Modified SMILE (mSMILE) and Intensity-Modulated Radiotherapy (IMRT) for extranodal NK-T lymphoma nasal type in a single center population.

Paola Ghione[1], Shunan Qi[2,3], Brandon S. Imber[2], Venkatraman Seshan[4], Alison Moskowitz[1], Natasha Galasso[1], Matthew Lunning[1], David Straus[1], Craig Sauter[5], Dahi Parastoo[5], Ahmet Dogan[6], Joachim Yahalom[2], Steven Horwitz[1]

[1]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center New York, NY; [2]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center New York, NY; [3]Department of Radiation Oncology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [4]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; [5]Bone Marrow Transplant Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [6]Hematopathology Service, Memorial Sloan Kettering Cancer Center, New York, NY.

Abstract

In the last ten years, a modification of the SMILE regimen with dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide (mSMILE) followed by Intensity-Modulated Radiotherapy (IMRT), has been adopted as standard of care for extranodal NK/T cell lymphoma (ENKL) at our institution. The mSMILE is a short course, intensive chemotherapy regimen incorporating pegylated asparaginase. Patients were consolidated with lower dose RT than traditionally given for ENKL, using conformal IMRT.

Among the 28 patients with ENKL treated with this approach, response post mSMILE was 93% (CR 68%) and response post IMRT was 95% (CR 87.5%). Among early-stage patients/low PINK-E (n=13), overall survival (OS) was 100% at the median follow up of 31 months, and progression-free survival (PFS) was 92%. However, there were two subsequent events: one death due to relapse and one due to unrelated causes in remission. Advanced stage and intermediate/high PINK-E patients fared similarly (OS 43%, PFS 33.3% at the median follow-up). 14% of the patients required dose reductions, 32% experienced G3-4 non-hematologic toxicity, all patients experienced hematologic toxicity, G3-4 in 75%.

Most localized-stage patients achieved long-term disease control. Despite high response rates, most of the advanced stage patients relapsed quickly. As expected, treatment-related toxicity was high.

Introduction

Extranodal NK/T cell lymphoma (ENKL) is a rare and aggressive type of lymphoma, poorly responsive to anthracycline-based chemotherapy. Radiation therapy plays an important role, especially for localized disease(Horwitz, Ansell et al. 2018). ENKL is characterized by the presence of the Epstein-Barr virus (EBV) in the tumor cells and typically, but not exclusively, involves the nasal cavity(Swerdlow, Campo et al. 2016, Suzuki 2018). Treatment and prognosis are largely driven by stage, and the recently introduced PINK and PINK-E scores appear to further refine the prognosis(Kim, Yoon et al. 2016).

Outcomes for patients with ENKL, particularly with localized disease, have improved with the introduction of L-asparaginase containing regimens into combined modality approaches. Based on the reported efficacy of the SMILE regimen(Yamaguchi, Suzuki et al. 2008), in 2009, we adopted a modified (m)SMILE (dexamethasone, methotrexate, ifosfamide, peg-asparaginase, etoposide) regimen given every 3 weeks, followed by radiotherapy (RT) as our standard approach(Yamaguchi, Suzuki et al. 2008, Yamaguchi, Kwong et al. 2011). The main differences from the classical SMILE approach are: I) a shorter course of chemotherapy, limited to two cycles for patients with localized stage and three for advanced stage; II) the use of peg-asparaginase (with a dose reduction to the current 1500 U/sm); and III) incorporation of a lower dose (45 Gy instead of 50 Gy or more) and more conformal Intensity-Modulated Radiotherapy (IMRT) consolidation.(Qi, Yahalom et al. 2016)

Here we describe the safety and efficacy of the mSMILE plus IMRT program in 28 patients with ENKL treated at our institution from 2009 to 2019.

Methods

After institutional review board approval, we referenced our T cell lymphoma database to identify patients with ENKL whose diagnostic pathology had been confirmed at MSKCC on the basis of standard WHO criteria(Horwitz, Ansell et al. 2018). We included in this analysis the patients that were treated with at least one complete cycle of mSMILE from 10/2009 to 3/2019 and followed at Memorial Sloan Kettering Cancer Center. We excluded patients that were treated and followed at other institutions.

We collected demographic variables including age, sex and ethnic origin. Disease-related variables included performance status, detailed staging (both with Ann Arbor and the staging criteria by Lee at al(Lee, Park et al. 2005)), LDH, EBV status, pathology, IPI(Aviles, Diaz et al. 2000, Cheung, Chan et al. 2002, Chim, Ma et al. 2004, You, Chi et al. 2004), Korean NK(Lee, Suh et al. 2006), PINK and PINK-E(Kim, Yoon et al. 2016) prognostic scores. Disease response was evaluated at the end of the mSMILE treatment and at the end of the whole program (mSMILE + IMRT, or mSMILE + transplant). Responses were re-reviewed as part of this analysis and Lugano criteria(Cheson, Fisher et al. 2014) was retrospectively applied.

Toxicity was assessed using the Common Terminology Criteria for Adverse Events from the National Cancer Institute version 4.03. We calculated the PINK, PINK-E, Korean and IPI scores as previously described.(Chim, Ma et al. 2004, Lee, Suh et al. 2006, Kim, Yoon et al. 2016)

Statistical methods

Common variables are described with percentages and median values. Overall Survival (OS) is defined as time from ENKL diagnosis to death from any cause. Progression-free survival (PFS) is defined as time from ENKL diagnosis to progression of disease or death from any cause. We estimated survival with the Kaplan-Meier method. Median follow-up is estimated with the reverse Kaplan-Meier method. Graphs were obtained with GraphPad prism 7th version software.

Therapy details

Early-stage patients received 1-2 cycles of mSMILE and involved field IMRT of 45 Gy; advanced stage patients received 3-4 cycles of mSMILE +/- RT and often autologous or allogeneic bone marrow transplantation (AutoSCT or AlloSCT). The mSMILE regimen was: methotrexate 2000 mg/m2, intravenously on day 1 (2 patients with CNS involvement got 3000-3500 mg/m2) ; dexamethasone, 40 mg/day intravenously on days 2-4; ifosfamide 1500 mg/m2 intravenously on days 2-4; etoposide, 100 mg/m2 on days 2-4; peg-asparaginase 1500-2500 UI/m2 intravenously (in 24 patients) or intramuscularly (in 4 patients, only once a cycle at a median of 7 days from the beginning of the cycle (range: 5-31 days). Also, leucovorin 25 mg flat dose every six hours beginning 30 hours after the start of methotrexate was administered, for 12 total doses or until methotrexate level <100 nmol/L and MESNA 300 mg/m2 30 minutes prior, then 4 and 8 hours post each Ifosfamide dose. Regular prophylaxis with granulocytes growth factor, antiviral, anti-fungal and anti-pneumocystis jiroveci was given to all the patients.

