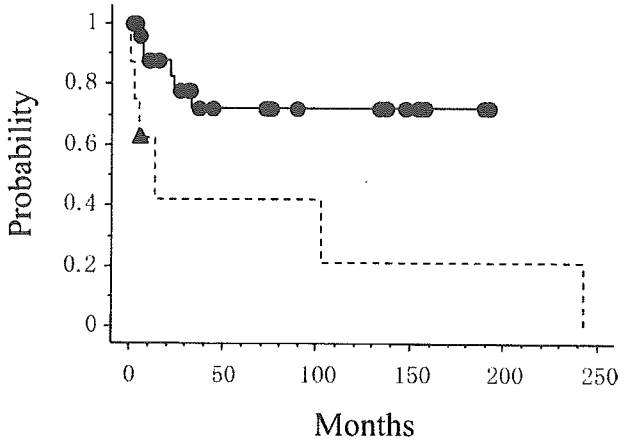

FIGURE 2. This graph illustrates the local control probability as a function of radiotherapy (RT) field. Solid line: an RT field that encompassed all sinuses, the nasopharynx, and macroscopic lesions; dashed line: an RT field that included macroscopic lesions with a margin.

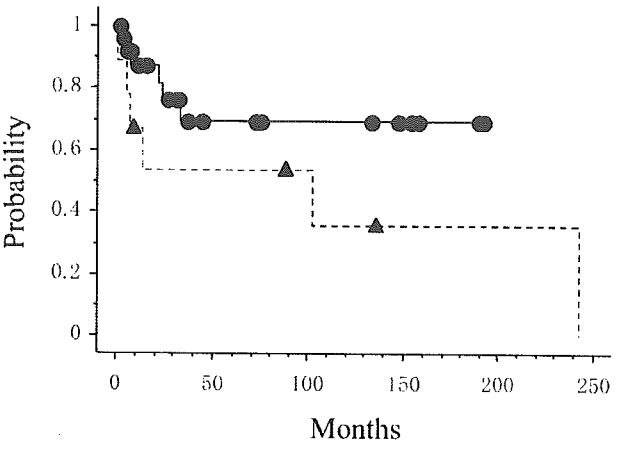

FIGURE 3. This graph illustrates the local control probability as a function of radiotherapy dose. Solid line: doses ≥ 50 grays (Gy); dashed line; doses < 50 Gy.

that included all macroscopic lesions and sites of potential contiguous spread (i.e., all paranasal sinuses, the palate, and the nasopharynx) with adequate margins. The RT field in the remaining eight patients encompassed all macroscopic lesions with generous margins. Although there were six local recurrences in the former group, all but two patients in the latter group experienced local disease recurrence. The LCP at 5 years was 71.9% versus 41.7%, respectively (P = 0.007) (Fig. 2).

Next, we assessed whether there was a dose-response relation for local control. Among the 26 patients who received ≥ 50 Gy of RT, 20 patients were able to achieve local control; however, only 3 of 9 patients in the low-dose group obtained local control (Fisher exact test; P = 0.038). Figure 3 illustrates the LCP as a function of RT dose. The 5-year LCP for patients who received ≥ 50 Gy versus patients who received < 50 Gy was 69.2% (95% CI, 47.9–90.5%) and 53.3% (95% CI, 19.4–87.3%), respectively (P = 0.13). The OAS and DFS rates for patients who received ≥ 50 Gy were 47.7% (95% CI, 28.6–68.6%) and 41.6% (95% CI, 21.3–61.9%), respectively, which did not differ significantly from patients who received < 50 Gy.

Prognostic Factors

The clinical and treatment factors that we assessed for potential prognostic impact included age, gender, primary site, B symptoms, LDH elevation, disease stage, dose of RT, and chemotherapy. However, none of those variables was identified as an independent prognostic factor for OAS and LCP. The only factor that was found to be associated with OAS, DFS, and LCP was the RT field (P = 0.027, P = 0.020, and P = 0.007, respectively). However, multivariate analysis failed to identify any prognostic factors for those three endpoints.

DISCUSSION

Extranodal NK/T-cell lymphoma, nasal type, which was recognized previously as angiocentric lymphoma, has a distinct position in the new World Health Organization classification system.[1] It is characterized by CD56 and cytoplasmic CD3 expression, a germline configuration of the T-cell receptor gene, and a strong association with Epstein–Barr virus (EBV). Many groups have reported treatment outcomes for patients with nasal non-Hodgkin lymphoma.[7–30] Some groups treated patients only with RT,[7,8,10,13,23] but others delivered both chemotherapy and RT.[9,11,12,14–22,24–30] Those studies demonstrated OAS and LCP rates at 5 years of 24–86%, and 31–84%, respectively. Although there are many suggestions in the literature regarding the management and natural history of nasal lymphoma, many of these reports included patients with B-cell lymphoma and patients who did not receive immunohistochemical examinations, which led to a great deal of confusion in relation to the roles of chemotherapy, failure patterns, and treatment outcomes.

