Supportive Care in Cancer (2024) 32:727
https://doi.org/10.1007/s00520-024-08932-2

RESEARCH

Quality of life in disease-free survived patients with early-stage extranodal nasal-type NK/T-cell lymphoma after definitive intensity-modulated radiotherapy: a cross-sectional study of 310 cases

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Received: 25 June 2024 / Accepted: 7 October 2024

Abstract

Purpose Radiotherapy is a critical treatment for early-stage extranodal nasal-type NK/T-cell lymphoma (ENKTL) and has yielded favorable survival outcomes. However, their postradiotherapy quality of life (QOL) has not been investigated. Here, we conducted a cross-sectional study to assess the QOL of ENKTL patients with disease-free survival after definitive radiotherapy and to identify factors associated with QOL and treatment optimization.

Methods This cross-sectional study included 310 patients with stage I–II ENKTL of the upper aerodigestive tract (UADT) who had received simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) with a consistent design and achieved disease-free survival. The median postradiotherapy time was 47.2 months (range, 3.1–115.7). The EORTC QLQ-H&N35 questionnaire was used to assess symptom-related QOL, and nine additional items were added to incorporate nasal, optical, and aural-related symptoms. The scores indicate the severity of the symptoms.

Results The most common postradiotherapy symptoms among patients with ENKTL were nose problems (49.7%), dry mouth (44.8%), tooth problems (41.3%), sensory problems (32.6%), and less sexuality (25.8%). Tooth problems had the highest average score of 18.6, which is still acceptable. The severity of these symptoms decreased over time and reached a plateau in the second year after radiotherapy. Multivariable regression analysis showed that whole-neck irradiation was an independent predictive factor for xerostomia ($P = 0.013$, OR = 1.114), while age > 60 years was a predictive factor for lower sexuality ($P < 0.001$, OR = 1.32).

Conclusion The QOL of patients with early-stage ENKTL after radiotherapy was favorable, and most symptoms improved over time. Radiotherapy was correlated with specific symptoms, which may suggest a direction for further improvement in SIB-IMRT.

Keywords Quality of life · Extranodal NK/T-cell lymphoma · Radiotherapy · Postradiotherapy symptoms

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Plain English summary

With the increase in extranodal natural killer/T-cell lymphoma (ENKTL) survivors after radiotherapy, it is an important issue to address their postradiotherapy quality of life (QOL). In this cross-sectional study, we interviewed ENKTL patients with disease-free survival after definitive radiotherapy and assessed the symptom related QOL using the EORTC QLQ-H&N35 questionnaire. The results found that most symptoms got improved with time and reached a plateau in the second year after radiotherapy. Age and neck irradiation were identified as predictive factors associated with postradiotherapy QOL. Findings from this study provide new insights on the impact of radiotherapy on QOL for ENKTL patients and their rehabilitation from radiotherapy. Finally, this study indicates radiotherapy optimization.

Extended author information available on the last page of the article

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL) is a distinct subtype of mature T and natural killer cell lymphoma that primarily involves the nasal cavity, Waldeyer's ring, and other upper aerodigestive tract (UADT) sites. It is more common in East Asian and South American populations, and approximately 80% of cases are diagnosed in the early stages [1]. Radiotherapy (RT) is a critical component of curative therapy for early-stage ENKTL, and intensity-modulated radiotherapy (IMRT) has been shown to provide favorable overall survival (84.7–88.8%) and local regional control with tolerable toxicity [2–7]. Our prospective phase II clinical study and successive treatment observations revealed that early-stage ENKTL patients who received

Published online: 15 October 2024

extended involved-site three-dose gradient simultaneous integrated boost IMRT (SIB-IMRT) with a curative prescription dose after P-Gemox (pegaspargase, gemcitabine, and oxaliplatin) induction chemotherapy achieved a 5-year overall survival (OS) rate of 88.3% [8].

