

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Survival outcomes in early-stage NKTCL treated with primary radiotherapy reported in the literature

| | Cohort | Total | | | | Median RT | 5-year OS | 5-year PFS |
|-----------------------|--------|--------|-------|----------------------------|-------------------------------|-----------|-------------|-------------|
| Author | number | number | Stage | Treatment | Chemotherapy regimen | dose (Gy) | (%) | or DFS (%) |
| Cheung 2002 [35] | 1 | 79 | I-II | CMT: 61 | anthracycline-based | 50 | 40 | 36 |
| Kim 2005 [36] | 2 | 53 | I-II | RT: 33, CMT: 20 | CHOP 100% | 45 | 69 | NA |
| Li 2006 [13] | 3 | 105 | I-II | RT: 31, CMT: 71, CT: 3 | CHOP 100% | 50 | 71 | 59 |
| Huang 2008 [14]† | 4 | 82 | I-II | RT: 9, CMT: 65 | CHOP 100% | 50 | 57 | 42 |
| Ma 2010 [37] | 5 | 64 | I-II | RT: 23, CMT: 41 | CHOP 90% | 54 | 59 | 52 |
| Li 2011 [38] | 6 | 214 | I-II | RT: 96, CMT: 118 | CHOP 85% | 50 | 72 | 65 |
| Li 2012 [15] | 7 | 87 | I | RT: 87 | No | 50 | 80 | 69 |
| Yamaguchi 2012 [8] | 8 | 33 | I-II | CCRT: 33 | DeVIC 100% | 50 | 73 | 67 |
| Fang 2014 [39] | 9 | 124 | II | CMT: 84, RT: 30, CT: 10 | CHOP 83% | 50 | 60 | 48 |
| Oh 2015 [19] | 10 | 62 | I-II | CCRT: 62 | VIPD 52%, L-ASP- based 48% | 40 | 83 (3-year) | 77 (3-year) |

| | | | | | | | | |
|--------------------|----|-----|------|--|---|---------|-------------|-------------|
| Dong 2016 [40] | 11 | 78 | I-II | CMT: 33 | DICE-L-ASP 100% | 45/55 | 89 | 82 |
| | 12 | | | RT: 45 | | | 49 | 49 |
| Moon 2016[41]† | 13 | 158 | I-II | CT + RT: 61 | CHOP 47%, non-anthracycline-based 53% | 43.2 | 78 | 63 |
| | 14 | | | CRT + CT:55 | | 43.2 | 70 | 53 |
| Huang 2017 [42] | 15 | 44 | I-II | IMRT + CT: 44 | GDP | | 85 (3-year) | 77 (3-year) |
| Cao 2017 [44]† | 16 | 94 | I-II | CRT: 43 | CHOP | 50 | 42 | 36 |
| Yang 2017 [45] | 17 | 37 | I-II | RT ± CT: 29, RT alone 8 | CHOP 55%, LVP 28, others 15% | 50 | 76 (3-year) | 64 (3-year) |
| Kwong 2017 [43]* | 18 | 303 | I-II | RT ± CT: 271, CT alone: 32 | Non-anthracycline-based | 40–52.8 | NA | NA |
| Yamaguchi 2017[4]* | 19 | 257 | I-II | CCRT: 183, SCRT: 39, RT alone: 22, CT alone 11 | Non-anthracycline-based 78% (DeVIC 66%) | 50 | 68 | 56 |
| Vargo 2017 [5]* | 20 | 642 | I-II | CMT: 161 | NA | 50 | 58 | NA |
| | 21 | | | RT alone: 65 | | | 45 | NA |

| | | | | | | | | |
|-------------------|----|-----|------|------------------------|----|----|----|----|
| SEER (1992-2013)* | 22 | 306 | I-II | CMT: 218, RT alone: 88 | NA | NA | 52 | NA |
|-------------------|----|-----|------|------------------------|----|----|----|----|

* multicenter cohort.

† patients who received chemotherapy only were excluded from this analysis.

