

LETTER TO THE EDITOR



A 10-year survival update on early-stage extranodal natural killer/T-cell lymphoma with ‘sandwich’ therapy

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ARTICLE HISTORY Received 6 January 2022; accepted 8 February 2022

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL) is an aggressive subtype of T/natural killer (NK) cell lymphoma according to the World Health Organization (WHO) classification of tumors [1]. Due to the geographical disparity of disease distribution, ENKTL is the most common T/NK cell lymphoma in Asia, with an incidence of 22.4%, whereas its incidence is 5.1% in North America and 4.3% in Europe [2]. At present, there is no standard therapy strategy for early-stage ENKTL; radiotherapy combined with asparaginase-containing chemotherapy is firmly established as the initial therapy [3]. However, the preference for the sequence of radiotherapy and chemotherapy in ENKTL remains controversial. ‘Sandwich’ treatment is defined as 2–3 cycles of chemotherapy followed by radiotherapy (50–56 Gy in 25–28 fractions, once a day, and 5 fractions every week), again followed by 2–3 cycles of chemotherapy. It exhibited a complete response (CR) rate of 80.8%–83.3% in our previous prospective studies and 64% for both the 5-year progression-free survival (PFS) and the overall survival (OS) [4–6]. Here, we report the 10-year survival outcomes of populations with ENKTL from these two studies.

Material and methods

The design and conduct of our studies have been described in detail previously [4,6]. Briefly, 92 patients with early-stage ENKTL were included in these two studies from July 2008 to November 2009 (26 patients) and from April 2010 to December 2012 (66 patients). We summarized OS using the Kaplan-Meier method and compared the difference in OS between the groups using log-rank test. All data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY), and a two-sided $p < 0.05$ was considered as a statistically significant difference. OS was calculated from the time taken from diagnosis to death by any cause or until the last follow-up. The study was done under regulatory requirements and

Table 1. Clinical characteristics of patients with early-stage ENKTL treated with the ‘sandwich’ method.

Characteristics	No. of patients (%), $n = 84$
Age, years (median = 43, range = 13–79)	
≤60	73 (86.9%)
>60	11 (13.1%)
Sex	
Male	61 (72.6%)
Female	23 (27.3%)
ECOG performance status	
0	42 (50.0%)
1	37 (44.0%)
2	5 (6.0%)
Ann Arbor stage	
IE	50 (59.5%)
IIE	34 (40.5%)
Serum LDH	
Normal	48 (57.1%)
Increased	36 (42.9%)
B symptoms	
Absent	34 (40.5%)
Present	50 (59.5%)
PINK score	
0	70 (83.3%)
1	14 (16.7%)
Chemotherapy	
LVP	18 (21.4%)
VDLP	66 (78.6%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase; PINK: Prognostic Index of Natural Killer lymphoma; LVP: L-asparaginase, vincristine, and prednisone; VDLP: L-asparaginase, cisplatin, etoposide, and dexamethasone.

approved by the Ethics Committee of West China Hospital of Sichuan University.

Results

Patient characteristics are summarized in Table 1. Ninety-two patients were included in this study, eight of whom were later excluded due to loss to follow-up. The median age at diagnosis was 43 years with male dominance, and 86.9% of the total study population were aged ≤60 years. There were 59.5% of the cases classified as stage IE and 40.5% as stage IIE. According to the Prognostic Index of Natural Killer