With the increase in the number of ENKTL survivors after radiotherapy, more attention should be given to their quality of life (QOL). Several population-based studies based on non-Hodgkin lymphoma patients have revealed that chemotherapy results in worse psychological and social well-being and health-related quality of life (HRQL) and that older age and comorbidities predict poor QOL [9–11]. However, no study has specifically investigated the QOL of survivors of ENKTL. A cross-sectional study of nasopharyngeal cancer patients indicated that long-term survivors after IMRT displayed moderate to high rates of neurocognitive impairment as well as clinically significant apathy, disinhibition, and executive dysfunction, which was proven to be associated with a high radiation dose sparing the temporal lobes [12]. Given their distinct anatomical sites and treatment strategies, ENKTL survivors may experience unique QOL problems compared to those with head and neck cancer. Research is needed to strengthen the evidence about the relationships between ENKTL and post-RT QOL and to explore the clinical characteristics influencing QOL, which will assist in improving patient rehabilitation and radiotherapy.

Therefore, we conducted a cross-sectional investigation based on the EORTC QLQ-H&N35 questionnaire to assess the mid- to long-term quality of life and the detailed occurrence and severity of chief symptoms in patients with UADT primary early-stage ENKTL after definitive IMRT with uniform target delineation principles and gradient doses.

Materials and methods

Patients

In September 2022, we conducted a cross-sectional survey of patients with ENKTL who had undergone radical IMRT at Sun Yat-sen University Cancer Center between March 2012 and December 2021. The inclusion criteria were as follows: (1) had stage I–II ENKTL with primary lesions in the UADT; (2) had diagnoses confirmed by pathology and staging imaging; (3) received extended involved-site SIB-IMRT without interruption, and the target volume was delineated according to previously described principles with three dose gradients [8]; (4) had no evidence of tumor recurrence or metastasis at any follow-up period; (5) had no history of mental or psychological diseases; and (6) provided full cooperation and accurate descriptions of their current life conditions, with or without aid from their families.

A total of 351 patients were followed up, and 41 ineligible patients were excluded, leaving 310 patients included in this study (Supplemental Fig. 1). There were 225 males and 85 females, and their median age was 41.5 years (range 13–81 years). A total of 190 (61%) patients presented with Ann Arbor stage I ENKTL, whereas 120 (39%) presented with stage II tumors. Most patients (n = 198, 63.9%) had a primary lesion in the nasal cavity. Additional patient characteristics are shown in Table 1.

Treatment information

All patients received SIB-IMRT with a consistent design of target volumes and conventional fractions. The patients were immobilized in the supine position with a perforated thermoplastic head mask, followed by routine CT simulation. Treatment planning CT images indexed every 3 mm were acquired, extending from the vertex of the skull to the inferior clavicular head. A 5-mm bolus and customized bite block were applied to 91 patients to compensate for the defect in dose distribution in the nasal skin and minimize the radiation dosage to the tongue. A detailed protocol for target volume delineation was established. The gross tumor volume (GTV) was defined as the primary tumor and involved regional lymph nodes delineated based on pretreatment images. The clinical target volume (CTV) was designed for the GTV plus potential contiguous spread sites with adequate margins. Depending on the risk of potential involvement, two clinical target volumes (high-risk CTV1 and low-risk CTV2) were set, as indicated in previous studies. It is important to note that cervical region coverage was not routine, except when the regional lymph nodes (120 patients) or Waldeyer's ring (112 patients) were involved. In such patients, elective upper- to whole-neck irradiation was administered, with a prophylactic dose to the cervical region, such as CTV1 or CTV2. These target delineations and three gradient dose settings (54.6 Gy for PTV-GTV, 50.7 Gy for PTV-CTV1, 45.5 Gy for PTV-CTV2, in 26 fractions) have been validated in a phase II clinical trial and showed satisfactory treatment outcomes [8]. This dose gradient was used in most (178) patients in the current study; however, another two dose levels were also adopted according to the clinician's judgment and preference, with prescription doses of 50.4 Gy/45.6 Gy/40.8 Gy in 24 fractions (29 patients) and 55 Gy/50 Gy/45 Gy in 25 fractions (103 patients).

A total of 288 patients (92.9%) received L-asparaginase-based chemotherapy before or after radiotherapy. With the emerging role of immunotherapy in treatment [13], 48 patients received immunotherapy before or after radiotherapy, and the commonly used drugs were sintilimab (33 patients), toripalimab (10 patients), pembrolizumab (3 patients), tislelizumab (1 patient), and camrelizumab (1 patient).