Abbreviations: NKTCL, extranodal NK/T-cell lymphoma, nasal-type; RT, radiotherapy; CT: chemotherapy; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; NA, not available; CMT, combined modality therapy; CCRT, concurrent chemoradiotherapy; SCRT: sequential chemoradiotherapy; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; IMEP: ifosfamide, methotrexate, etoposide and prednisone; DeVIC: dexamethasone, etoposide, ifosfamide, and carboplatin; DEP: dexamethasone, VP-16 and cisplatin; GELOX, gemcitabine, oxaliplatin, and *L*-asparaginase; VIDP: etoposide, ifosfamide, cisplatin, and dexamethasone; L-ASP, *L*-asparaginase; GEM-based, gemcitabine-based; CEOP: cyclophosphamide, epirubicin, vincristine and prednisone; DICE: etoposide, cyclophosphamide, cisplatin, and dexamethasone; VIDL: etoposide, ifosfamide, dexamethasone, and *L*-asparaginase; GDP, gemcitabine, dexamethasone, and cisplatin; EPOCH, etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone; LVP, *L*-asparaginase, vincristine, and prednisone; DICE-L-ASP, cisplatin, ifosfamide, etoposide, dexamethasone, *L*-asparaginase; SEER, the Surveillance, Epidemiology and End Results.

eTable 2. Clinical characteristics of the overall cohort of patients with early-stage NKTCL treated with first-line radiotherapy

| Characteristics | Number (%) |
|------------------------|-------------|
| Gender | |
| Male | 1414 (70.2) |
| Female | 601 (29.8) |
| Age (years) | |
| ≤ 60 | 1754 (87.0) |
| > 60 | 261 (13.0) |
| B symptoms | |
| No | 1259 (62.5) |
| Yes | 756 (37.5) |
| Stage | |
| I | 1383 (68.6) |
| II | 632 (31.4) |
| Primary tumor invasion | |
| No | 927 (46.0) |
| Yes | 1088 (54.0) |
| Elevated LDH | |

| | |
|-------------------------------|-------------|
| No | 1464 (72.7) |
| Yes | 551 (27.3) |
| ECOG score | |
| 0-1 | 1921 (95.3) |
| ≥ 2 | 94 (4.7) |
| Risk groups* | |
| Low (no risk factor) | 485 (24.1) |
| Intermediate (1 risk factor) | 718 (35.6) |
| High (≥ 2 risk factors) | 812 (40.3) |

*Risk factors included: age >60 years, stage II disease, ECOG score ≥ 2 , elevated LDH, and the presence of primary tumor invasion.

Abbreviations: NKTCL, extranodal nasal-type NK/T-cell lymphoma; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

eTable 3. Annual hazards of death and failure for patients with early-stage natural killer/T-Cell Lymphoma treated with radiotherapy

| | 1 year | 2 year | 3 years | 4 years | 5 years | 6 years | 7 years | 8 years | 9 years | 10 years |
|-------------------------------|-----------|-----------|---------|---------|---------|---------|---------|---------|---------|----------|
| All patients | | | | | | | | | | |
| Annual hazards of death (%) | 13.7 | 9.0 | 6.8 | 3.9 | 3.5 | 3.0 | 3.8 | 1.6 | 0.6 | 0 |
| 95% CI (%) | 13.0-14.3 | 8.5-9.5 | 6.3-7.2 | 3.7-4.2 | 3.3-3.8 | 2.7-3.3 | 3.4-4.2 | 1.4-1.8 | 0.5-0.6 | NA |
| Annual hazards of failure (%) | 22.1 | 13.0 | 7.5 | 3.7 | 4.2 | 3.7 | 3.6 | 1.8 | 1.2 | 1.6 |
| 95% CI (%) | 21.0-23.1 | 12.3-13.8 | 7.0-8.0 | 3.4-3.9 | 3.9-4.6 | 3.3-4.0 | 3.2-4.0 | 1.6-2.0 | 1.0-1.4 | 1.3-1.9 |
| Low-risk patients | | | | | | | | | | |
| Annual hazards of death (%) | 4.8 | 3.1 | 2.9 | 1.6 | 1.1 | 2.9 | 1.9 | 1.2 | 0 | 0 |
| 95% CI (%) | 4.4-5.3 | 2.8-3.5 | 2.6-3.3 | 1.4-1.8 | 0.9-1.2 | 2.4-3.4 | 1.5-2.2 | 0.9-1.4 | NA | NA |
| Annual hazards of failure (%) | 9.1 | 7.0 | 3.6 | 3.7 | 4.2 | 3.7 | 3.6 | 1.8 | 1.2 | 1.6 |
| 95% CI (%) | 8.3-10.0 | 6.3-7.7 | 3.1-4.0 | 3.4-3.9 | 3.9-4.6 | 3.3-4.0 | 3.2-4.0 | 1.6-2.0 | 1.0-1.4 | 1.3-1.9 |
| Intermediate -risk patients | | | | | | | | | | |
| Annual hazards of death (%) | 11.4 | 9.0 | 6.7 | 4.3 | 4.8 | 1.8 | 4.1 | 0 | 0 | 0 |
| 95% CI (%) | 10.5-12.3 | 8.2-9.8 | 6.0-7.4 | 3.9-4.8 | 4.1-5.4 | 1.5-2.1 | 3.4-4.8 | NA | NA | NA |
| Annual hazards of failure (%) | 20.1 | 14.1 | 7.7 | 4.6 | 3.0 | 3.4 | 3.7 | 0 | 0 | 3.6 |
| 95% CI (%) | 18.5-21.6 | 12.8-15.4 | 6.9-8.5 | 4.1-5.2 | 2.6-3.4 | 2.8-3.9 | 3.0-4.3 | NA | NA | 2.7-4.6 |

