The role of radiotherap and chemotherap in the treatment of earl stage extranodal natural killer/T cell l mphoma, nasal t pe, in the era of multimodal treatment

Tae Hyung Kim

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Chang-Ok Suh

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Tae Hyung Kim

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This certifies that the Master's Thesis

of Tae Hyung Kim is approved.

----------서창옥----------

Thesis Supervisor : Chang-Ok Suh

----------양우익----------

Thesis Committee Member#1 : Woo-Ick Yang

----------김진석----------

Thesis Committee Member#2 : Jin Seok Kim

The Graduate School
Yonsei University

June 2015

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Tae Hyung Kim

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ABSTRACT

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Tae Hyung Kim

Department of Medicine
The Graduate School, Yonsei University

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***Purpose*:** To evaluate the role of radiotherapy (RT) and chemotherapy in the treatment of early stage extranodal natural killer/T-cell lymphoma (ENKTL).

***Patients and Methods*:** Fifty-five patients with stage I or II ENKTL who were treated with RT between 1999 and 2013 were retrospectively analyzed. The median age was 54 years old (range, 24-81). Thirty-nine patients (71%) had Ann Arbor stage I diseases, and 16 patients (29%) had stage II diseases. Patients were grouped by treatment modalities: RT alone (n=19, 35%), upfront chemotherapy+RT (CT; n=16, 29%), and concurrent chemoradiotherapy (CCRT; n=20, 36%). Median RT dose was 48 Gy. Patient characteristics between each treatment group were well balanced. Patterns of failure and survival were analyzed.

***Results*:** The overall response rate after RT was 94.6%. The most common failure was distant failure (10 patients), and 7 patients experienced local failure, comprising 5 in-field failures and 2 out-field failures. Equal frequency (16%) of both local and distant failure occurred in RT alone group and the most common failure sites were local failures (19%) in upfront CT+RT group, and distant failures (25%) in CCRT group. After 56 months of median follow-up (range, 1-178 months), the 5-year overall survival (OS) and progression free survival (PFS) rates were 66% and 54%, respectively. The 5-year OS rates for RT alone, upfront CT+RT, and CCRT groups were 76%, 69%, and 55%, respectively.

***Conclusion*:** In the era of multimodal treatment for ENKTL, RT alone with advanced techniques deserves more attention for the local disease control. Maintenance treatment containing more effective chemotherapy should be considered for distant disease control.

Key words: Extranodal natural killer/T cell lymphoma, Radiotherapy, Pattern of failure

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I. INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma (ENKTL), nasal type, formerly referred to as polymorphic reticulosis, midline malignant reticulosis and T-cell angiocentric lymphoma, was classified as NK/T cell lymphoma by 1998 WHO classification for the first time. ENKTL are relatively prevalent in East Asia, comprised 3rd most common lymphoma in Korea, according to nationwide study of malignant lymphomas.[1] ENKTL in early-stage is usually localized within upper aerodigestive tract, and is associated with Epstein-Barr Virus (EBV). It is usually characterized by extensive angioinvasion and necrosis.

The optimal management of ENKTL has been changed continuously. Before classified as lymphoma, disease was treated with radiotherapy (RT) alone. In the

report from our institution,[2] patients treated with RT alone experienced 83.7% of overall response rate, but 50% of local failure and 25% of systemic failure resulted in 40% of 5-year survival rate. After classified as lymphoma, upfront chemotherapy was given for the primary treatment. However, frequent local failure was observed.[3] Although combination of multiple chemotherapy agent such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), EPOCH (etoposide, predinisone, vincristine, cyclophosphamide, doxorubicin), and SMILE (steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide) was used for primary treatment; concurrent chemoradiotherapy (CCRT); or sequential CCRT, neither the incidence of systemic relapse nor the prognosis is significantly altered by the use of chemotherapy, and local control is comparable to RT alone which utilized advanced modern radiation technique.[4] Then, CCRT followed by maintenance chemotherapy is considered as one of the treatment options. According to Korean lymphoma consortium,[5] CCRT followed by VIPD chemotherapy (vp-16, ifosfamide, cisplatin, and dexamethasone), showed promising outcomes resulting in 73% CR and 86.2% in 3-year overall survival. Nonetheless, distant failures did not decrease compared to RT alone data.

There has been no clear consensus on optimal management for the disease, and no randomized trial comparing RT alone with CCRT. National Comprehensive Cancer Network guideline recommended radiotherapy (RT) alone or concurrent chemoradiotherapy (CCRT) or sequential CCRT for stage I ENKTL without any risk

factors.

This study analyzed the clinical outcomes including local failure, survival and toxicity in the patients with stage I & II ENKTL. The purpose of this study was to investigate the role of RT and chemotherapy after introducing chemotherapy for the treatment of ENKTL.

II. MATERIALS AND METEHODS

1. Patients

Between 1999 and 2013, 82 patients with ENKTL were treated with RT at Yonsei Cancer Center in Seoul, Korea. Retrospectively reviewing their pathologic reports and medical records, 17 patients with Ann Arbor stage III or IV disease and 8 patients with primary tumor in non-head and neck area were excluded from this analysis. Two patients were excluded from this analysis because they were treated with salvage intent after failure of first treatment. This study used the analysis of 55 eligible patients with ENKTL. The pathologic diagnosis of ENKTL was based on either atypical CD56 expressing lymphoid cell proliferation or nuclear EBER mRNA and cytoplasmic cytotoxic molecule expressing atypical lymphoid cell proliferation if they did not express CD56. Pretreatment evaluation were performed at diagnosis, which included history taking; physical examination; complete blood count; serum biochemistry with lactate dehydrogenase (LDH); bone marrow aspiration and biopsy; computed tomography scanning and/or magnetic resonance imaging (MRI) of the involved lesion; and positron emission tomography (PET). PET was done for 41 patients (74.5%).