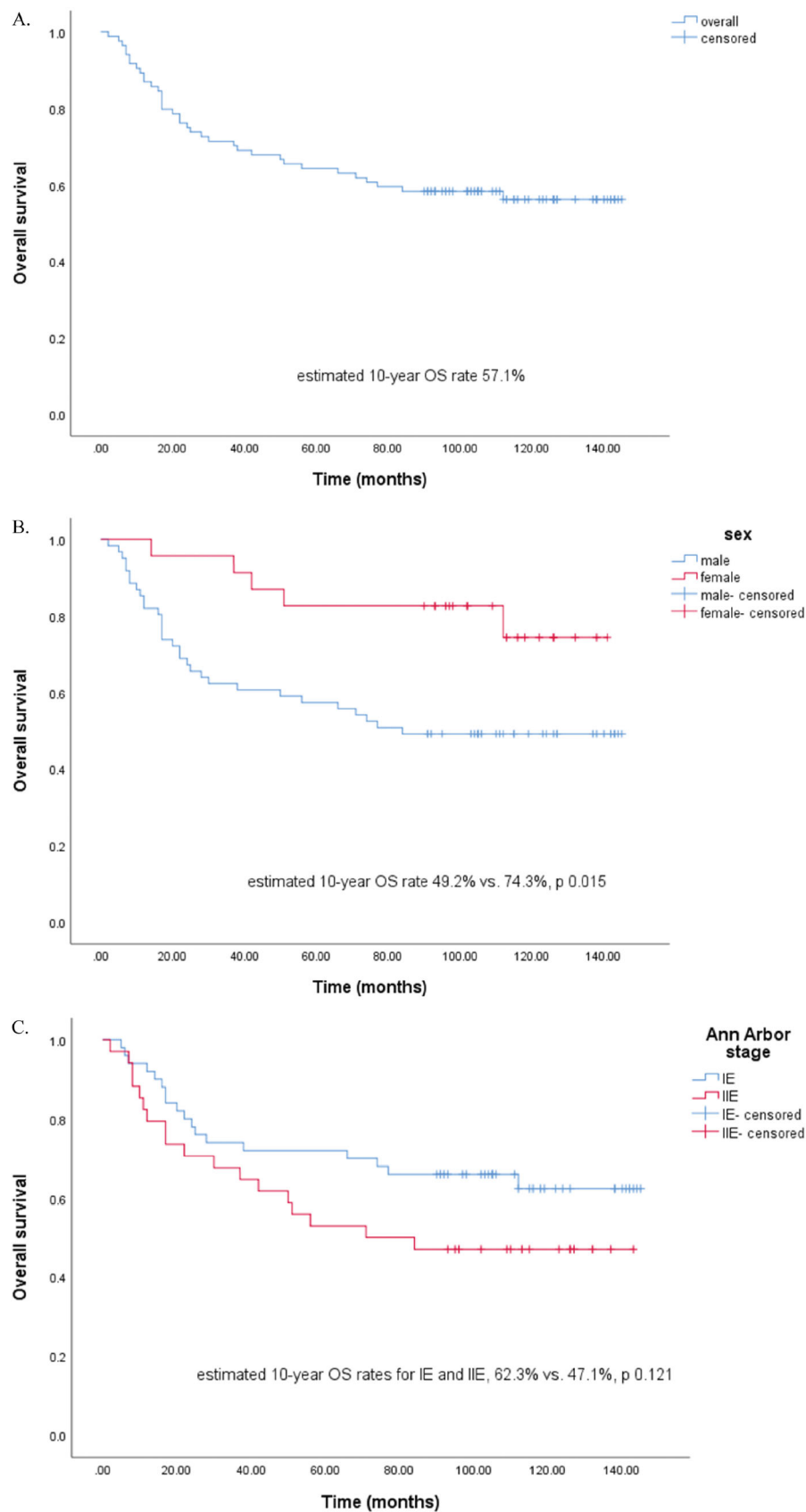


Figure 1. Probability of OS at 10 years of patients with ENKTL treated with the 'sandwich' therapy. Kaplan–Meier curve of OS in total (A) and stratified by sex (B), Ann Arbor stage (C), age (D), and chemotherapy regimens (E).