| High-risk patients | | | | | | | | | | |
|-------------------------------|-----------|-----------|----------|---------|---------|---------|---------|---------|---------|----|
| Annual hazards of death (%) | 21.6 | 13.6 | 10.4 | 5.9 | 4.6 | 4.8 | 5.7 | 4.7 | 2.2 | 0 |
| 95% CI (%) | 20.0-23.2 | 12.4-14.8 | 9.3-11.5 | 5.2-6.7 | 3.9-5.3 | 3.9-4.6 | 4.5-6.9 | 3.5-5.8 | 1.6-2.9 | NA |
| Annual hazards of failure (%) | 32.7 | 17.0 | 11.1 | 3.5 | 5.9 | 5.4 | 5.2 | 5.2 | 2.6 | 0 |
| 95% CI (%) | 30.2-35.2 | 15.4-18.6 | 9.8-12.4 | 3.0-4.0 | 5.0-6.8 | 4.4-6.4 | 4.0-6.3 | 3.9-6.6 | 1.8-3.4 | NA |

Abbreviations: CI, confidence interval; NA, not available.

eTable 4. Five-year conditional overall survival probabilities for different risk groups over time

| Risk groups | | Time since treatment | | | | | |
|-----------------------------------|--------------|----------------------|-----------|-----------|-----------|-----------|--------------|
| | | 0 year | 1 year | 2 years | 3 years | 4 years | 5years |
| Low-risk | 5-year COS | 87.2 | 89.1 | 90.2 | 91.9 | 93.4 | 94.4 |
| | 95% CI | 83.2-90.3 | 84.4-92.4 | 84.9-93.7 | 86.1-95.4 | 87.5-96.6 | 88.6-97.4 |
| Intermediate-risk | 5-year COS | 69.3 | 76.5 | 80.5 | 86.1 | 90.0 | 94.4 |
| | 95% CI | 65.0-73.1 | 71.8-80.5 | 75.0-84.9 | 80.6-90.2 | 84.4-93.5 | 89.1-97.2 |
| High-risk | 5-year COS | 57.5 | 67.5 | 73.0 | 77.1 | 80.2 | 83.6 |
| | 95% CI | 53.2-61.5 | 62.0-72.3 | 66.1-78.7 | 68.6-83.5 | 70.7-86.8 | 73.7-90.1 |
| Intermediate-risk vs. low-risk | HR for death | 2.41 | 2.42 | 2.21 | 2.15 | 1.95 | 1.37 |
| | 95% CI | 1.79-3.24 | 1.66-3.53 | 1.38-3.53 | 1.18-3.93 | 0.96-4.00 | 0.56 to 3.20 |
| | P | < 0.001 | < 0.001 | 0.001 | 0.010 | 0.06 | 0.47 |
| High-risk vs. low-risk | HR for death | 4.01 | 3.66 | 3.31 | 3.15 | 2.93 | 2.58 |
| | 95% CI | 3.01-5.33 | 2.52-5.30 | 2.07-5.29 | 1.70-5.80 | 1.41-6.12 | 1.11-5.99 |
| | P | < 0.001 | < 0.001 | < 0.001 | <0.001 | 0.003 | 0.02 |

Abbreviations: COS, conditional overall survival; HR, hazard ratio; CI, confidence interval.