Table 1 The clinical characteristics of all interviewed patients

Patient characteristics	Overall
Total (*N*)	310 (%)
Age (*N* (%))	
≤ 60 yr	52 (16.8)
> 60 yr	258 (83.2)
Sex (*N* (%))	
Female	85 (27.4)
Male	225 (72.6)
Primary site (*N* (%))	
Nasal cavity involved	198 (63.9)
Waldeyer's ring involved	55 (17.7)
Both nasal cavity and Waldeyer's ring involved	57 (18.4)
Stage (*N* (%))	
Stage I	190 (61.3)
Stage II	120 (38.7)
Bike stock during RT (*N* (%))	
No	219 (70.6)
Yes	91 (29.4)
Peg-based chemotherapy regimen (*N* (%))	
No	22 (7.1)
Yes	288 (92.9)
Chemotherapy cycles (*N* (%))	
≥ 3	270 (87.1)
< 3	40(12.9)
Immunotherapy (*N* (%))	
No	274 (84.5)
Yes	48 (15.5)
Neck radiation (*N* (%))	
No neck radiation	78 (38.1)
Whole-neck radiation	120 (38.7)
Half neck radiation	112 (23.2)
Radiation dose (*N* (%))	
5040 cGy	29 (9.4)
5460 cGy	178 (57.4)
5500 cGy	103 (33.2)
Post_RT time interval (years) (*N* (%))	
0–1	32 (10.3)
1–2	31 (10.0)
2–3	25 (8.1)
3–4	43 (13.9)
4–5	37 (11.9)
5–6	28 (9.0)
6–7	26 (8.4)
7–8	27 (8.7)
8–9	13 (4.2)
9–10	9 (2.9)

Research methods

The EORTC QLQ-H&N35 (version 1.0) questionnaire, which was developed by the Quality of Life Study Group of the European Organization for Research and Therapy of Cancer in 1994 and consisted of 35 specific questions related to head and neck symptoms, was used [14, 15]. The 35 items were divided into seven multi-item scales and 11 single items. The multi-item scales covered pain, swallowing, sensory problems, speech problems, trouble with social eating, trouble with social contact, and less sexuality, whereas the single items included teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, pain killers, feeding tubes, weight gain, and weight loss. The questionnaire was scored using the EORTC QLQ-C30 scoring manual, which involves calculating the average of the contributing items and standardizing the raw score using a linear transformation algorithm to obtain scores ranging from 0 to 100, with higher scores indicating more problems. In addition, the overall QOL score of each patient was computed as the average score of all multi-item scales and single-symptom items. The detailed computational procedures are listed in Table 2.

Perinasal local tumor invasion and extensive facial destruction are common in patients who need escalated doses of radiotherapy, resulting in many postradiotherapy symptoms related to nasal, optical, and aural health. To investigate these issues, nine additional items, including nose bleeding, nasal congestion, altered nose appearance, xerostomia, runny nose, watery eyes, hearing loss, vision loss, and cataracts, were incorporated into the EORTC QLQ-H&N35 questionnaire. Nasal-related symptoms were grouped together on a multi-item scale called "nasal problems". These additional symptom items were scored using the same method described previously. Although these questions of interest were added, the integrity of the original EORTC questionnaire was preserved, and its validity was not affected. The final symptom questionnaire is shown in Supplemental Table 1. After incorporating these new items, a combined EORTC QLQ-H&N35 score was calculated as the average score of all items.

All 351 patients were followed up by telephone, mail, or inquiry at the outpatient clinic. The participants were asked to complete the questionnaires independently and truthfully. Elderly patients were allowed to receive aid from their families when necessary. Prior to answering the questionnaire, participants provided informed consent and were assured that their subsequent follow-up and rehabilitation advice would not be affected, even if they chose not to participate