This schedule was repeated every 21 days. Radiotherapy of 45 Gy was administered in fractions of 1.8 Gy five days a week to the involved site(s) with a margin of 1-2 cm to include suspected reservoirs of microscopic disease and to account for treatment setup errors. Patients were simulated using PET imaging whenever possible as per institutional standard. We did not administer prophylactic irradiation to the regional nodes.

Results

Patients

We identified 32 patients with ENKL diagnosed at our center between 2009 and 2019. Four patients with disseminated disease could not get the mSMILE regimen: 2 of them died before receiving a full chemotherapy cycle (within the first week), one could not start any chemotherapy for rapid onset of coma due to central nervous system involvement; one patient presented with sepsis at the time of diagnosis and received only single agent methotrexate, expiring shortly thereafter from infection and progression of disease. Two patients received a different regimen: PEG-asparaginase, methotrexate and dexamethasone due to age, performance status and comorbidities. We included in this analysis the 28 patients that were treated with at least one cycle of mSMILE and followed at our center. Patients characteristics are summarized in table 1. Of note, our population was mainly non-Asian 21/28 (75%).

Prognostic evaluation

Staging at diagnosis was evaluated on PET/CT scan (done in 27/28 patients), maxillo-facial MRI (done in 24/28 patients), direct visualization with laryngoscopy in patients with nasal cavity involvement, and bone marrow biopsy. Eighteen patients (64%) had localized Ann Arbor stage - IE in 14 (50%), IIE in 4 (14%). Of these patients, 9 were classified as upper aerodigestive tract (UNKTL) localized and 9 as locally invasive UNKTL following the classification according to Lee[8]. Ten patients had diffuse stage (III-IV or extra (E)UNKTL) (36%). A detail of prognostic scores at diagnosis is present in table 1. One patient was not evaluable for PINK-E for lack of EBV-DNA results on peripheral blood at baseline.

Treatment and response

Median time on chemotherapy was 2.3 months (0.2 – 3.8). Patients with localized stage disease received a median of 2 mSMILE cycles (1-3). For them, median time on chemotherapy was 1.8 months. Patients with advanced stage disease received a median of 3 mSMILE cycles (2-4), and median time on chemotherapy was 2.4 months. When a 3rd cycle of mSMILE was planned (advanced stage), if given, radiotherapy was administered between the second and the third cycle of mSMILE.

Radiotherapy (RT) was delivered as part of the treatment regimen for 24/28 patients (86%) including all patients with localized disease. In total, 22/24 received IMRT consolidation post 1-2 mSMILE the majority of whom (n=16) received 45 Gy. One patient whose disease was non-nasal and located on the skin of the leg was consolidated with conventional electron beam therapy to a total of 54 Gy. Six of the 10 advanced stage patients received RT. Of these, 3 patients received TBI conditioning prior to AlloSCT. One patient received solely low dose TBI (400 cGy) whereas the other two received consolidation IMRT to involved nasal regions (2520-3360 cGy) followed by full dose TBI (1375 cGy) conditioning with chest wall electron beam compensation. An example of IMRT field design for localized vs locally advanced disease is shown in the figure. (figure 1)

A total of eight patients underwent a transplant procedure, one patient with localized stage and 7 with diffuse disease (stage III-IV) (70%). The patient with localized disease is alive and in remission, but he relapsed after autologous transplant, and received additional therapy. Among the patients with diffuse disease, 3 (30%) underwent AutoSCT as consolidation of the first line, all 3 patients progressed or relapsed and died of their lymphoma. Two patients underwent AlloSCT consolidation after first line, and two patients at relapse. Two of these allo-transplanted patients are alive and in remission. One patient died during transplant due to treatment-related toxicity (TRM), the other relapsed and died from lymphoma progression.

Overall response rate (ORR) to mSMILE in this population was 93% (19/28, 68% complete remission, CR and 7/28 partial remission, PR). One patient reached only a stable disease (SD) after mSMILE (3.5%), another progressed (PD, 3.5%). After mSMILE, stage I-II patients by Ann Arbor had an ORR of 16/18, 88.9% (12/16, 75% CR, and 4/16, 25% PR), stage IV patients had an ORR of 10/10, 100% (7/10, 70% CR, 3/10, 30% PR).

Response to the whole frontline program (mSMILE 1-2 cycles and RT for localized disease, mSMILE 2-3 cycles and auto or allo-transplant for stage III-IV) was achieved in 27/28 patients (97%), with 24/28 CR (86%). According to stage: localized stage I-II patients had 94% ORR (17/18, 16 CR, 89%), one patient progressed. All 10 patients with higher stage disease responded to the program (CR was 80%)

Survival

After a median follow-up of 31 months (range 5-105), 17 patients are alive (61%). In our population of ENKL treated with mSMILE, median OS was 50 months (OS 49.6% at 5 years), and median PFS is 47 months (PFS 46.8% at 5 years). Median OS in patients with localized disease (IE) was not reached, vs 10.9 months in patients with disseminated disease (IV). Median PFS was not reached in localized stage patients and 7.6 months in advanced stage patients. (figure 2)

Localized stage ENKL

We analyzed staging of patients with localized disease in detail, to describe their status with the existing systems (Ann Arbor and staging according to Lee[8]). In total, 14 patients were classified as IE and 4 patients as IIE with the Ann Arbor staging. The classification according to Lee and colleagues identified 9 patients as upper aerodigestive tract (UNKTL) – localized disease and 9 UNKTL – locally invasive. Local invasiveness was assessed with PET or MR, according to the 2002 TNM classification of the American Joint Committee on Cancer, as reported by Lee[8].The sample is too small to make statistical conclusions, but the outcomes appear similar with both Ann Arbor and Lee classifications. (figure 3)

Progression of disease in localized cases was variable and no precise pattern could be identified. Four patients with localized NKTL relapsed, 2 with disseminated disease, out of the radiation field. One patient relapsed with a very slow growing mass in the nasal cavity again, within the radiotherapy field; another patient relapsed outside of the radiation field in the right nostril. The original localization of the lymphoma for this patient was in the nasopharynx.

Advanced stage

In patients with advance stage disease, median OS was 11 months (range: 7 – 80 months), with an OS at 5 years of 15%. Median PFS was 8.7 months (range: 2 – 80 months).

Survival prediction with the new PINK and PINK-E scores

Kaplan-Maier survival curves according to the PINK and PINK-E scores are shown in figure 4.

In our cohort, median OS and PFS with PINK were not reached for low-PINK risk group (n=13), 39 and 14.6 months respectively for the intermediate-PINK risk group (n=6) and 11.9 and 7.11 months respectively for the high-PINK risk group.