Patient characteristics are summarized in table 1. The median age was 54 years (range, 24-81). Seventeen patients (68%) were younger than 60 years of age. The male/female ratio was about 6:4. Thirty nine patients (71%) had Ann Arbor stage

I and 16 patients (29%) had stage II disease. Forty seven patients (86%) had disease in sinonasal area. Thirteen patients (24%) had high EBV titer. Systemic "B" symptoms were present in 13 patients (24%). Twenty one (38%) patients and 28 patients (51%) were in the low risk and low-intermediate risk categories of the International Prognostic index[6], respectively. According to NK/T cell lymphoma prognostic index (NKPI)[7], which includes the presence of "B" symptoms, lesions at stages III or IV, elevated serum LDH concentration, and lymph node involvement, 15 patients (28%) grouped into group III or IV (ie, those with >two risk factors). Patient characteristics such as sex, age, stage, performance status, primary site, serum LDH, presence of "B" symptoms, IPI and NKPI were well balanced between three different treatment modality groups; RT alone (n=19, 35%), upfront chemotherapy (CT) + RT (n=16, 29%), and CCRT (n=20, 36%) (Table2.).

Table 1. Patient characteristics

Variables	Groups	n	%
Sex	Male	34	62%
	Female	21	38%
Age (years)	Median (range)	54 (24-81)	
	≥60	17	32%
	<60	38	68%
Ann arbor stage	I	39	71%
	II	16	29%
Performance status	ECOG 0, 1	52	94%

Variables	Groups	n	%
	ECOG 2	3	6%
Primary site	Sinonasal	47	86%
	Others	8	14%
Eptein-Barr Virus	Yes	13	24%
	Not checked	42	76%
Serum LDH	Elevated	26	68%
	Normal	12	32%
B symptoms	Yes	13	24%
	No	42	76%
IPI	1 (Low)	21	38%
	2 (Low intermediate)	28	51%
	3 (high inter)	6	11%
	4 (high)	0	0%
NKPI	Group1	19	35%
	Group2	21	38%
	Group3	13	24%
	Group4	2	4%

Abbreviations: IPI = international prognostic index; NKPI = NK/T cell lymphoma prognostic index

Table 2. Patient characteristics according to treatment modalit groups

Variables	Groups	RT alone, n (%)	Upfront CT+RT, n (%)	CCRT, n (%)	*P*-value
Sex	Male	10 (53%)	12 (75%)	12 (60%)	0.395
	Female	9 (47%)	4 (25%)	8 (40%)	
Age (years)	≥60	12 (63%)	14 (88%)	12 (60%)	0.169
	<60	7 (37%)	2 (12%)	8 (40%)	

Variables	Groups	RT alone, n (%)	Upfront CT+RT, n (%)	CCRT, n (%)	*P*-value
Stage	I	15 (79%)	11 (69%)	13 (65%)	0.656
	II	4 (21%)	5 (31%)	7 (35%)	
Performance	ECOG 0, 1	19 (100%)	16 (100%)	17 (85%)	0.102
	ECOG 2	0 (0%)	0 (0%)	3 (15%)	
Primary site	Sinonasal	15 (79%)	13 (81%)	19 (95%)	0.352
	Others	4 (21%)	3 (19%)	1 (5%)	
Serum LDH	Elevated	5 (71%)	9 (82%)	12 (60%)	0.476
	Normal	2 (29%)	2 (18%)	8 (40%)	
B symptoms	Yes	3 (16%)	3 (19%)	7 (35%)	0.376
	No	16 (84%)	13 (81%)	13 (65%)	
IPI	1	10 (53%)	7 (44%)	4 (20%)	0.225
	2	8 (42%)	8 (50%)	12 (60%)	
	3	1 (5%)	1 (6%)	4 (20%)	
NKPI	Group1	10 (53%)	5 (31%)	4 (20%)	0.302
	Group2	7 (37%)	6 (38%)	8 (40%)	
	Group3	2 (11%)	4 (25%)	7 (35%)	
	Group4	0 (0%)	1 (6%)	1 (5%)	

Abbreviations: IPI = international prognostic index; NKPI = NK/T cell lymphoma prognostic index

2. Treatment

Before 1987, our treatment policy for stage I or II disease was to administer involved-field RT alone. Subsequently, the patients received either chemotherapy followed by RT or RT alone. Recently, the patients were treated with either CCRT alone or CCRT followed by maintenance chemotherapy. Nineteen patients (35%)

received RT alone. Sixteen patients (29%) had upfront chemotherapy followed by RT and 15 out of 16 patients received maintenance chemotherapy after RT. Seven patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); 5 patients were treated with CAVOP (cyclophosphamide, vincristine, vp-16, doxorubicin, and prednisone); and 4 patients were treated with IMVP-16 (ifosfamide, methotrexate, and vp-16). Twenty patients (53%) had cisplatin based CCRT, and 15 out of 20 patients were treated with adjuvant chemotherapy, mainly consisted of VIPD.