Table 2 Summary of EORTC H&N35 symptom scales

Scale/items	Items	Raw score	Standardized score	Summary of symptom scale scores			
				N	Rate	Average score	Median score [25 ~ 75%]
Nose_problems	31 ~ 35	$(I_{31}+I_{32}+I_{33}+I_{34}+I_{35})/5$	(RS-1)/3*100	154	49.7%	5.7	0 [0 ~ 6.667]
Dry_mouth	11	I_{11}	(RS-1)/3*100	139	44.8%	17.1	0 [0 ~ 33.333]
Teeth	9	I_9	(RS-1)/3*100	128	41.3%	18.6	0 [0 ~ 33.333]
Sense_problems	13, 14	$(I_{13}+I_{14})/2$	(RS-1)/3*100	101	32.6%	11.2	0 [0 ~ 16.667]
Less_sexuality	29, 30	$(I_{29}+I_{30})/2$	(RS-1)/3*100	80	25.8%	17.2	0 [0 ~ 29.167]
Sticky_saliva	12	I_{12}	(RS-1)/3*100	67	21.6%	8.3	0 [0 ~ 0]
Swallowing	5 ~ 8	$(I_5+I_7+I_6+I_8)/4$	(RS-1)/3*100	38	12.3%	1.8	0 [0 ~ 0]
Trouble_with_social_eating	19 ~ 22	$(I_{19}+I_{20}+I_{21}+I_{22})/4$	(RS-1)/3*100	36	11.6%	2.0	0 [0 ~ 0]
Impaired vision	38	I_{38}	(RS-1)/3*100	36	11.6%	4.7	0 [0 ~ 0]
Hearing lose	37	I_{37}	(RS-1)/3*100	35	11.3%	4.6	0 [0 ~ 0]
Paradoxic lacrimation	36	I_{36}	(RS-1)/3*100	34	11.0%	4.2	0 [0 ~ 0]
Felt_ill	17	I_{17}	(RS-1)/3*100	23	7.4%	2.8	0 [0 ~ 0]
Trouble_with_social_contacting	18, 25 ~ 28	$(I_{18}+I_{25}+I_{26}+I_{27}+I_{28})/5$	(RS-1)/3*100	22	7.1%	1.3	0 [0 ~ 0]
Speech_problems	16, 23, 24	$(I_{16}+I_{23}+I_{24})/3$	(RS-1)/3*100	15	4.8%	0.9	0 [0 ~ 0]
Opening_mouth	10	I_{10}	(RS-1)/3*100	14	4.5%	1.6	0 [0 ~ 0]
Pain	1 ~ 4	$(I_1+I_2+I_3+I_4)/4$	(RS-1)/3*100	11	3.5%	0.5	0 [0 ~ 0]
Cataract	43	I_{43}	(RS-1)/1*100	11	3.5%	3.5	0 [0 ~ 0]
Coughing	15	I_{15}	(RS-1)/3*100	8	2.6%	1.0	0 [0 ~ 0]
Weight_loss	42	I_{42}	(RS-1)/1*100	5	1.6%	1.6	0 [0 ~ 0]
Nutritional_supplement	40	I_{40}	(RS-1)/1*100	4	1.3%	1.3	0 [0 ~ 0]
Pain_killers	39	I_{39}	(RS-1)/1*100	0	0.0%	0	0 [0 ~ 0]
Feeding_tube	41	I_{41}	(RS-1)/1*100	0	0.0%	0	0 [0 ~ 0]

in the interviews. A doctor was assigned to collect the questionnaires and input data into the system. This study was performed in accordance with the Declaration of Helsinki. Informed consent is available for all participants. This study was approved by the Institutional Review Board of the Sun Yat-sen University Cancer Center.

Statistical analysis

In this study, normally distributed variables are expressed as the mean ± standard deviation ($\bar{x} \pm S$), while nonnormally distributed variables are presented as medians with interquartile ranges (IQRs). Categorical variables are represented as counts and percentages in each category. The chi-square test and Kruskal−Wallis test were used for comparing multiple groups, depending on the variable type. A broken line graph was generated to identify the relationship between the QLQ-H&N35 scale score and postradiotherapy duration. Logistic regression analysis was conducted to explore the factors that predict the severity of postradiotherapy quality of life (QOL). The odds ratio (OR) was used to describe the efficiency of these predictions. Statistical analysis was performed using R 4.0 and SPSS 22.0 software. A significance level of $P < 0.05$ was considered statistically significant.