eTable 5. Five-year conditional failure-free survival probabilities for different risk groups over time

| | | Time since treatment | | | | | |
|--------------------------------|-------------------------|----------------------|-----------|-----------|-----------|-----------|-----------|
| Risk groups | | 0 year | 1 year | 2 years | 3 years | 4 years | 5years |
| Low-risk | 5-year CFFS | 76.7 | 82.1 | 86.3 | 88.1 | 88.7 | 92.4 |
| | 95% CI | 71.8-80.8 | 76.8-86.4 | 80.4-90.6 | 81.4-92.5 | 80.7-93.5 | 84.0-96.5 |
| Intermediate-risk | 5-year CFFS | 61.1 | 72.3 | 80.2 | 86.5 | 90.6 | 90.0 |
| | 95% CI | 56.8-65.0 | 67.3-76.7 | 76.4-84.8 | 80.6-90.7 | 84.7-94.3 | 81.9-94.6 |
| High-risk | 5-year CFFS | 50.4 | 65.4 | 73.2 | 77.4 | 78.2 | 83.0 |
| | 95% CI | 46.2-54.5 | 59.5-70.6 | 65.8-79.2 | 68.3-84.2 | 67.9-85.5 | 72.2-89.9 |
| Intermediate-risk vs. low-risk | HR for failure or death | 1.96 | 1.77 | 1.60 | 1.36 | 1.23 | 1.59 |
| | 95% CI | 1.55-2.47 | 1.30-2.42 | 1.05-2.44 | 0.81-2.28 | 0.66-2.27 | 0.74-3.43 |
| | P | < 0.001 | < 0.001 | 0.03 | 0.25 | 0.52 | 0.23 |
| High-risk vs. low-risk | HR for failure or death | 2.83 | 2.26 | 2.15 | 1.70 | 1.85 | 2.19 |
| | 95% CI | 2.26-3.54 | 1.66-3.08 | 1.41-3.28 | 0.99-2.91 | 0.99-3.45 | 0.98-4.91 |
| | P | < 0.001 | < 0.001 | < 0.001 | 0.05 | 0.05 | 0.05 |

Abbreviations: CFFS, conditional failure-free survival; HR, hazard ratio; CI, confidence interval.

eTable 6. Three-year conditional overall survival probabilities stratified by treatment in low-risk patients

| Treatment | | Time since treatment | | | | | |
|-----------------------|------------|----------------------|-----------|-----------|-----------|-----------|----------|
| | | 0 year | 1 year | 2 years | 3 years | 4 years | 5years |
| RT and new CT regimen | 3-year COS | 91.1 | 93.9 | 92.3 | 92.2 | 92.2 | NA |
| | 95% CI | 86.3-96.2 | 89.6-98.5 | 84.6-100 | 82.3-100 | 82.3-100 | NA |
| RT and old CT regimen | 3-year COS | 88.3 | 90.5 | 94.1 | 95.4 | 95.4 | 96.3 |
| | 95% CI | 83.3-93.5 | 95.7-95.6 | 89.9-98.5 | 91.0-99.9 | 91.0-99.9 | 92.4-100 |
| RT alone | 3-year COS | 89.8 | 94.1 | 96.0 | 97.3 | 95.7 | 90.9 |
| | 95% CI | 84.4-95.5 | 89.2-99.3 | 91.7-100 | 93.6-100 | 87.7-100 | 79.6-100 |
| | P | 0.64 | 0.56 | 0.83 | 0.97 | 0.76 | 0.99 |

Abbreviations: RT, radiotherapy; CT: chemotherapy; COS, conditional overall survival; HR, hazard ratio; CI, confidence interval; NA, not available.

eTable 7. Three-year conditional overall survival probabilities stratified by treatment in intermediate-risk patients