Contrast enhanced computed tomography simulation with a thermoplastic device was mandatory and mouth piece to space out tongue from radiation field was used in the patients who received nasal cavity irradiation. All patients received involved-site RT (ISRT). Limited field ISRT included all gross lesions and adequate margins. Extended field ISRT included all gross lesions, bilateral nasal cavities and paranasal sinus in case of an Ann Arbor stage I disease, and all gross lesions, bilateral nasal cavities, paranasal sinus, and involved side of cervical neck lymph node chains in case of an Ann Arbor stage II disease. In case of gross lesions at outside of nasal cavity, target volume of extended field ISRT included gross lesions, Waldeyer's ring, and bilateral cervical neck lymph node chains. Ten patients (18%) received two-dimensional (2D) RT, 35 patients (64%) received three-dimensional conformal radiotherapy (3D-CRT) by using 6 MV photons generated from a linear accelerator and 10 patients (18%) received intensity-modulated radiotherapy (IMRT) by using

tomotherapy. Using 3D CRT, the most common field arrangements was the three-field technique, consisting of field arrangements weighted in favor of anterior field and two wedged lateral field. After total dose of 45 Gy irradiated to gross tumors, a boost dose in the range 9-18 Gy (up to a total dose of 54 -63 Gy) was administered to persistent tumors. Using IMRT, simultaneously integrated boost (SIB) technique was used. Clinical target volume (CTV) 1 encompassed gross lesions and CTV2, encompassed margins of CTV1, which is different in case of limited/extended field ISRT. CTV was modified to reduce dose of organs at risk (OARs), such as spinal cord, optic apparatus (optic nerves and chiasm), mandible, pharynx, larynx and esophagus. The maximal dose constraints to spinal cord, optic apparatus and mandible were below 45 Gy, below 55 Gy and below 70 Gy, respectively. Other OARs, such as larynx, pharynx, and esophagus were also delineated and were set at doses as low as possible. For the planning target volume (PTV), a 0.3-cm margin was applied to CTV considering patient motion and daily setup error. Two different dose prescriptions were used, which is 20 fractions or 25 fractions. In 20 fractions' prescription, total dose of CTV1 and CTV2 were 48 Gy and 40 Gy, respectively. In 25 fractions' prescription, total dose of CTV1 and CTV2 were 53 Gy and 45 Gy, respectively.

The radiation doses ranged from 22 to 63 Gy (median, 48 Gy) at a dose per fraction of 1.8-2.4 Gy within 4-6 weeks. Forty two patients (76%) received more than 45 Gy. Assuming an α/β ratio of 10 Gy, 24 patients (43.6%) received 40-45 Gy, 20 patients (36.4%) received 46-50.4 Gy, and 9 patients (16.4%) received 54-63 Gy in a

1.8 Gy- equivalent dose. Two patients (3.6%) received lower than 40 Gy. One patient (a 68-year-old man) who received cisplatin based CCRT died as a result of pneumonia exacerbation after 22 Gy. One patient (a 50-year-old man) who received RT after upfront chemotherapy consisted of IMVP-16 refused RT after 23.4 Gy because of grade IV oral mucositis.

3. Assessment and evaluation

Treatment response was assessed according to WHO criteria. CR was defined as disappearance of all previously measurable lesions and absence of any new tumor lesions. PR was defined as a decrease of at least 50% in the product of two perpendicular diameters of each measurable lesion. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in tumor size, and progressive disease (PD) was defined as greater than 25% increase in the product of the two diameters of at least one tumor or as the presence of a newly developed lesion.

Treatment failure was categorized as local failure, regional failure, or distant failure. Distant failure was defined as the appearance of systemic disease at sites other than the head and neck and cervical neck lymph node chains. Distant failure was diagnosed on the basis of the clinical and/or radiologic findings. Local failure was categorized, proposed previously by Koom et al.[8], into true recurrence (TR), occurring within RT fields; marginal recurrence (MR), occurring near contiguous

areas of the primary site, but just outside the border of the RT field; and elsewhere recurrence (ER), occurring at another extranodal site of the head and neck.

Posttreatment evaluations were performed at 1 month after treatment to monitor disease progression including local/regional/distant failures, and repeated every 3 to 6 months thereafter.

Treatment-related toxicities were assessed at every follow-up visit. Toxicity was graded based on the Common Toxicity Criteria Version 4.0 from the National Cancer Institute (NCI-CTC v4.0).

4. Statistical anal sis

All statistical analysis used SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). Overall survival (OS), progression free survival (PFS), and local failure free survival (LFFS) were plotted using the Kaplan-Meier method and the differences were evaluated using the log-rank test. Survival time was measured from the date of diagnosis to the date of death of any cause or the last follow-up. PFS was estimated to the date of initial relapse or death. LFFS was estimated to the date of local failure or death. A p-value <0.05 was considered statistically significant.

III. RESULTS

1. Response to RT and patterns of treatment failure

Response to RT was assessed by physical examination, computed tomography and/or MRI performed within 6 weeks after the completion of RT. Response to RT and treatment outcomes are summarized in Figure 1. Forty two patients (76.4%) achieved a CR and 10 patients (18.2%) achieved a PR. The remaining 3 patients (5.4%) did not complete the RT and/or died from progressive disease during or immediately after RT.