Results

Overview of QOL after long-term survival

All 351 patients completed the questionnaires with a median postradiotherapy time of 47.2 months (range, 3.1–115.7 months). Each questionnaire was thoroughly checked, and no missing answers were found. As described in the methodology section, the QOL score was calculated, and a score greater than zero indicated the presence of the corresponding symptom scales. The five most common postradiotherapy symptoms reported by cancer survivors were nose problems (49.7%), dry mouth (44.8%), tooth problems (41.3%), sense problems (32.6%), and reduced sexuality (25.8%). The results are summarized in Table 2.

The symptoms were generally mild, with a median score of 0 and an average score of 5.5 (range 0–18.6). Tooth problems had the highest average score of 18.6, followed by reduced sexuality, with an average score of 17.2; dry mouth, 17.1; sense problems, 11.2; sticky saliva, 8.3; and nose problems, 5.7. The average score for other symptoms was less than 5, as shown in Fig. 1.

To examine the potential correlations between postradiotherapy symptoms, we conducted a correlation analysis, and the results are shown in Fig. 1. As expected, there was a close correlation between "dry mouth" and "sticky saliva." Furthermore, "tooth problems" were often associated with "social eating trouble," and a similar relationship was also found between "social eating" and "social contact," indicating a close connection between these symptoms.

Time-dependent QOL

With respect to the impact of time on QOL, we investigated posttreatment symptom scores according to different time intervals after radiotherapy. Postradiotherapy time was categorized as each posttreatment year. Broken line graphs were plotted to demonstrate the variation in trends of symptom scores with postradiotherapy time (Fig. 2).

There was a significant trend in certain symptoms in which patients tended to report severe symptom-specific QOL in the first or second year after radiotherapy but mild QOL in the other years. For example, "dry mouth" and "sticky saliva," two common late-term symptoms, were reported to be significantly more common in patients 1 year after radiotherapy ($P < 0.001$), and the score remained stable with no statistical significance among patients who had finished radiotherapy for 2 or more years. The same trend was observed for the other symptoms, including "less sexuality," "trouble with social eating," "trouble with social contact," "felt ill," and "sense problems."

In contrast, no time-dependent differences were found in other symptom items (Fig. 2B). Among these symptom scores, "pain," "speech problems," "feeding tube," and "pain-killers" remained zero all the time. Notably, several symptom scales, including "teeth problems," "nose problems," "hearing loss," "impaired vision," and "paradoxic lacrimation," remained relatively high after radiotherapy.

The combined score was computed as the average score of all symptom scales and applied to illustrate the general landscape of the QLQ-H&N35 symptom items (Fig. 2C). It varied with postradiotherapy time, with the highest sum score in patients who were in the first year after radiotherapy. This finding indicates the special role of the first year in QOL improvement and symptom recovery.

Predictive factors of QOL

Logistic regression was performed with patient characteristics as independent variables and the severity of the QLQ-H&N35 symptom scale score as the outcome variable. Symptoms were defined as severe (> median score) or mild (≤ median score) based on their scores. The multivariable regression results for nose problems, dry mouth, tooth problems, sense problems, less sexuality, sticky saliva, and the combined QLQ-H&N35 scores are shown in Table 3 and Fig. 3.