Median OS and PFS with PINK-E were not reached in the low-PINK-E risk group (n=15), 9.8 and 6.8 months respectively in the intermediate-PINK-E risk group (n=4) and 10.9 and 5.6 months respectively in the high PINK-E risk group (n=8). (figure 4)

Among the low risk PINK score patients, overall survival (OS) was 100% at the median follow up, and progression-free survival (PFS) was 92%. However, there were two subsequent events: one death due to relapse and one due to unrelated causes in remission.

Toxicity

Detailed information on hematological and non-hematological toxicity from the chemotherapy portion, mSMILE, is available for all subjects.

As expected, all patients experienced hematologic toxicity of some level. Maximum grade of non-hematologic toxicity was grade 1-2 in 19/28 patients (68%), and grade 3-4 in 9/28 patients (32%). Milder (grade 1-2) events were mainly fatigue, nausea, diarrhea, low grade fever, mucositis and transient transaminase elevation with retained liver function. One patient experienced an allergic reaction at the second dose of PEG-asparaginase and was switched to L-asparaginase without recurrent reactions. Another patient received the full dose of PEG-asparaginase in both cycles, but hours after the second infusion had transient tongue swelling and neuropathy in his fingers and was hospitalized with subsequent resolution the following day. We recorded 3 cases of acute kidney injury. One patient with localized, stage IE disease experienced grade 3 acute kidney injury from methotrexate, followed by norovirus infection. This resulted in a prolonged recovery and the second cycle of mSMILE was omitted. Restaging after cycle 1 showed a complete response and he proceeded to radiotherapy. He remains in

remission. No cases of pancreatitis or deep venous thrombosis were recorded. Details on toxicity is displayed in table 2.

No death events were directly related to mSMILE toxicity. The major cause of death was progression of lymphoma, which occurred in 7/9 deceased patients. One patient died for allo-transplant related toxicity (TRM). One patient died in remission, 5 years from treatment, likely due to sepsis. (figure 5)

Discussion

In the present study, we report on the treatment of 28 patients with newly diagnosed ENKL at MSKCC with a modification of the SMILE regimen (mSMILE) and IMRT. The key changes of the regimen from the previously published version are: I) adoption of peg-asparaginase instead of L-asparaginase: this modification allows asparaginase to be given only once in the cycle (at a median of 7 days from the beginning of the cycle (range 5-31 days). In most cases our patients could receive mSMILE every 21 days; II) fewer number of cycles (mainly 1-2 cycles for early stage disease, 3 cycles in higher stages); III) lower dose and more conformal radiotherapy (45 Gy instead of 50 or higher).

In the original study of the PINK and PINK-E prognostic indices, that included 527 patients treated with non-anthracycline based chemotherapy with or without radiotherapy, only 25% of the patients were treated with SMILE. Ann Arbor stage I-II patients demonstrated an OS of 61-77% (the higher % if nasal involvement) at 3 years; stage III-IV patients had an OS of 15-38% (the higher % if nasal involvement) at 3 years. According to the PINK, the OS was: 81% for low, 62% for intermediate and 25% for high risk at 3 years. According to the PINK-E, the OS was: 81% for low, 55% for intermediate, and 28% for high risk patients at 3 years(Kim, Yoon et al. 2016).

Despite the absence of a standard of care for ENKL, for localized disease it appears that non-anthracycline based regimens like mSMILE, achieve a higher rate of durable response then seen in series with radiotherapy alone (25-49% relapse rate(Wang, Li et al. 2009, Kim and Kim 2010)) or other anthracycline-based chemotherapy (5 year OS, 73,3% vs 60,9%, $p < 0.001$; 5 year PFS, 64,0% vs 47.6%, $p< 0.001$)(Qi, Yang et al. 2019). In this context, the original SMILE regimen demonstrated an ORR of 82%, with a CR rate of 78%(Kwong, Kim et al. 2012). The LVP-RT-LVP (L-asparaginase, cisplatin, dexamethasone)(Jiang, Zhang et al. 2012) regimen

showed an ORR of 81%, an OS of 64% and a PFS of 64% at 5 years. A schema called IMRT-GDP (gemcitabine, dexamethasone and cisplatin)(Huang, Yang et al. 2017), with radiotherapy dose in the range of 50-56 Gy, followed by chemotherapy, showed an ORR of 89% and OS of 85% and PFS of 77% at 3 year in early-stage patients. Concurrent chemo-radiotherapy, like the DeVIC scheme (dexamethasone, etoposide, ifosfamide, and carboplatin) at 2/3 of the dose, achieved an ORR of 80% and a 5-year OS of 70%(Yamaguchi, Tobinai et al. 2009, Yamaguchi, Suzuki et al. 2018). Similarly, the VIPD regimen (etoposide, ifosfamide, cisplatin, dexamethasone) with concurrent radiotherapy showed 80% ORR and 86% OS and PFS at 3 years.(Kim, Kim et al. 2009)

For patients with advanced stage disease, the standard treatment remains chemotherapy, and - similarly to limited stage disease, non-anthracycline based regimens seem to achieve better survival (OS 39.8% vs 29.9%. p=0.013; PFS, 30.1% vs 18.8%, p=0.003 at 5 years).(Qi, Yang et al. 2019)In this context, SMILE demonstrated an ORR of 25%-80%.(Yamaguchi, Kwong et al. 2011) However, durable responses and long term remissions were rare in these patients. Retrospective analysis suggest that consolidation with either allogeneic or autologous stem cell transplantation – this latter showing a 5 year OS of 55% - might be beneficial for patients who achieve a CR.(Kwong 2009, Tse, Chan et al. 2014, Fox, Boumendil et al. 2015) In our series, the limited experience with autologous transplant consolidation was poor, with all the 4 patients relapsing, and 3/4 dying of their disease.

In our retrospective series, we confirmed the overall high response rate with mSMILE in patients with ENKL. Both localized and diffuse disease show high ORR (after mSMILE ORR: 88.9% in stage I-II, 100% in stage III-IV; after mSMILE +/- IMRT ORR: stage I-II 94%, stage III-IV 100%), with high percentages of patients achieving complete remission, particularly at the end of the entire program with IMRT. The PFS and OS were excellent for those with early-stage disease/favorable prognostic indices. In this group of patients, we didn't observe a significant difference in prognosis based on local invasiveness, as described by Lee[8]. This might be due to the efficacy of the mSMILE chemotherapy, even coupled with a lower dose of radiation.