Nineteen patients had treatment failure (Fig 2.). Only 2 patients had multiple sites of failure, and remaining 17 patients had only a single site of failure. The most common failure was distant failure (10 patients), 8 patients had skin metastasis, 1 patient had lung metastasis, and 1 patient had para-aortic lymph node metastasis. Four patients (7%) experienced regional failure. Three patients had stage I disease, whereas 1 patient had stage II disease. Except for 2 patients who had primary tumors of a tonsil area, 37 patients of stage I disease received extended field ISRT and 3 patients (8%) experienced untreated regional node failure. Of 16 patients of stage II disease, 14 patients who received bilateral neck node irradiation did not experience regional failure. However, 1 of 2 patients (50%) who received involved neck node irradiation experienced untreated regional node failure.

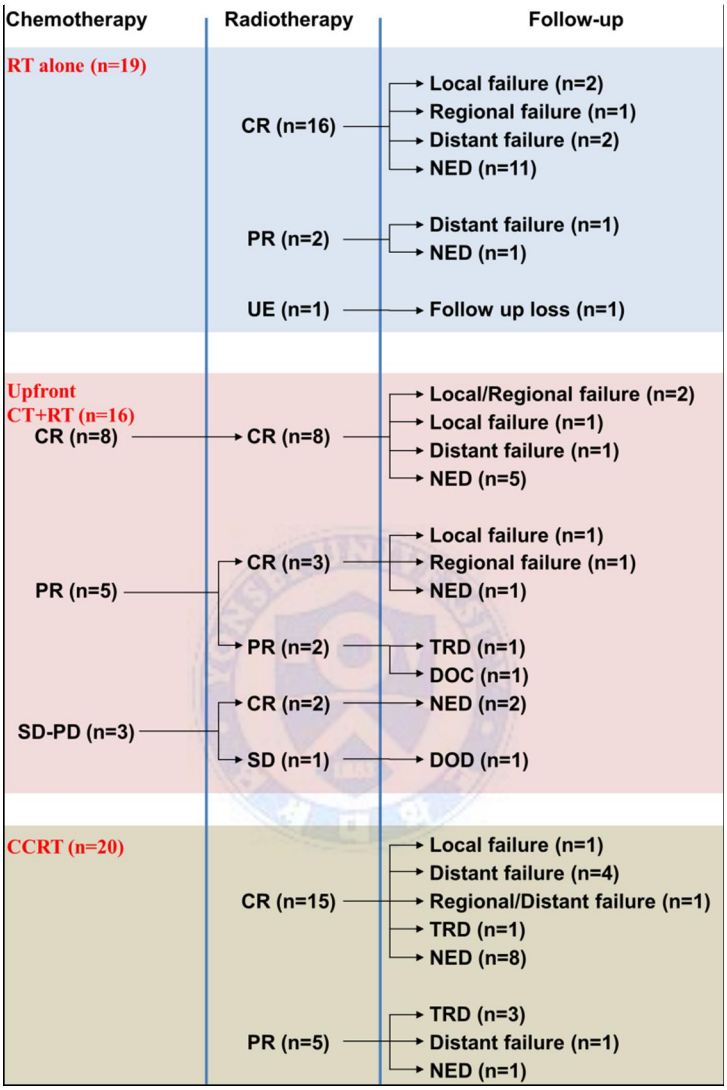

Fig 1. Summar of treatment outcomes and treatment failures

Abbreviations: RT = radiotherapy; CR = complete response; PR = partial response; UE = unevaluable; CT = chemotherapy; SD = stable disease; PD = progressive

disease; NED = no evidence of disease; TRD = treatment related death; DOC = death of other cause; DOD = death of disease; CCRT = concurrent chemoradiotherapy

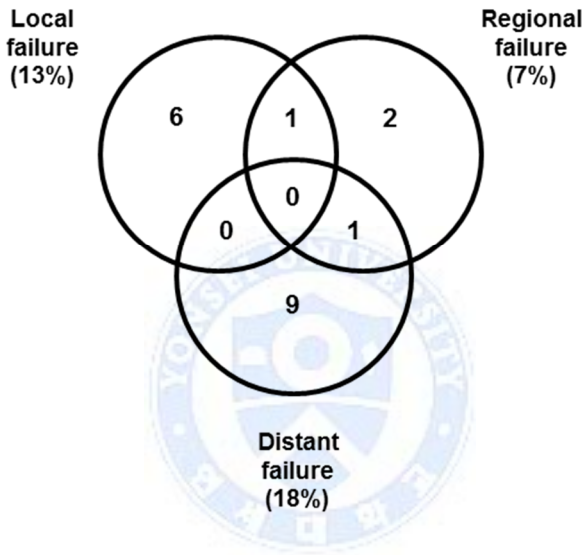

Fig 2. Patterns of failure

The characteristics of seven patients (11%) who experience local failure, comprising TR in 5 patients and ER in 2 patients, are summarized in table 2. Five patients had stage I disease, and 2 patients had stage II disease. Three patients

received upfront chemotherapy followed by RT, 3 patients received RT alone, and 1 patient received CCRT. Six patients received less than 50 Gy, mostly 45 Gy in 25 fx. Six patients had no evidence of disease after salvage treatment, consisted of chemotherapy and/or re-irradiation.