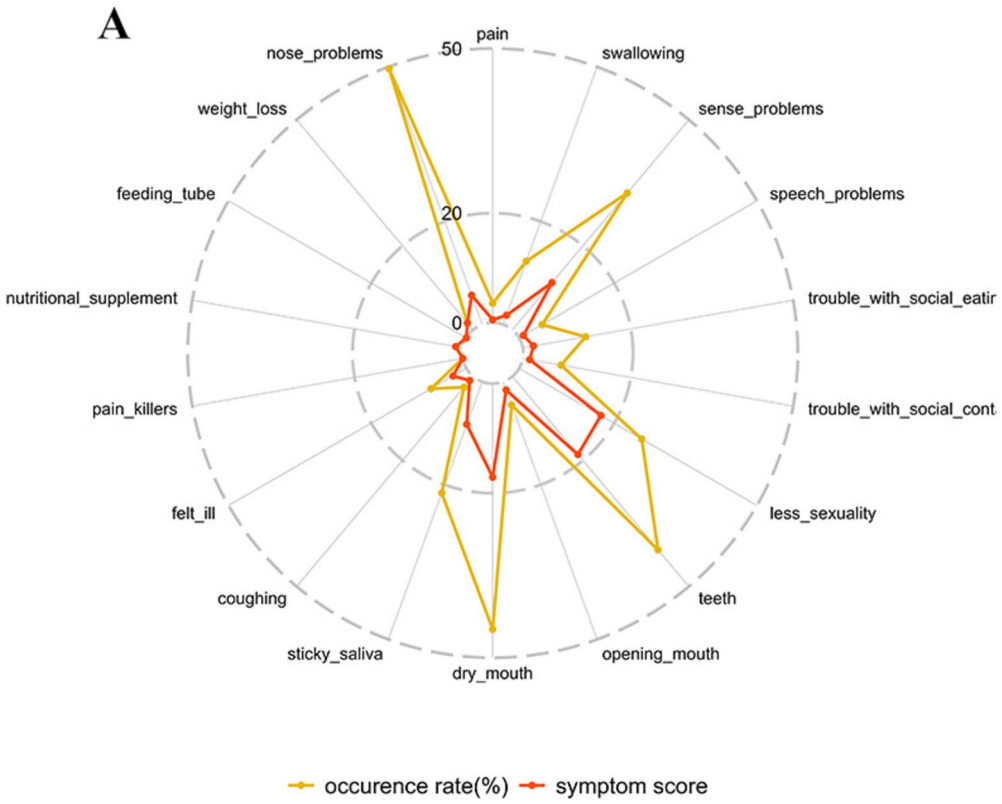
According to the multivariable regression analysis, whole-neck irradiation was a predictive factor for severe dry mouth ($P = 0.016$, OR = 1.267). Age > 60 years was a predictive factor for lower sexual status ($P = 0.001$, OR = 1.285). Postradiotherapy time protected patients from the occurrence of severe dry mouth or sensory problems ($P = 0.001$ and 0.031, OR = 0.957 and 0.972, respectively). In addition, radiation doses of 5460 cGy and 5500 cGy tended to induce severe nasal problems ($P = 0.006$ and 0.055, OR = 1.226 and 1.184, respectively).

With regard to the combined QLQ-H&N35 score, age > 60 years was a predictive factor for severe post-RT QOL ($P = 0.007$, OR = 1.24), whereas the post-RT time interval served as a potential protective factor for the QLQ-H&N35 score ($P = 0.001$, OR = 0.96). No other predictive factors were identified among the patient characteristics.

Discussion

Assessing the QOL of cancer survivors, which involves physiology, psychology, and sociology, is difficult but important [9, 11, 16, 17]. However, few studies have focused on the QOL of ENKTL patients after radiotherapy because of low patient volume, suboptimal treatment results, and less uniform radiotherapy target regimens at most individual institutions. A retrospective study compared the survival and side effects of IMRT with those of 3D-CRT in 94 patients with stage I–II ENKTL and revealed that the common adverse events after radiotherapy included oral mucositis, xerostomia, hyposmia, and hearing loss; in the IMRT group, the incidence of dry mouth reached 30% within the first 2 years [7]. The application of IMRT technology can potentially improve survival and is also expected to facilitate posttreatment rehabilitation owing to advantageous radiation dose coverage [3]. For more than 10 years, we have applied SIB-IMRT with three dose gradients in early-stage ENKTL and achieved satisfactory treatment outcomes with mild posttreatment symptom burden [3, 8, 18]. To our knowledge, this series constitutes the largest report of long-term QOL outcomes in ENKTL survivors.