The reduction of the RT dose from 50-56Gy to 45Gy was meant to reduce acute or delayed RT toxicity that has been described in previous studies, as well as to reduce the duration of the RT treatment. In the literature, lower dose (<50Gy) RT has been associated with inferior outcome(Isobe, Uno et al. 2006, Vargo, Patel et al. 2017, Yang, Cao et al. 2017), however, in the phase II Korean trial with VIPID concurrent chemo-radiotherapy, the RT dose was safely

decreased to 40Gy(Kim, Kim et al. 2009). In a recent multicenter retrospective study conducted in China, a modern RT technique like IMRT was associated to improved outcome if compared to the older technique of 3-dimentional conformal radiation therapy, especially in patients with bulky disease(Wu, Yang et al. 2018). Our results show that this is a feasible approach, and we believe contributing factors were the improved imaging quality together with enhanced RT techniques, as well as the efficacy of the mSMILE regimen. Despite the small numbers in our series, the excellent local infield control and low outfield local recurrence support use of this RT schema.

The mSMILE is an intensive chemotherapy regimen with very high response rates in this population. However, in our cohort it was often associated with acute hematologic and non-hematologic toxicity. Acute kidney injury from methotrexate, encephalopathy from ifosfamide (reversible), and two cases of allergic reaction to PEG-asparaginase, appeared to be directly related to the treatment.

There remains significant room for improvement for patients with more advanced disease and higher risk factors. The recent identification of new agents including the anti PD1 pembrolizumab(Kwong, Chan et al. 2017, Li, Cheng et al. 2018) and sintilimab(Tao, Fan et al. 2019), and the anti-CD38 daratumumab(Wang, Wang et al. 2015, Hari, Raj et al. 2016) open up the possibility of designing new less toxic but still highly effective approaches for these patients.

Acknowledgements

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748. **SMH** reports grants and personal fees from Aileron, Seattle Genetics, Takeda, Kyowa Hakka Kirin, Verastem, Portola, Corvus, Celgene, Spectrum, Forty-Seven, outside of the submitted work. **ML** received research support from: Celgene, Curis, Jannsen Scientific Affairs, LLC, Juno Therapeutics, MiRagen, TG Therapeutics, ML consulted for AbbVie, Bayer, Celgene, DAVA, Gilead Sciences, Inc, Janssen, Juno Therapeutics, Kite, Novartis, OncLive, Portola, Seattle Genetics, Spectrum, TG Therapeutics. **AM** reports grants and personal fees from: Seattle Genetics, Bristol-Myers Squibb, Kyowa Hakko Kirin Pharma, Miragen Therapeutics, Takeda Pharmaceuticals, ACD Therapeutics, Cell Medica, Erytech Pharma, Seattle Genetics, Merck and Company, Incyte. **AD** reports grants and personal fees from Roche, Novartis AG,

Seattle Genetics, Celgene, Corvus. **BI** was supported by the Mortimer J. Lacher lymphoma fellowship.

Figures and tables

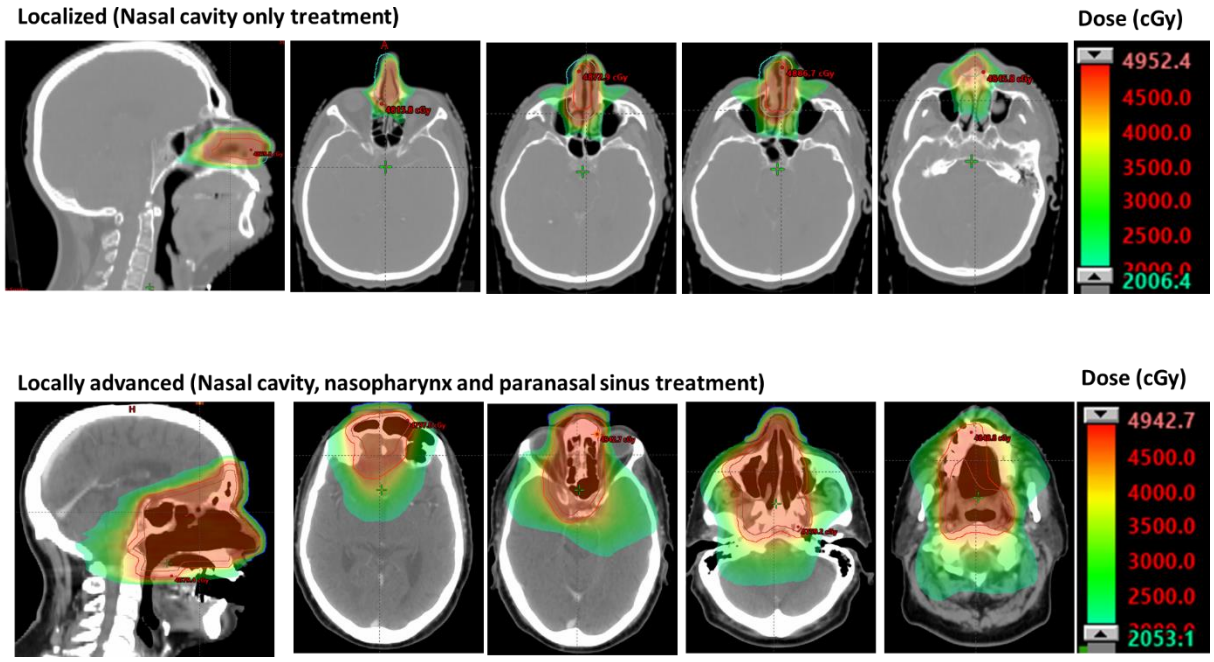

Figure 1. Example of IMRT treatment fields for localized and locally-advanced cases.