Table 3. Details of patients who experienced local failure

#	Age	Sex	Stage	Primary site	Treatment group	RT dose	Failure site	Time to failure	Salvage treatment	Current status
1	52	M	IA	Rt. nasal cavity	Upfront CT+RT	45 Gy/25 fx	Rt. Mandible (ER)	6months	CT, RT (41.4 Gy)	NED 112 months
2	52	F	IA	Lt. nasal cavity	CCRT	44 Gy/20 fx	Rt. Nasal cavity (TR)	81months	CT	NED 87 months
3	44	F	IA	Rt. nasal cavity	Upfront CT+RT	45 Gy/25 fx	Rt. Nasal cavity (TR)	33months	CT	DOD 88 months with regional, distant failures
4	36	F	IA	Rt. nasal cavity	RT alone	50.4 Gy/28 fx	Rt. Nasal cavity (TR)	65 months	reRT (40 Gy)	NED 133months
5	46	M	IIA	Nasopharynx	Upfront CT+RT	45 Gy/25 fx	Lt. Nasal cavity (ER)	9months	CT	NED 98months
6	54	M	IIA	Oropharynx	RT alone	45 Gy/25 fx	Oropharynx (TR)	7monhts	reRT(34.8 Gy)	NED 178months
7	74	F	IA	Rt. nasal cavity	RT alone	45 Gy/25 fx	Lt. Nasal cavity (ER)	149 months	reRT (44 Gy)	NED 159 months

Abbreviations: CT = chemotherapy; RT = radiotherapy; CRT = conformal radiotherapy; CR = complete response; ER = elsewhere recurrence; LN = lymph node; reRT = re-radiotherapy; NED = no evidence of disease; TR = true recurrence; DOD = dead of disease

Patterns of failure are analyzed according to treatment groups. Equal frequency (16%) of local and distant failure occurred in RT alone group and the most common failures in upfront chemotherapy group and CCRT group were local failure (19%) and distant failure (25%), respectively (Table 3.).

Table 4. Patterns of failure according to treatment modalit groups

Patterns of failure	Treatment groups			*P*-value
	RT alone (n=19)	Upfront CT+RT (n=16)	CCRT (n=20)	
Local failure	3 (16%)	3 (19%)	1 (5%)	0.361
Regional node failure	1 (5%)	2 (13%)	1 (5%)	0.67
Distant failure	3 (16%)	1 (6%)	5 (25%)	0.345

Abbreviations: RT = radiotherapy; CT = chemotherapy; CCRT = concurrent chemoradiotherapy

2. Survival anal sis and prognostic factors

The median follow-up time was 26 months (range, 1 to 178 months) for all patients and 56 months (range, 1-178 months) for patients who still alive at the time of analysis. The median follow-up time for treatment groups; RT alone, upfront CT+RT, and CCRT was 44 months, 50 months, and 19.5 months, respectively. The 5-year OS rate and PFS rate for all 55 patients were 66% and 54%, respectively. The 5-

year OS rate for treatment groups; RT alone, upfront CT+RT, and CCRT was 76%, 69%, and 55%, respectively (p=0.388). The 5-year PFS rate for treatment groups; RT alone, upfront CT+RT, and CCRT was 70%, 47%, and 48%, respectively (p=0.48). The 5-year LFFS rate for treatment groups; RT alone, upfront CT+RT, and CCRT was 93%, 69%, and 100%, respectively (p=0.338) (Fig 3.)

The clinical and treatment factors assessed for potential prognostic impact included patient-related factors (age and gender); tumor related factors (primary site [nasal cavity vs. others], EBV [Yes vs. No], Ann Arbor stage [Stage I vs. Stage II], and B symptoms [presence vs. absence]); and treatment related factors (RT dose [<50 Gy vs. ≥50 Gy]; response to RT [CR vs. non-CR]), and treatment sequence [RT alone vs. Upfront CT+RT vs. CCRT] (Table 4.) Among these, achieving a CR from RT was the most powerful and the only statistically significant prognostic factor affecting OS. Patients with IPI group 3 (high intermediate) and NKPI group 4 showed worse OS than other group, which is not statistically significant (p=0.052 and 0.434, respectively).