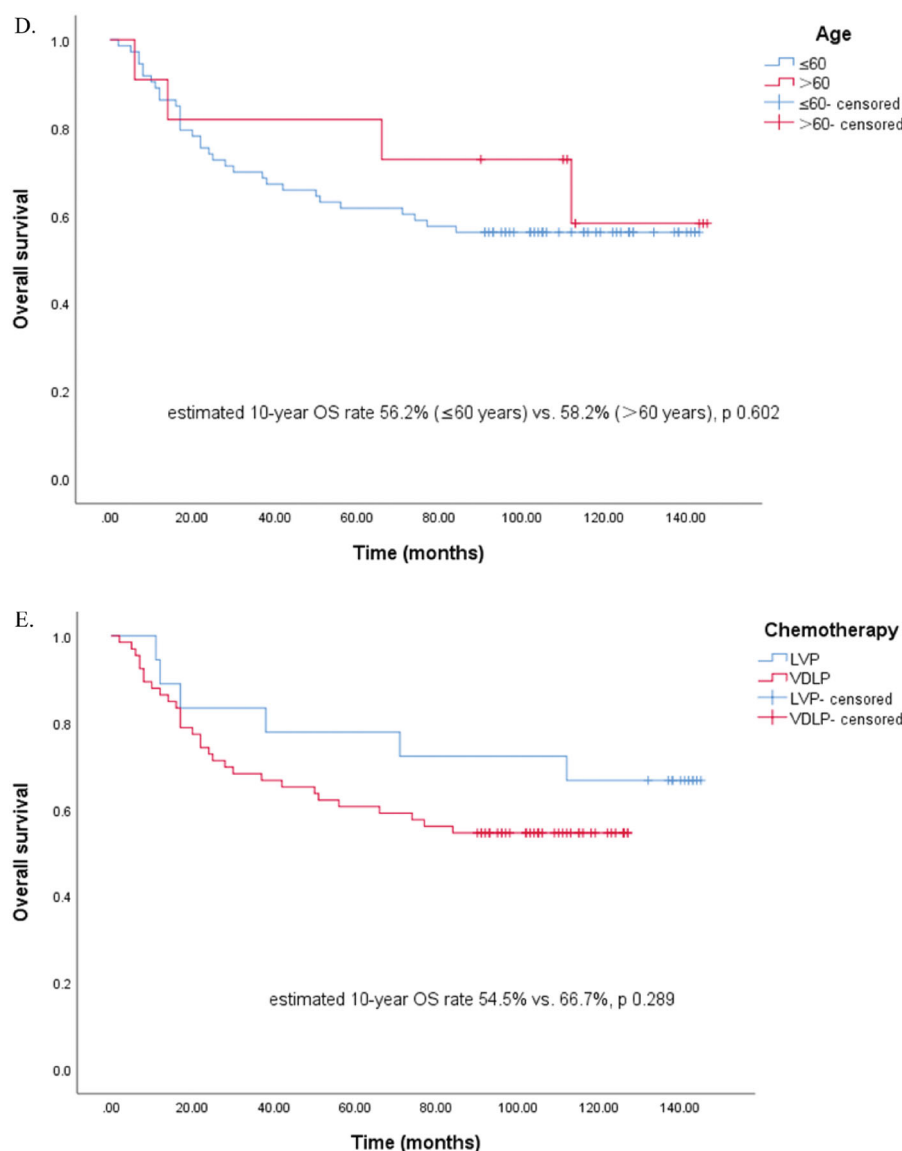


Figure 1. Continued.

lymphoma (PINK) score evaluation [7], 83.3% were assigned to the low-risk group. A total of 21.4% of patients were treated with LVP (L-asparaginase, vincristine, and prednisone) and 78.6% with VDLP (L-asparaginase, cisplatin, dexamethasone, and etoposide), and 50–56 Gy of radiation was applied in patients.