There were eight studies, including our previous work,[14] that included only patients who had immunophenotypically confirmed nasal NK/T-cell lymphoma.[14,16–22] Furthermore, of those eight studies, five included only patients who had both CD3ε-positive and CD56-positive expression to exclude peripheral T-cell lymphoma.[17,18,20–22] A summary of those eight

TABLE 3
Summary of the Literature

Reference	Phenotype	Treatment	No.	LFR	5-yr OAS (%)
Itami et al., 1991[14]	NK or T-cell	CT → RT or RT	9	6/9	NR
Aviles et al., 2000[16]	NK or T-cell	RT → CT	108	NR	86 (8 yrs)
Kim et al., 2001[17]	NK cell	CT → RT	17	NR	59 (3 yrs)
Yamaguchi et al., 2001[18]	NK cell	RT → CT or CT → RT	12	7/12	39
Ribrag et al., 2001[19]	NK or T-cell	RT → CT or CT → RT or RT	20	NR	NR
Cheung et al., 2002[20]	NK cell	CT → RT	79	31.1%	37.1
Chim et al., 2004[21]	NK cell	CT → RT	67	35/67	42.5 (10 yrs)
You et al., 2004[22]	NK cell	CT → RT	46	NR	36.5
Current study	NK or T-cell	CT → RT or RT	35	34.8%	47.3

LFR: local failure rate; OAS: overall survival; NK: natural killer; CT: chemotherapy; RT: radiotherapy; NR: not reported.

studies is provided in Table 3. According to those reports, the OAS ranged from 36.5–86%. Although the Mexican group demonstrated very surprising results,[16] the remaining 7 groups reported that OAS was approximately 40%,[14,17–22] which was comparable to the results of the current study. All eight series administered chemotherapy and RT and concluded that conventional chemotherapy followed by RT appeared to be ineffective for the majority of patients and that innovative treatment modalities are needed to improve outcomes. However, Yamaguchi et al. observed that patients who received treatment with concurrent chemoradiotherapy or with RT followed by chemotherapy enjoyed favorable outcomes.[18] Therefore, those authors concluded that RT followed by, or combined with, chemotherapy was best as initial treatment, and they recommended nonanthracycline-containing chemotherapy (dexamethasone, etoposide, ifosphamide, and carboplatin) based on their previous observation that nasal NK/T-cell lymphomas express P-glycoprotein.[34] Since 1998, Cheung et al. also have employed concurrent chemoradiotherapy in an attempt to intensify local treatment.[20] Those authors selected cisplatin as the chemotherapeutic agent in this concurrent setting. Conversely, Kim et al. also administered anthracycline-containing chemotherapy concurrently with RT in two patients.[17] Furthermore, Ribrag et al. observed that two patients who were treated with alternated chemotherapy and RT achieved a CR.[19] The sequence of chemotherapy and RT that will most effectively achieve a satisfactory local control rate will be resolved by future studies; however, it can be concluded that chemotherapy followed by RT is disadvantageous.

In addition to controlling systemic disease, it is indispensable to achieve high LCP in patients with localized nasal NK/T-cell lymphoma. Local recurrence rates ranged from 31–67%, and these high local failure rates led to very poor outcomes.[14,16–22] Although it is evident that RT should play an essential role in achieving local disease control, the dose to be delivered and the field to be covered have not been resolved. With regard to treatment volume, Cheung et al. administered RT to the nasal cavity and nasopharynx,[20] two investigational groups encompassed all paranasal sinuses and the Waldeyer ring in addition to the nasal cavity,[21,22] and four investigational groups delivered RT to the tumor with an adequate margin.[14,17–19] The remaining Mexican investigators delivered RT with an extended field, but to our knowledge the details were not reported.[16] In the current study, we observed that the patients who received RT to macroscopic lesions with a margin achieved an inferior local control rate compared with patients who received with an RT field that encompassed all paranasal sinuses, the palate, and the nasopharynx in addition to the nasal cavity. In contrast, Cheung et al. recommended meticulous CT conformal planning with the aid of magnetic resonance imaging scans to deliver RT to the macroscopic tumor with an adequate margin.[20] Although the majority of reports in the literature do not mention the recommended RT field, three groups of investigators advocated that the RT field should encompass the paranasal sinuses in addition to macroscopic lesions,[7,23,24] a recommendation that is consistent with our current observations.