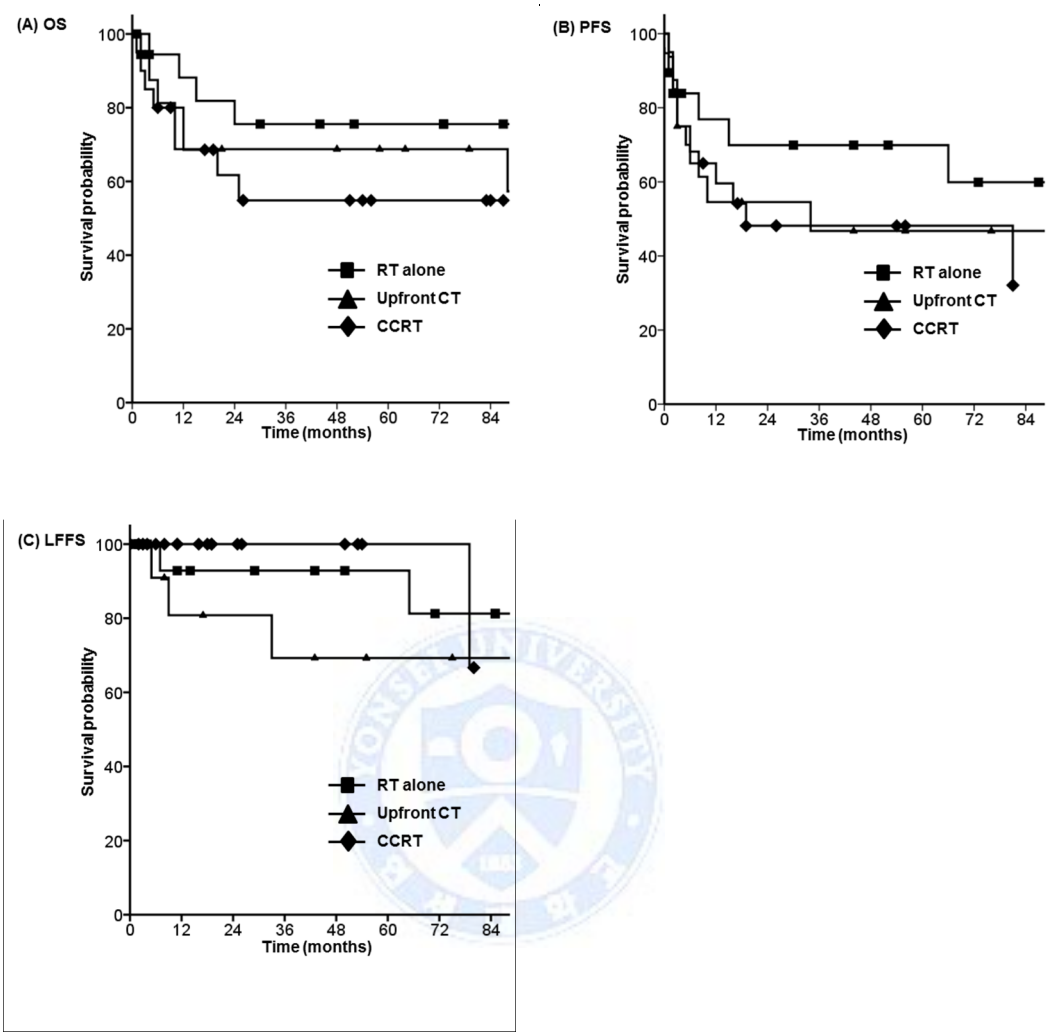

Figure 3. Overall survival (A), progression free survival (B), and local failure free survival (C)

Table 5. Prognostic factors for overall survival

Factor	5-yr OS rate	p-value (uni)
Age (y)		0.5
<54	72%	
≥54	61%	
Gender		0.9
Male	66%	
Female	66%	
Primary site (sinonasal vs. others)		0.2
Sinonasal	63%	
Other	83%	
Ann Arbor stage (I vs. II)		0.5
I	68%	
II	60%	
Systemic B symptoms		0.7
Yes	66%	
No	67%	
Epstein-Barr virus		0.37
Yes	79%	
No	59%	
RT dose		0.3
<5000 cGy	63%	
≥5000 cGy	70%	
RT response		0.02
CR	74%	
Non CR	42%	
Treatment sequence		0.4
RT alone	76%	
Upfront CT+RT	69%	
CCRT	55%	

Abbreviations: OS = overall survival; RT = radiotherapy; CR = complete response; CT = chemotherapy; CCRT = concurrent chemoradiotherapy

3. Toxicit

Radiation induced toxicity was minimal during treatment; grades 1 or 2 mucositis were observed in 17 patients (31%): RT alone (n=2), upfront CT+RT (n=3), and CCRT (n=12), and grade 1 or 2 nausea/vomiting were observed in 13 patients (24%): RT alone (n=1), upfront CT+RT (n=3), and CCRT (n=9). However, a patient (a 50-year-old man) who received upfront chemotherapy followed by RT experienced grade 4 oral mucositis during RT.

Hematologic toxicity occurred during CCRT or maintenance chemotherapy. Of 36 patients who received chemotherapy, grade 1 or 2 leukopenia was observed in 8 patients (22%): upfront CT+RT (n=1), and CCRT (n=7). Grade 3 or 4 leukopenia/thrombocytopenia was observed in 4 patients (11%) during CCRT.

There were 5 treatment related deaths: upfront CT+RT (n=1) and CCRT (n=4). One patient died when received maintenance chemotherapy after the upfront chemotherapy followed by RT because of gram-positive sepsis. Four patients died because of neutropenic fever and pneumonia aggravation during maintenance chemotherapy after CCRT.

IV. DISCUSSION

Previously, several authors reported that RT alone produced a good complete response rate in patients with early stage ENKTL, but frequent distant and local failures within 2 years of the completion of treatment were a major obstacle to successful treatment.[2,8] Therefore, a new treatment strategy incorporating chemotherapeutic agent was introduced. At first, upfront chemotherapy with anthracycline, such as CHOP or CHOP-like regimens was tried. ENKTL showed a poor response to anthracycline based chemotherapy, resulted in 30-40% of complete remission and frequent local failure and disease progression during upfront chemotherapy was observed.[9,10] The frequent expression of a multidrug-resistant P-glycoprotein in ENKTL was reported to be an underlying mechanism of the poor response.[11] Next, dose intensified upfront chemotherapy was tried in order to prevent disease progression during chemotherapy.[12] Although CR rate was increased to 53%, 3-year overall survival was similar (67%) with 2 treatment related death (12%) and distant failures did not decrease (29%). Therefore, trials of CCRT with chemotherapy as a radiosensitizer were designed.[5,13] Although higher radiation dose, greater than 50 Gy, was suggested in RT alone setting,[8] lower radiation dose, less than 50 Gy, was applied to reduce the toxicities. Treatment paradigm had continuously moved from RT alone to CCRT without conclusive study results comparing RT alone with CCRT.