In the present study, the EORTC QLQ-H&N35 questionnaire with nine additional items was used to assess the postradiotherapy QOL of ENKTL patients based on both symptom incidence and severity. The results revealed that nasal symptoms, including nasal secretions, nasal congestion, nasal dryness, nasal bleeding, and nasal appearance changes, had the highest incidence rate (49.7%) and persisted for years without improvement. This is primarily due to both tumorigenic tissue invasion and destruction and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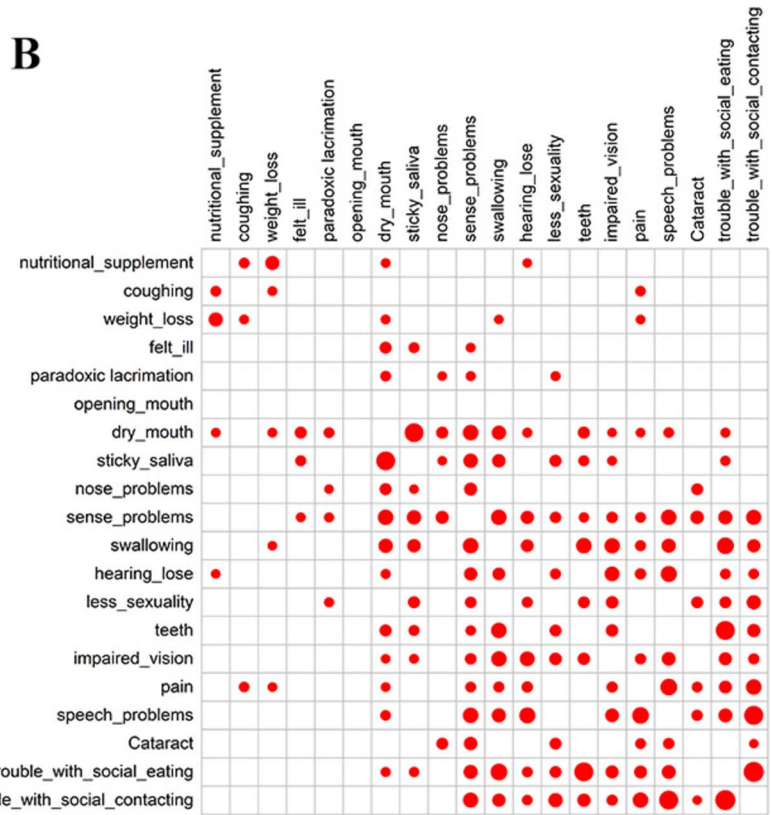
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teeth
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pain
speech_problems
Cataract
trouble_with_social_eating
trouble_with_social_contacting

◂**Fig. 1** Patient-reported EORTC HN35 symptom scores. **A** Radar plot showing various occurrence rates and scores of the QLQ-H&N35 symptom items. **B** Correlation heatmap between symptom scales. The red dots on the heatmap represent significant correlations ($P > 0.05$), whereas the blank dots indicate no significant correlations ($P < 0.05$). The size of the dots corresponds to the coefficients, with larger dots indicating higher coefficients

direct radiation of the nasal cavity, paranasal sinus, and nasopharynx in most cases. Although multivariable analysis suggested that a higher radiation dose is an indicator of severe nasal problems, we acknowledge that selection bias exists because a decreased dose is inevitably reserved for low-risk patients with limited local tumor invasion (LTI). A study conducted in patients with nasopharyngeal carcinoma revealed that the incidence and severity of sinus mucosa diseases, detected via magnetic resonance imaging and endoscopy, were the highest during the third month postradiotherapy and then decreased steadily [19]. Although these sinonasal symptoms may not seem serious, they can directly affect the quality of life and recovery of patients [19, 20]. In contrast to nasopharyngeal cancer, ENKTL often invades the nasal cavity and paranasal sinus, and these structures are subsequently included in the target volume of radiotherapy. Direct irradiation may induce more frequent and severe perinasal symptoms. Therefore, it is important to actively manage symptomatic treatment during radiotherapy and to provide full-scale instructions for rehabilitation during follow-up.