With a median follow-up of 115 months (range, 107–122 months), all patients' estimated 10-year OS rate was 57.1% (95% CI, 43.8%–68.6%, Figure 1(A)), and the median OS time was not reached. In the subgroup analysis, we observed an inferior survival rate in male patients than in female patients, with an estimated 10-year OS rate of 49.2% (95% CI, 36.7%–61.7%) vs. 74.3% (95% CI, 53.5%–95.1%, p = 0.015; Figure 1(B)). Additionally, there was a beneficial survival trend for patients with Ann Arbor stage IE without statistical difference (Figure 1(C)), IE vs. IIE, and an estimated 10-year OS rate of 62.3% vs. 47.1%, p = 0.121). For patients aged ≤60 years, our data did not show a longer survival time than that for elderly patients (Figure 1(D)), with an estimated 10-year OS of 56.2% (≤60 y) vs. 58.2% (>60 y),

p = 0.602. As VDLP regimen is different from the LVP, we also investigated the impact of difference in chemotherapy regimens on OS and found an estimated 10-year OS rate of 54.5% (VDLP) vs. 66.7% (LVP), p = 0.289 (Figure 1(E)). Notably, during 5–10 years after treatment, only two patients died in the LVP group, whereas four deaths were seen in the VDLP group.

Discussion

The updated survival analysis of the 'sandwich' method in patients with early-stage ENKTL demonstrated that with a median follow-up of 115 months, the estimated 10-year OS rate was 57.1%. The analysis indicated that this 'sandwich' therapy results in a robust, sustainable, and efficacious outcome. To our knowledge, this is the first report regarding the long-term survival data of patients with ENKTL treated with 'sandwich' chemoradiation. In previous studies, the 5-year PFS and OS rates of patients with early-stage ENKTL treated with sequential chemoradiotherapy were 64–83%

and 64–89%, respectively, of which, only our study reported the 5-year survival outcomes of ‘sandwich’ method; other studies were on chemotherapy followed by radiotherapy [5,8]. Moreover, there is a lack of reports on long-term survival data. Recently, a study from the International T-Cell Lymphoma Project showed that in 76 patients with ENKTL staged IE-IIIE, the 5-year OS was 55% for IE cases and 42% for IIE [9]. Our results showed a 10-year OS of 62.3% (IE) and 47.1% (IIE) and with only six deaths reported 5–10 years after treatment, which indicates that the 5-year OS could predict the long-term prognosis and that the ‘sandwich’ method is a promising treatment strategy for the long-term management of ENKTL. The impact of sex differences on the OS of ENKTL was studied using the Surveillance, Epidemiology, and End Results (SEER) data, which showed that female patients had better OS than male patients [10]. Our study conforms to this finding, and the 10-year OS of females in our study was superior to that of males (74.3% vs. 49.2%, $p = 0.015$) with asparaginase-containing chemotherapy and radiotherapy. Age >60 years is a poor prognostic marker in the PINK and nomogram-revised risk index models [7,11]. We observed no significant survival difference between patients aged ≤60 years and those aged >60 years in early-stage patients treated with our protocols; however, considering that only a minority of patients were diagnosed at >60 years, more samples are needed to verify this finding. Collectively, the data presented in this 10-year analysis demonstrate that the ‘sandwich’ method involving asparaginase-containing chemotherapy followed by radiotherapy and then consolidation with chemotherapy had a reasonable OS in patients with newly diagnosed early-stage ENKTL. As small sample size is a limitation of this study, more data collected with this method from a larger sample size are needed to explore the long-term efficacy of the ‘sandwich’ therapy.

Conclusion

A reasonably good 10-year OS can be expected with the ‘sandwich’ therapy, with only few deaths 5–10 years after treatment. Studies evaluating the 10-year OS could predict the long-term prognosis in these patients effectively. The long-term follow-up results of the ‘sandwich’ treatment in ENKTL presented a promising treatment strategy for long-term management and enhanced the importance of radiotherapy in early-stage ENKTL.

Disclosure statement

The authors declare that they have no conflict of interest.

Data availability statement

At this time, we will not be able to share individual patient-level data outside our institution.

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