This study attempted to evaluate the role of RT and chemotherapy in the treatment of ENKTL. Study cohort represents a change of treatment paradigm: RT alone patients were mostly treated in 1999-2004, upfront chemotherapy in 2002-2006, and CCRT in 2007-2013. Although the current study also contained the potential biases associated with the retrospective analysis of patients treated without a consistent protocol, the results contained herein showed a remarkable improvement of treatment outcomes of ENKTL compared to RT alone results previously reported. We previously reported that a half of patients treated with RT alone experienced local failure and 5-year overall survival rate was about 40%.[2,8] However, recent RT alone results has been markedly improved. According to Ye-Xiong Li et al,[14] only 5% of patients who treated with RT alone experienced local failure and 5-year overall survival rate was 80%, which is comparable to our study. In this study, 3 patients (16%) treated with RT alone experienced local failure and 5-year overall survival rate was 76%. There are several reasons of improved RT alone results. With development of imaging modalities, disease extent was determined thoroughly before treatment start. IMRT and image guided radiotherapy (IGRT) is used in almost all cases in head and neck area recently. Most patients with ENKTL received involved-site RT (ISRT), which radiate the area where the disease existed. Limited field ISRT included all gross lesions and adequate margins. Extended field ISRT included all gross lesions as well as any affected adjacent organs (e.g., paranasal sinuses, orbits, nasopharynx, oral cavity, and cervical neck lymph node chains).[14-17] In this study, all patients were

treated with extended field ISRT, and most of patients (82%) were treated with IGRT, comprising 64% of 3D-CRT and 18% of IMRT. In order to identify accurate tumor extent, diagnostic MRI was fused into simulation computed tomography. These modern RT techniques and advanced imaging modality resulted in only 7 patients (11%) experienced local failure during follow-up. There was only 1 patient (5%) who had local failure after CCRT. However, median follow-up period after CCRT was 19.5 months, which is relatively shorter than RT alone or upfront CT+RT, long term follow-up is needed to see whether CCRT reduces local failure.

A detailed review of patients who experienced local failure after RT would probably provide a clue about how to define the appropriate RT dose and RT field. Of 7 patients who experienced local failure, 4 patients had true recurrences and 3 patients had elsewhere recurrences. True recurrences had occurred at 81, 33, 65, 7 months, respectively. RT alone patient received 50.4 Gy, but 3 patients received lower than 50 Gy. As previous reported,[8] RT should be used with a tumor dose of at least 50 Gy to intensify local treatment. Even though chemotherapy was used before RT or with RT, RT dose of lower than 50 Gy seems insufficient, and insufficient RT dose might be associated with late recurrence. On the other hand, 3 patients had experienced elsewhere recurrence. One patient who had primary disease at nasopharynx experienced failure at left nasal cavity. Before introducing of IMRT, it was hard to encompass both nasal cavity and cervical lymph node chain in a radiation field. Because he had primary disease at nasopharynx, radiation field encompassed entire

pharynx and bilateral cervical lymph node chain and nasal cavity which was a recurrent site was not included. One patient who had primary disease at right nasal cavity experienced failure at right mandible, and 1 patient who had primary disease at right nasal cavity experienced failure at left nasal cavity. Radiation field for two patients was tightly defined in order to protect normal tissue such as oral cavity, both eyes and lens. Three cases of elsewhere recurrences imply that extended field ISRT with generous margin is needed for early stage ENKTL. However, our experiences do not justify the prophylactic irradiation of uninvolved sites, and we still don't have enough evidence about proper radiation volume.

Distant failure was still a dominant pattern of failure, even though chemotherapy is incorporated into treatment. Wang L et al. published results of upfront chemotherapy consisted of GELOX (gemcitabine, oxaliplatin, and L-asparaginase) followed by involved-field RT.[18] Overall response rate was 96.3% and 3 patients out of 27 (11%) experienced distant failure. Korean lymphoma consortium published results of CCRT for the early stage ENKTL.[5] Their treatment was consisted of weekly cisplatin-based CCRT followed by maintenance VIPD chemotherapy. The results were outstanding showing that 83.3% of overall response rate, 85% of 3-year OS, 86% of 3-year PFS and 10% of distant failure rate. However, 41% of grade IV toxicities during maintenance chemotherapy and short follow-up period provoked many controversies. Korean lymphoma consortium published results of CCRT followed by L-asparaginase-containing maintenance chemotherapy.[13] The results