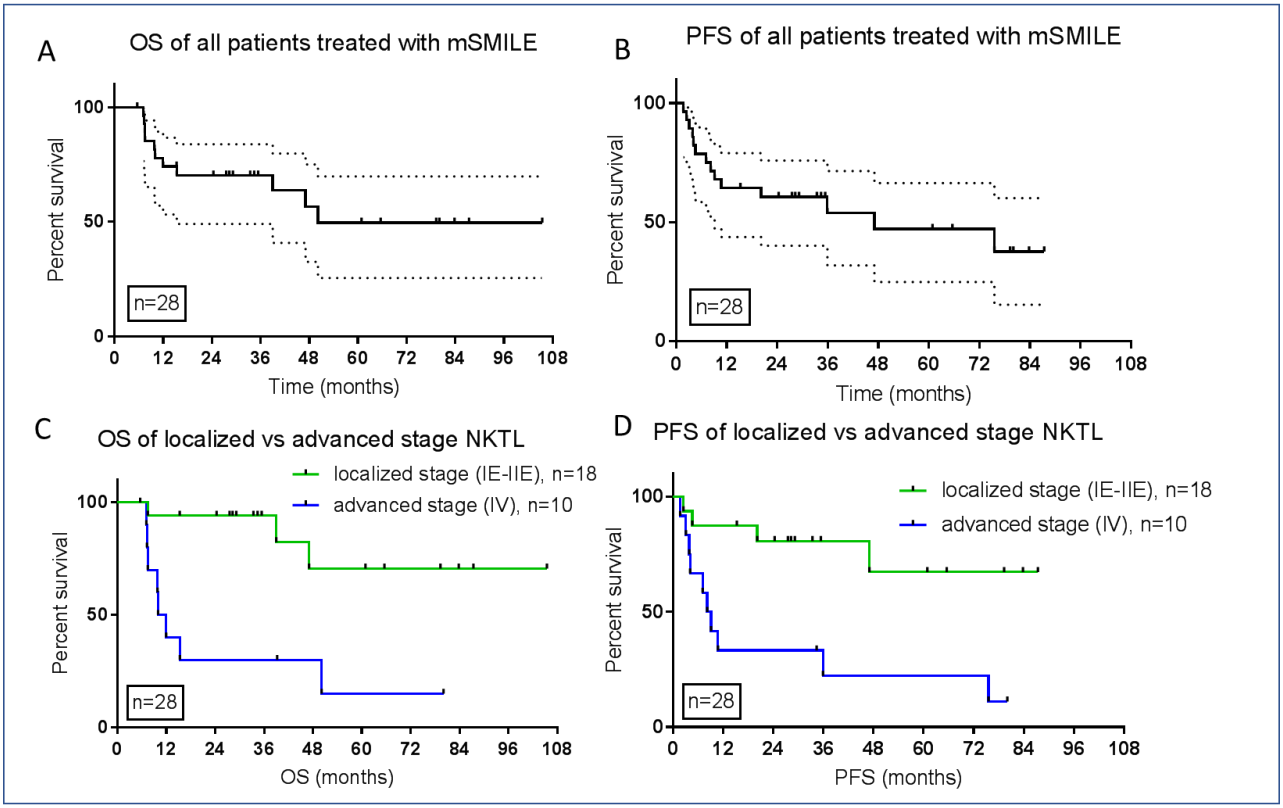

Figure 2. Overall survival (OS) and progression free survival (PFS) of the population treated with mSMILE. Panels A and B: OS and PFS of the whole population. Panels C and D: OS and PFS of localized vs advanced stage population.

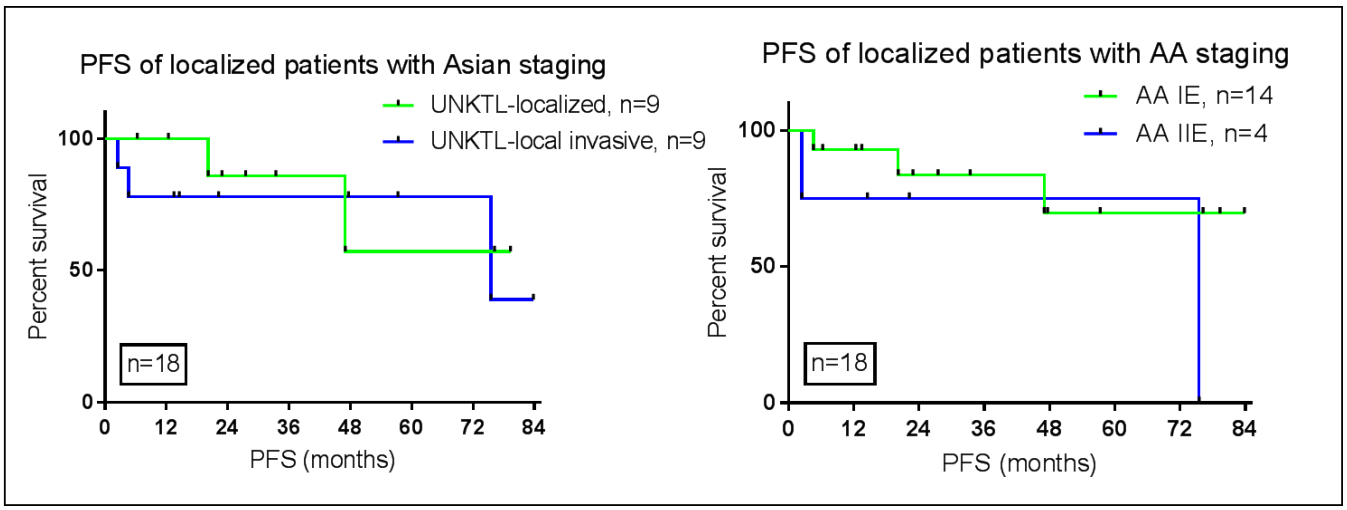

Figure 3. Progression free survival (PFS) of localized stage disease with Ann Arbor staging versus Asian staging.

