후를 보였다 ($p < 0.01$). 방사선 조사선량-반응 관계는

로지스틱 회귀분석을 통해 선량에 따른 국소 제어가 증가함을 알았다 (p =0.017). 그러나 20 Gy에서 54 Gy 범위에서는 에스자 형태의 증가를 보였으나, 그 이상의 방사선 조사선량에서는 편평하였다. 5년 생존율, 국소 무재발 생존율은 각각 42%, 53%였다. 완전관해 유무가 국소 재발의 가장 중요한 위험인자였다.

결 론: 본 연구는 혈관 중심위 T 세포성 및 NK/T 세포성 림프종의 방사선 단독 치료 시 국소 재발이 주요한 장애요인이고 완전관해 달성이 치료 성공에 중요한 인자임을 알 수 있었다. 비록 54 Gy 이상의 방사선 조사선량이 국소 재발을 낮추지는 못했으나 추가적 방사선 조사선량이 도움이 되는 소집단을 알아내는 것이 중요하다고 생각한다. 높은 국소 재발로 인해 방사선 민감제 혹은 효과적인 항암제가 방사선치료에 추가되는 연구가 진행되어야 할 것으로 사료된다.

핵심되는 말 : 혈관 중심위 림프종, 선량-반응 관계, 국소 재발