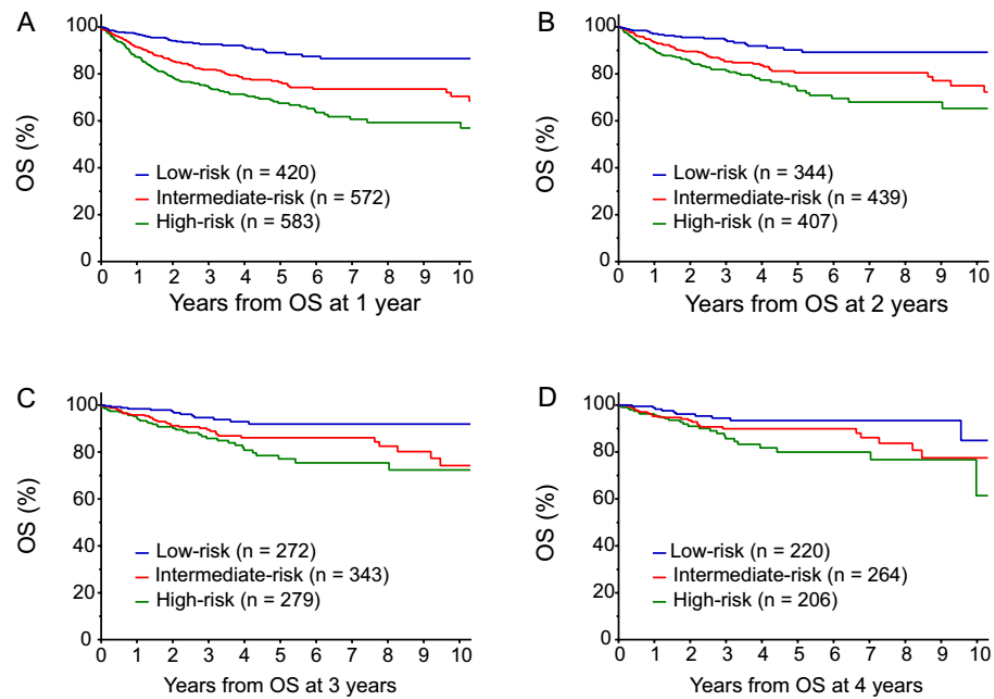
| Treatment | | Time since treatment | | | | | |
|-----------------------|------------|----------------------|-----------|-----------|-----------|-----------|-----------|
| | | 0 year | 1 year | 2 years | 3 years | 4 years | 5years |
| RT and new CT regimen | 3-year COS | 80.0 | 83.0 | 87.5 | 92.0 | 95.9 | NA |
| | 95% CI | 74.5-85.8 | 76.8-89.6 | 80.3-95.2 | 85.4-99.1 | 90.6-100 | NA |
| RT and old CT regimen | 3-year COS | 72.7 | 80.9 | 84.2 | 88.8 | 90.2 | 95.1 |
| | 95% CI | 67.5-78.3 | 75.7-86.3 | 79.0-89.8 | 83.8-94.2 | 85.1-95.7 | 91.0-99.4 |
| RT alone | 3-year COS | 75.7 | 83.2 | 86.7 | 92.1 | 89.7 | 93.2 |
| | 95% CI | 68.5-83.6 | 75.9-91.2 | 79.2-94.9 | 85.6-99.1 | 80.3-100 | 84.6-100 |
| | P | 0.12 | 0.67 | 0.53 | 0.82 | 0.66 | 0.43 |

Abbreviations: RT, radiotherapy; CT: chemotherapy; COS, conditional overall survival; HR, hazard ratio; CI, confidence interval; NA, not available.

eTable 8. Three-year conditional overall survival probabilities stratified by treatment in high-risk patients

| Treatment | | Time since treatment | | | | | |
|--|--------------|----------------------|-----------|-----------|-----------|-----------|-----------|
| | | 0 year | 1 year | 2 years | 3 years | 4 years | 5 years |
| RT and new CT regimen | 3-year COS | 73.3 | 81.4 | 87.8 | 88.4 | 93.2 | NA |
| | 95% CI | 68.3-78.7 | 75.3-87.9 | 80.9-95.4 | 78.9-99.1 | 84.3-100 | NA |
| RT and old CT regimen | 3-year COS | 60.0 | 71.0 | 78.9 | 85.0 | 84.8 | 86.8 |
| | 95% CI | 54.6-65.9 | 65.1-77.4 | 72.8-85.4 | 78.8-92.4 | 77.8-92.4 | 79.4-94.9 |
| RT alone | 3-year COS | 46.5 | 66.1 | 75.4 | 86.1 | 80.5 | NA |
| | 95% CI | 37.2-58.2 | 53.9-81.2 | 63.0-90.3 | 72.3-100 | 62.0-100 | NA |
| RT and old CT regimen vs. RT and new CT regimen | HR for death | 1.49 | 1.60 | 1.77 | 1.34 | 1.81 | NA |
| | 95% CI | 1.13-1.95 | 1.07-2.39 | 0.94-3.33 | 0.54-3.56 | 0.41-8.01 | NA |
| | P | 0.004 | 0.02 | 0.07 | 0.53 | 0.43 | NA |
| RT alone vs. RT and new CT regimen | HR for death | 2.42 | 1.82 | 2.69 | 1.57 | 1.84 | NA |
| | 95% CI | 1.73-3.39 | 1.05-3.17 | 1.23-5.90 | 0.46-5.28 | 0.30-11.2 | NA |
| | P | <0.001 | 0.03 | 0.01 | 0.47 | 0.50 | NA |

Abbreviations: RT, radiotherapy; CT: chemotherapy; COS, conditional overall survival; HR, hazard ratio; CI, confidence interval; NA, not available.



Supplemental Fig. 1

eFigure. Kaplan-Meier curves of overall survival stratified by risk groups

Kaplan-Meier curves of overall survival (OS) between low-risk, intermediate-risk and high-risk patients who were surviving at (A) 1 year, (B) 2 years, (C) 3 years and (D) 4 years.