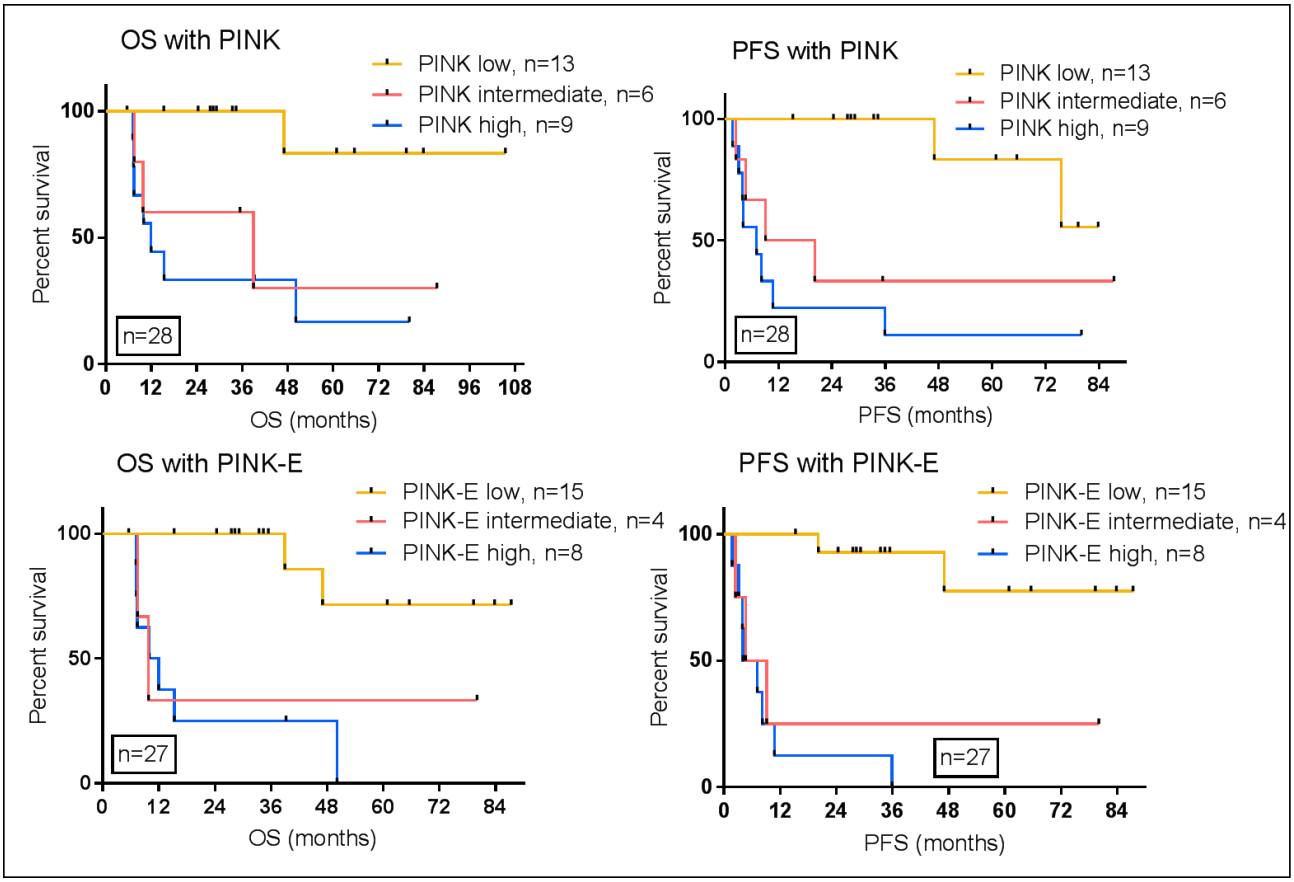

Figure 4. OS and PFS with the new prognostic scores PINK and PINK-E[13]

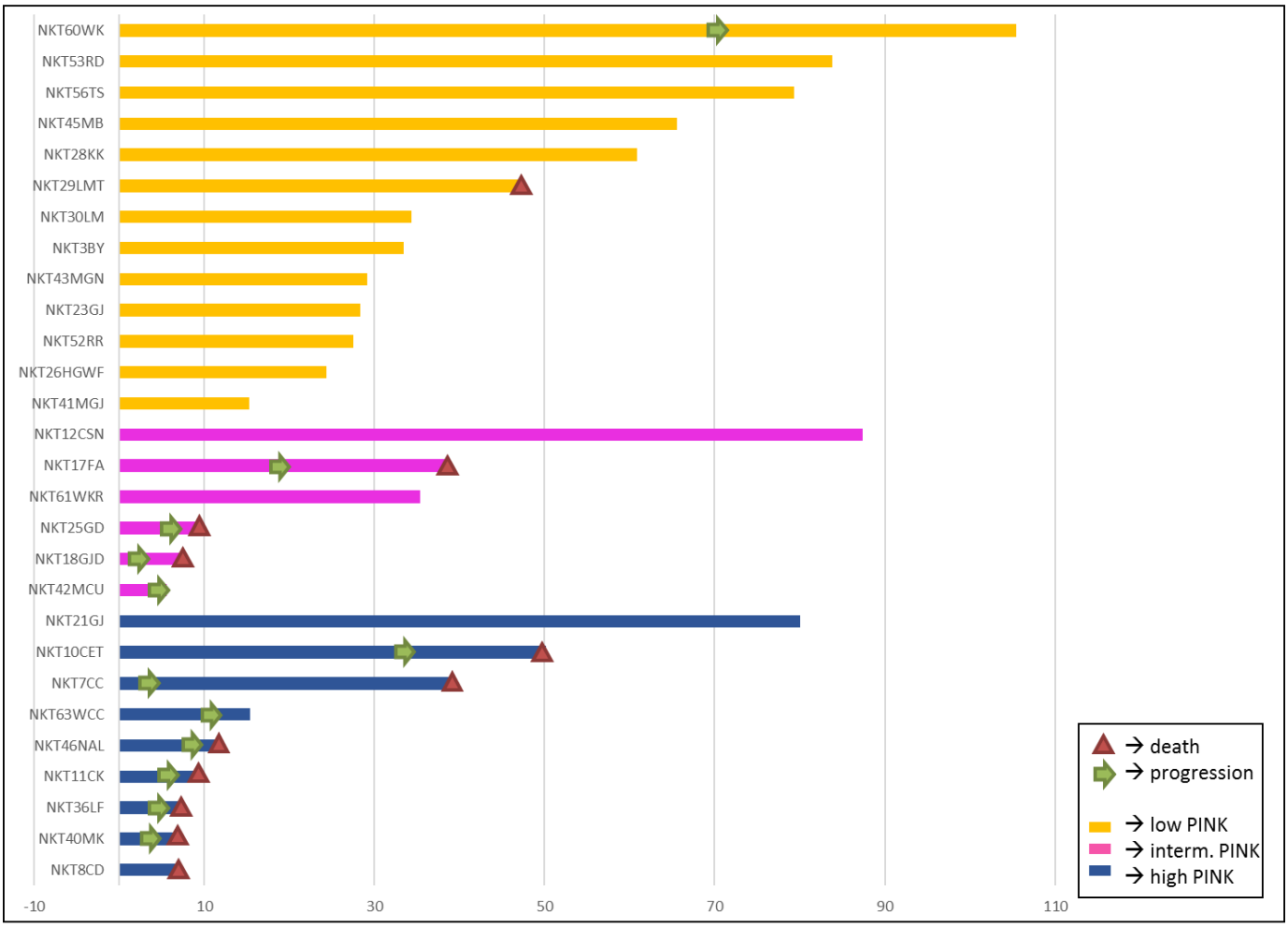

Figure 5. Detail of the study population.

Demographics and baseline characteristics	**All population (n=28)**				**Localized AA stage (I-II) (n=18)**				**High AA stage (III-IV) (n=10)**			
Demographics												
Age (y), median (range)	52 (24-69)				51 (29-68)				55 (24-69)			
Sex, male, n (%)	13 (46)				10 (55)				3 (30)			
Ethnie, asian, n (%)	7 (25)				2 (11)				5 (50)			
Stage by Lee, Eur J Cancer 2005)	9 (32)				9 (50)				0			
UNKTL localized, n (%)	9 (32)				9 (50)				0			
UNKTL locally invasive, n (%)	10 (36)				0				10 (100)			
EUNKTL, n (%)												
EBV detectable in PB, n (%)	13 (48), 1 NA				8 (44), 1 NA				5 (50)			
Prognostic scores	**L**	**I**	**H**	**VH**	**L**	**I**	**H**	**VH**	**L**	**I**	**H**	**VH**
PINK	13(46)	6(21)	9(32)		13(72)	5(28)	0		0	1(10)	9(90)	
PINK-E	15(54)	4(14)	8(28)		15(83)	2(17)	0		0	2(20)	8(80)	
IPI	18(64)	4(14)	6(21)		17(94)	1(6)	0		1(10)	3(30)	6(60)	
Korean NKT score	8(28)	9(32)	3(11)	8(28)	8(44)	8(44)	2(12)	0	0	1(10)	1(10)	8(80)

Table 1. Patients characteristics at diagnosis

AA: Ann Arbor; UNKTL: upper aerodigestive tract NKTL; EUKNTL: extra-upper aerodigestive tract NKTL; IPI: international prognostic index; PINK: prognostic index for natural killer lymphoma; PINK-E: prognostic index for natural killer lymphoma - Ebstein-Barr virus (lancet Oncology 2016); L: low, I; Intermediate, H: high, VH: very high.