Many researchers have delivered 30–60 Gy to control macroscopic lesions. In the current study, we suggested that patients who received ≥ 50 Gy had a tendency to achieve superior local control rates compared with patients who received < 50 Gy, which is well in accordance with the observation of Cheung et al.[20] You et al. administered higher RT doses (54–60 Gy) and achieved an 83.3% failure-free survival rate at 5 years.[22] Furthermore, although 50% of their patients did not have immunohistochemical confirmation of nasal NK/T-cell lymphoma, a Korean group demonstrated a clear dose-response relation within the range

of 20–54 Gy with a plateau at doses in excess of approximately 54 Gy.[13] Conversely, 2 other groups reported that 45 Gy appeared to be an effective dose for local control.[16,17] Those data indicated that it is necessary to deliver at least 45 Gy of RT to achieve a favorable local control rate; however, whether higher doses would achieve better local control rates remains unresolved.

We were able to identify that the RT field was a significant prognostic factor for LCP, DFS, and OAS. Several groups have advocated that disease stage,[15,17,20,22] performance status,[20] B symptoms,[17,20] LDH elevation,[22] and the International Prognostic Index (IPI)[21,22] are of prognostic importance. However, Aviles et al. reported that there was no evidence that the IPI was applicable in patients with nasal NK/T-cell lymphoma,[16] and there have been no widely accepted prognostic factors. With regard to molecular markers, Lin et al. examined 19 true NK-lineage nasal NK/T-cell lymphomas and demonstrated that CD94 expression was a favorable prognostic factor.[35] In addition, Au et al. demonstrated that the EBV DNA level at the time of presentation was correlated with disease stage and LDH, and high presentation EBV DNA levels were associated significantly with inferior DFS. Furthermore, patients with EBV DNA levels that increased further or that failed to become undetectable during treatment had significantly inferior survival. Those investigators concluded that, in patients with EBV-positive lymphomas, the plasma EBV DNA level is valuable as a tumor biomarker and for prognosis.[36] The significance of these new molecular markers will be elucidated in future clinical trials.

The rarity of this type of lymphoma limits large-scale, prospective, randomized trials. However, several of our findings have important implications in the management of nasal NK/T-cell lymphoma. The high efficacy of RT in achieving a CR with an RT field that encompasses all paranasal sinuses, the nasopharynx, and the palate, in addition to macroscopic lesions, and with RT doses $\geq$ 50 Gy suggests that it may be advantageous to incorporate adequate RT up-front in the treatment strategy. The occurrence of failures at distant sites implies that systemic chemotherapy also should be administered. Accordingly, we have launched a prospective study to evaluate the efficacy and toxicity of concurrent chemoradiotherapy for patients with nasal NK/T-cell lymphoma.