showed 90% of overall response rate, 73% of 5-year PFS and 60% of OS with manageable toxicities compared with toxicities treated with VIPD chemotherapy. JCOG (Japan Clinical Oncology Group) also published results of CCRT consisted of 50 Gy of RT with concurrent DeVIC (dexamethasone, etoposdie, ifosfimide, carboplatin) chemotherapy.[19] The overall response rate was 81% and 2-year overall survival rate was 78%, but distant failure rate was 33%, which is not decreased even with chemotherapy. The overall distant failure rate in this study was 18 %, which is superior to the rates reported in previous studies of RT alone, upfront chemotherapy, and CCRT. PET scan was done to identify diseases outside the nasal cavity in 74.5% of patients in this study. Whole body scan may have been related to fewer distant failure rates. Until recently, a high risk factor for distant failure had not been determined. Cyclooxygenase-2, which is identified by immunohistochemical staining, could serve as a predictive factor for higher distant failure.[20] ENKTL is generally very aggressive, and if it is left untreated, it is uniformly fatal. Some investigators classified ENKTL in two subgroups: nasal and extra-nasal/nasal-type, the former being characterized by locoregional aggressiveness and the latter being mostly extra-nasal and associated with early multifocal distant dissemination.[21] High prevalence of distant failure is probably due to heterogeneity of this cohort, composed of two different ENKTL subgroups. In this study, there were 8 patients (14%) who had primary disease in extranasal area, but differences in distant failure rate was not

observed. Seeking a prognostic factor to predict early distant failure is needed for patients who would beneficial with administrating chemotherapy.

There are some limitations in this study. First, this was an institutional based retrospective study of patients treated without a consistent protocol. There were differences in treatment protocol, RT modality, RT dose, and chemotherapy regimens. However, this heterogeneity makes it possible to speculate the role of RT and chemotherapy in the treatment of early stage ENKTL. Second, because of rarity of the disease, a small number of patients could be analyzed, and this makes it impossible to find any statistically significant prognostic factor. The clinical factors predicting poor survival, such as old age, advanced Ann Arbor stage, disease associated with EBV, elevated LDH, presence of Systemic "B" symptoms, IPI and NKPI, were not statistically associated with survival in this study. However, patients with IPI group 3 and NKPI group 4 showed worse OS than other group, which is not statistically significant. There were more patients with IPI group3 and NKPI group 4 in CCRT group than other groups, and this imbalance in patients' characteristics should be noted.

V. CONCLUSION

In this study, the outcome of early stage ENKTL was improved with advance of RT technique. Local control rate in RT alone group was similar with combined chemo-radiotherapy groups. Systemic chemotherapy did not decrease the distant failure rate, and was associated with considerable toxicities. In the era of multimodal treatment for ENKTL, RT alone with advanced techniques deserves more attention for the local disease control. Maintenance treatment containing more effective chemotherapy should be considered for distant disease control.

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ABSTRACT(IN KOREAN)

복합치료시대에서 초기 병기의 비강타입 자연 살해 세포/T-세포 림프종 치료 시 방사선치료와 항암치료의 역할

<지도교수 서 창 옥>

연세대학교 대학원 의학과

김 태 형

목적: 초기 병기의 비강타입 자연 살해 세포/T-세포 림프종의 치료에 있어서 방사선치료와 항암치료의 역할에 대해 살펴보기 위함이다.

대상 및 방법: 1999년에서 2013년 사이에 자연 살해 세포/T-세포 림프종으로 치료받은 55명의 환자를 대상으로 연구가 진행되었다. 환자들의 중앙 연령은 54세 (범위, 24-81세) 였고, 39 명의 환자 (71%) 가 1기의 병기였으며 16명의 환자 (29%) 가 2기의 병기였다. 환자들을 치료 방식에 따라 나누어 보았을 때, 방사선 치료 단독군 (n=16, 35%), 우선적인 항암 치료군 (n=16, 29%), 동시 항암방사선 치료군 (n=20, 36%) 이었다. 환자들이 조사받은 방사선 치료 선량의 중앙값은 48 Gy 였다. 치료 방식에 따라 세 군의 환자특성은 균형

잡혀 있었다.

결과: 94.6% 의 환자에서 방사선 치료에 대한 반응이 있었다. 가장 주요한 재발 양상은 원격재발 (10명) 이었으며 국소재발은 7명의 환자가 경험하였다. 7명의 국소재발 중 5명은 치료받은 범위내의 재발이었고 2명은 치료받은 범위 외에서 재발하였다. 치료방식에 따른 가장 주요한 재발의 양상은 다음과 같다. 방사선 치료 단독군은 국소재발 (16%) 과 원격재발 (16%) 이 동일한 빈도로 나타났으며, 우선적인 항암 치료군에서는 국소재발 (19%) 이 가장 많았다. 동시 항암방사선치료군에서는 원격전이(25%) 가 가장 많았다. 대상 환자의 중앙추적조사기간은 56.0 개월 (범위, 1-178.0 개월) 이었다. 5년 생존률, 무진행 생존률은 각각 66% 54% 였다. 치료방식에 따른 생존률을 보았을 때, 방사선 치료 단독군은 76%, 우선적인 항암 치료군은 69%, 동시 항암방사선치료군은 55% 였다.

결론: 복합치료시대에서 초기 병기의 비강타입 자연 살해 세포/T-세포 림프종의 치료에 있어 발전된 기술을 이용한 방사선치료는 국소

질병 조절을 위해 필요하다. 원격 전이 조절을 위해 더욱 효과적인 항암 치료를 이용한 유지치료가 필요할 것으로 사료된다.

핵심되는 말 : 자연 살해 세포/T-세포 림프종, 방사선치료, 재발양상