Aviles, A., N. R. Diaz, N. Neri, S. Cleto and A. Talavera (2000). "Angiocentric nasal T/natural killer cell lymphoma: a single centre study of prognostic factors in 108 patients." Clin Lab Haematol **22**(4): 215-220.

Cheson, B. D., R. I. Fisher, S. F. Barrington, F. Cavalli, L. H. Schwartz, E. Zucca and T. A. Lister (2014). "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification." J Clin Oncol **32**(27): 3059-3068.

Cheung, M. M., J. K. Chan, W. H. Lau, R. K. Ngan and W. W. Foo (2002). "Early stage nasal NK/T-cell lymphoma: clinical outcome, prognostic factors, and the effect of treatment modality." Int J Radiat Oncol Biol Phys **54**(1): 182-190.
Chim, C. S., S. Y. Ma, W. Y. Au, C. Choy, A. K. Lie, R. Liang, C. C. Yau and Y. L. Kwong (2004). "Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index." Blood **103**(1): 216-221.
Fox, C. P., A. Boumendil, N. Schmitz, H. Finel, J. J. Luan, G. Sucak, D. Blaise, J. Finke, K. H. Pfluger, H. Veelken, N. C. Gorin, X. Poire, A. Ganser, P. Dreger and A. Sureda (2015). "High-dose therapy and autologous stem cell transplantation for extra-nodal NK/T lymphoma in patients from the Western hemisphere: a study from the European Society for Blood and Marrow Transplantation." Leuk Lymphoma **56**(12): 3295-3300.
Hari, P., R. V. Raj and H. Olteanu (2016). "Targeting CD38 in Refractory Extranodal Natural Killer Cell-T-Cell Lymphoma." N Engl J Med **375**(15): 1501-1502.
Horwitz, S. M., S. M. Ansell, W. Z. Ai, J. Barnes, S. K. Barta, M. Choi, M. W. Clemens, A. Dogan, J. P. Greer, A. Halwani, B. M. Haverkos, R. T. Hoppe, E. Jacobsen, D. Jagadeesh, Y. H. Kim, M. A. Lunning, A. Mehta, N. Mehta-Shah, Y. Oki, E. A. Olsen, B. Pro, S. A. Rajguru, S. Shanbhag, A. Shustov, L. Sokol, P. Torka, R. Wilcox, B. William, J. Zain, M. A. Dwyer and H. Sundar (2018). "NCCN Guidelines Insights: T-Cell Lymphomas, Version 2.2018." J Natl Compr Canc Netw **16**(2): 123-135.
Huang, Y., J. Yang, P. Liu, S. Zhou, L. Gui, X. He, Y. Qin, C. Zhang, S. Yang, P. Xing, Y. Sun and Y. Shi (2017). "Intensity-modulated radiation therapy followed by GDP chemotherapy for newly diagnosed stage I/II extranodal natural killer/T cell lymphoma, nasal type." Ann Hematol **96**(9): 1477-1483.
Isobe, K., T. Uno, J. Tamaru, H. Kawakami, N. Ueno, H. Wakita, J. Okada, J. Itami and H. Ito (2006). "Extranodal natural killer/T-cell lymphoma, nasal type: the significance of radiotherapeutic parameters." Cancer **106**(3): 609-615.
Jiang, M., H. Zhang, Y. Jiang, Q. Yang, L. Xie, W. Liu, W. Zhang, X. Ji, P. Li, N. Chen, S. Zhao, F. Wang and L. Zou (2012). "Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma." Cancer **118**(13): 3294-3301.
Kim, S. J., K. Kim, B. S. Kim, C. Y. Kim, C. Suh, J. Huh, S. W. Lee, J. S. Kim, J. Cho, G. W. Lee, K. M. Kang, H. S. Eom, H. R. Pyo, Y. C. Ahn, Y. H. Ko and W. S. Kim (2009). "Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-Cell Lymphoma: Consortium for Improving Survival of Lymphoma study." J Clin Oncol **27**(35): 6027-6032.
Kim, S. J. and W. S. Kim (2010). "Treatment of localized extranodal NK/T cell lymphoma, nasal type." Int J Hematol **92**(5): 690-696.
Kim, S. J., D. H. Yoon, A. Jaccard, W. J. Chng, S. T. Lim, H. Hong, Y. Park, K. M. Chang, Y. Maeda, F. Ishida, D. Y. Shin, J. S. Kim, S. H. Jeong, D. H. Yang, J. C. Jo, G. W. Lee, C. W. Choi, W. S. Lee, T. Y. Chen, K. Kim, S. H. Jung, T. Murayama, Y. Oki, R. Advani, F. d'Amore, N. Schmitz, C. Suh, R. Suzuki, Y. L. Kwong, T. Y. Lin and W. S. Kim (2016). "A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis." Lancet Oncol **17**(3): 389-400.
Kwong, Y. L. (2009). "High-dose chemotherapy and hematopoietic SCT in the management of natural killer-cell malignancies." Bone Marrow Transplant **44**(11): 709-714.
Kwong, Y. L., T. S. Y. Chan, D. Tan, S. J. Kim, L. M. Poon, B. Mow, P. L. Khong, F. Loong, R. Au-Yeung, J. Iqbal, C. Phipps and E. Tse (2017). "PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase." Blood **129**(17): 2437-2442.
Kwong, Y. L., W. S. Kim, S. T. Lim, S. J. Kim, T. Tang, E. Tse, A. Y. Leung and C. S. Chim (2012). "SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group." Blood **120**(15): 2973-2980.