REFERENCES

1. Chan JKC, Jaffe ES, Ralfkiaer E. Extranodal NK/T-cell lymphoma, nasal type. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classifications of tumors. Pathology and genetics of tumours of haematopoietic and lymphoid tissue. Lyon: IARC Press, 2001:204–207.
2. Stewart JP. Progressive lethal granulomatous ulceration of the nose. *J Laryngol Otol.* 1933;48:657–701.
3. Eichel BS, Harrison EG, Devine KD, Scanlon PW, Brown HA. Primary lymphoma of the nose including a relationship to lethal midline granuloma. *Am J Surg.* 1966;112:597–605.
4. Kassel SH, Echevarria RA, Guzzo FP. Midline malignant reticulosis (so-called lethal midline granuloma). *Cancer.* 1969;23:920–935.
5. Harris NL, Jaffe ES, Stein H, et al. A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood.* 1994;84:1361–1392.
6. Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. *Pathol Int.* 2000;50:696–702.
7. Halperin EC, Dosoretz DE, Goodman M, Wang CC. Radiotherapy of polymorphic reticulosis. *Br J Radiol.* 1982;55:645–649.
8. Smalley SR, Cupps RE, Anderson JA, et al. Polymorphic reticulosis limited to the upper aerodigestive tract—natural history and radiotherapeutic considerations. *Int J Radiat Oncol Biol Phys.* 1988;15:599–605.
9. Yu KH, Yu S, Teo P, Chan A, Yeo W, Chow J. Nasal lymphoma: results of local radiotherapy with or without chemotherapy. *Head Neck.* 1997;19:251–259.
10. Kim GE, Cho JH, Yang WI, et al. Angiocentric lymphoma of the head and neck: patterns of systemic failure after radiation therapy. *J Clin Oncol.* 2000;18:54–63.
11. Kim GE, Lee S, Chang SK, et al. Combined chemotherapy and radiation versus radiation alone in the management of localized angiocentric lymphoma of the head and neck. *Radiother Oncol.* 2001;61:261–269.
12. Li CC, Tien HF, Tang JL, et al. Treatment outcome and pattern of failure in 77 patients with sinonasal natural kill/T-cell or T-cell lymphoma. *Cancer.* 2004;100:366–375.
13. Koom WS, Chung EJ, Yang WI, et al. Angiocentric T-cell and NK/T-cell lymphomas: radiotherapeutic viewpoints. *Int J Radiat Oncol Biol Phys.* 2004;59:1127–1137.
14. Itami J, Itami M, Mikata A, et al. Non-Hodgkin's lymphoma confined to the nasal cavity: its relationship to the polymorphic reticulosis and results of radiation therapy. *Int J Radiat Oncol Biol Phys.* 1991;20:797–802.
15. Kwong YL, Chan A, Liang R, et al. CD56+ NK lymphomas: clinicopathological features and prognosis. *Br J Haematol.* 1997;97:821–829.
16. Aviles A, Diaz NR, Neri N, Cleto S, Talavera A. Angiocentric nasal T/natural killer cell lymphoma: a single center study of prognostic factors in 108 patients. *Clin Lab Haematol.* 2000;22:215–220.
17. Kim WS, Song SY, Ahn YC, et al. CHOP followed by involved field radiation: is it optimal for localized nasal natural killer/T-cell lymphoma? *Ann Oncol.* 2001;12:349–352.
18. Yamaguchi M, Ogawa S, Nomoto Y, et al. Treatment outcome of nasal NK-cell lymphoma: a report of 12 consecutively diagnosed cases and a review of the literature. *J Clin Exp Hematopathol.* 2001;41:93–99.
19. Ribrag V, Ell Hajj M, Janot F, et al. Early locoregional high-dose radiotherapy is associated with long-term disease control in localized primary angiocentric lymphoma of the nose and nasopharynx. *Leukemia.* 2001;15:1123–1126.

20. Cheung MM, Chan JK, Lau WH, Ngan RK, Foo WW. Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality. *Int J Radiat Oncol Biol Phys.* 2002;54:182–190.
21. Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. *Blood.* 2004; 103:216–221.
22. You JY, Chi KH, Yang MH, et al. Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. *Ann Oncol.* 2004;15:618–625.
23. Senan S, Symonds RP, Brown IL. Nasal peripheral T-cell lymphoma: a 20-year review of cases treated in Scotland. *Clin Oncol.* 1992;4:96–100.
24. Liang R, Todd D, Chan TK, et al. Treatment outcome and prognostic factors for primary nasal lymphoma. *J Clin Oncol.* 1995;13:666–670.
25. Chen HH, Fong L, Su IJ, et al. Experience of radiotherapy in lethal midline granuloma with special emphasis on centrofacial T-cell lymphoma: a retrospective analysis covering a 34-year period. *Radiother Oncol.* 1996;38:1–6.
26. Logsdon MD, Ha CS, Kavadi VS, Cabanillas F, Hess MA, Cox JD. Lymphoma of the nasal cavity and paranasal sinuses. *Cancer.* 1997;80:477–488.
27. Sakata K, Hareyama M, Ohuchi A, et al. Treatment of lethal midline granuloma type nasal T-cell lymphoma. *Acta Oncol.* 1997;36:307–311.
28. Cheung MM, Chan JK, Lau WH, et al. Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. *J Clin Oncol.* 1998;16:70–77.
29. Li YX, Coucke P, Li JY, et al. Primary non-Hodgkin's lymphoma of the nasal cavity. *Cancer.* 1998;83:449–456.
30. Shikama N, Ikeda H, Nakamura S, et al. Localized aggressive non-Hodgkin's lymphoma of the nasal cavity: a survey by the Japan Lymphoma Radiation Therapy Group. *Int J Radiat Oncol Biol Phys.* 2001;51:1228–1233.
31. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol.* 1999;17:1233–1253.
32. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457–481.
33. Cox DR. Regression model and life-tables. *J R Stat Soc.* 1972;34:187–220.
34. Yamaguchi M, Kita K, Miwa H, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer.* 1995;76:2351–2356.
35. Lin CW, Chen YH, Chuang YC, Liu TY, Hsu SM. CD94 transcripts imply a better prognosis in nasal-type extranodal NK/T-cell lymphoma. *Blood.* 2003;102:2623–2631.
36. Au WY, Pang A, Choy C, Chim CS, Kwong YL. Quantification of circulating Epstein–Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. *Blood.* 2004;104:243–249.