Lee, J., Y. H. Park, W. S. Kim, S. S. Lee, B. Y. Ryoo, S. H. Yang, K. W. Park, J. H. Kang, J. O. Park, S. H. Lee, K. Kim, C. W. Jung, Y. S. Park, Y. H. Im, W. K. Kang, M. H. Lee, Y. H. Ko, Y. C. Ahn and K. Park (2005). "Extranodal nasal type NK/T-cell lymphoma: elucidating clinical prognostic factors for risk-based stratification of therapy." Eur J Cancer **41**(10): 1402-1408.
Lee, J., C. Suh, Y. H. Park, Y. H. Ko, S. M. Bang, J. H. Lee, D. H. Lee, J. Huh, S. Y. Oh, H. C. Kwon, H. J. Kim, S. I. Lee, J. H. Kim, J. Park, S. J. Oh, K. Kim, C. Jung, K. Park and W. S. Kim (2006). "Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study." J Clin Oncol **24**(4): 612-618.
Li, X., Y. Cheng, M. Zhang, J. Yan, L. Li, X. Fu, X. Zhang, Y. Chang, Z. Sun, H. Yu, L. Zhang, X. Wang, J. Wu, Z. Li, F. Nan, L. Tian, W. Li and K. H. Young (2018). "Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma." J Hematol Oncol **11**(1): 15.
Qi, S., J. Yahalom, M. Hsu, M. Chelius, M. Lunning, A. Moskowitz and S. Horwitz (2016). "Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population." Leuk Lymphoma **57**(11): 2575-2583.
Qi, S., Y. Yang, W. Liu, L. Zhang, H. Su, Y. Yang, X. He, B. Qu, L. Qian, X. Hou, H. Wang, G. Li, Y. Zhang, X. Qiao, Y. Zhu, J. Cao, J. Wu, T. Wu, S. Zhu, M. Shi, L. Xu and Y. Li (2019). "TREATMENT BENEFIT ASSOCIATING WITH NON-ANTHRACYCLINE CHEMOTHERAPY IN EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE." **37**(S2): 101-102.
Suzuki, R. (2018). "NK/T Cell Lymphoma: Updates in Therapy." Curr Hematol Malig Rep.
Swerdlow, S. H., E. Campo, S. A. Pileri, N. L. Harris, H. Stein, R. Siebert, R. Advani, M. Ghielmini, G. A. Salles, A. D. Zelenetz and E. S. Jaffe (2016). "The 2016 revision of the World Health Organization classification of lymphoid neoplasms." Blood **127**(20): 2375-2390.
Tao, R., L. Fan, Y. Song, Y. Hu, W. Zhang, Y. Wang, L. Xu, H. Zhou and J. Li (2019). "Sintilimab for relapsed/refractory (r/r) extranodal NK/T-cell lymphoma (ENKTL): A multicenter, single-arm, phase 2 trial (ORIENT-4)." **37**(15_suppl): 7504-7504.
Tse, E., T. S. Chan, L. P. Koh, W. J. Chng, W. S. Kim, T. Tang, S. T. Lim, A. K. Lie and Y. L. Kwong (2014). "Allogeneic haematopoietic SCT for natural killer/T-cell lymphoma: a multicentre analysis from the Asia Lymphoma Study Group." Bone Marrow Transplant **49**(7): 902-906.
Vargo, J. A., A. Patel, S. M. Glaser, G. K. Balasubramani, R. J. Farah, S. M. Marks and S. Beriwal (2017). "The impact of the omission or inadequate dosing of radiotherapy in extranodal natural killer T-cell lymphoma, nasal type, in the United States." Cancer **123**(16): 3176-3185.
Wang, L., H. Wang, P. F. Li, Y. Lu, Z. J. Xia, H. Q. Huang and Y. J. Zhang (2015). "CD38 expression predicts poor prognosis and might be a potential therapy target in extranodal NK/T cell lymphoma, nasal type." Ann Hematol **94**(8): 1381-1388.
Wang, Z. Y., Y. X. Li, W. H. Wang, J. Jin, H. Wang, Y. W. Song, Q. F. Liu, S. L. Wang, Y. P. Liu, S. N. Qi, H. Fang, X. F. Liu and Z. H. Yu (2009). "Primary radiotherapy showed favorable outcome in treating extranodal nasal-type NK/T-cell lymphoma in children and adolescents." Blood **114**(23): 4771-4776.
Wu, T., Y. Yang, S. Y. Zhu, M. Shi, H. Su, Y. Wang, X. He, L. M. Xu, Z. Y. Yuan, L. L. Zhang, G. Wu, B. L. Qu, L. T. Qian, X. R. Hou, F. Q. Zhang, Y. J. Zhang, Y. Zhu, J. Z. Cao, S. M. Lan, J. X. Wu, C. Hu, S. N. Qi, B. Chen and Y. X. Li (2018). "Risk-adapted survival benefit of IMRT in early-stage NKTCL: a multicenter study from the China Lymphoma Collaborative Group." Blood Adv **2**(18): 2369-2377.
Yamaguchi, M., Y. L. Kwong, W. S. Kim, Y. Maeda, C. Hashimoto, C. Suh, K. Izutsu, F. Ishida, Y. Isobe, E. Sueoka, J. Suzumiya, T. Kodama, H. Kimura, R. Hyo, S. Nakamura, K. Oshimi and R. Suzuki (2011). "Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study." J Clin Oncol **29**(33): 4410-4416.
Yamaguchi, M., R. Suzuki, S. J. Kim, Y. H. Ko, M. Oguchi, N. Asano, K. Miyazaki, Y. Terui, N. Kubota, T. Maeda, Y. Kobayashi, J. Amaki, T. Soejima, B. Saito, E. Shimoda, N. Fukuhara, N. Tsukamoto, K. Shimada,

I. Choi, T. Utsumi, Y. Ejima, W. S. Kim and N. Katayama (2018). "Early disease progression in patients with localized natural killer/T-cell lymphoma treated with concurrent chemoradiotherapy." Cancer Sci **109**(6): 2056-2062.
Yamaguchi, M., R. Suzuki, Y. L. Kwong, W. S. Kim, Y. Hasegawa, K. Izutsu, J. Suzumiya, T. Okamura, S. Nakamura, K. Kawa and K. Oshimi (2008). "Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia." Cancer Sci **99**(5): 1016-1020.
Yamaguchi, M., K. Tobinai, M. Oguchi, N. Ishizuka, Y. Kobayashi, Y. Isobe, K. Ishizawa, N. Maseki, K. Itoh, N. Usui, I. Wasada, T. Kinoshita, K. Ohshima, Y. Matsuno, T. Terauchi, S. Nawano, S. Ishikura, Y. Kagami, T. Hotta and K. Oshimi (2009). "Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211." J Clin Oncol **27**(33): 5594-5600.
Yang, Y., J. Z. Cao, S. M. Lan, J. X. Wu, T. Wu, S. Y. Zhu, L. T. Qian, X. R. Hou, F. Q. Zhang, Y. J. Zhang, Y. Zhu, L. M. Xu, Z. Y. Yuan, S. N. Qi and Y. X. Li (2017). "Association of Improved Locoregional Control With Prolonged Survival in Early-Stage Extranodal Nasal-Type Natural Killer/T-Cell Lymphoma." JAMA Oncol **3**(1): 83-91.
You, J. Y., K. H. Chi, M. H. Yang, C. C. Chen, C. H. Ho, W. K. Chau, H. C. Hsu, J. P. Gau, C. H. Tzeng, J. H. Liu, P. M. Chen and T. J. Chiou (2004). "Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan." Ann Oncol **15**(4): 618-625.