Unexpectedly, tooth disease was found to be significant in both incidence and severity and can persist for years after

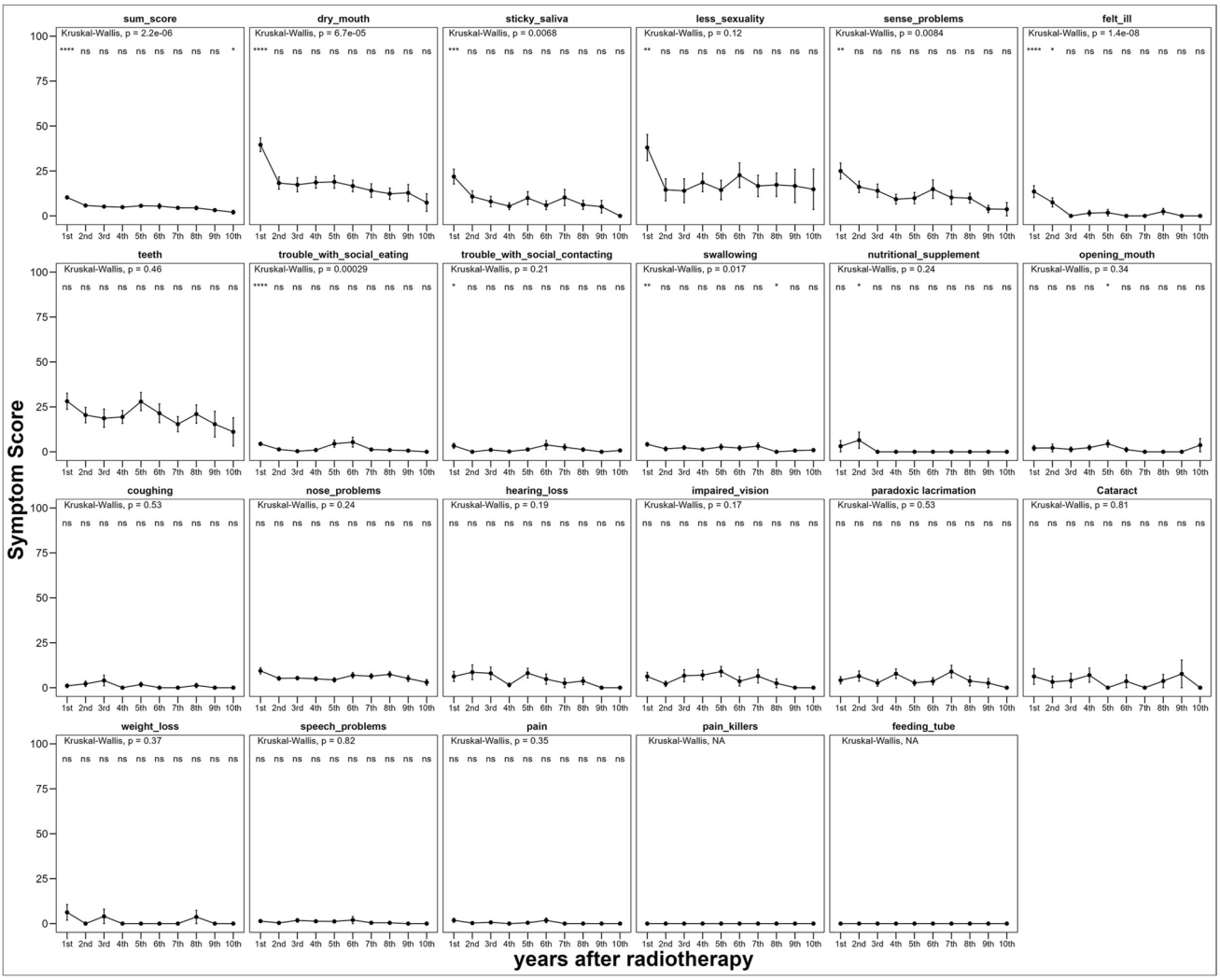

Fig. 2 The broken line graph of QOL symptom scores at different times after radiotherapy. The results showed diverse variation trends. On some symptom scales, such as "dry mouth" and "sum score," patients reported more severe symptom scores in the first or second year than at any other time. In contrast, certain symptom scores remained stable postradiotherapy, especially for "feeding tube" and "pain-killers." The Kruskal−Wallis test was used to screen for intergroup differences, and significant differences are marked with asterisks (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ns $P > 0.05$)

Table 3 Results of multivariable logistics regression of major QOL scales/items

	Nose problems		Dry mouth		Tooth problems		Sense problems		Less sexuality	
	P	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)
Age										
Age > 60	0.219	1.099 [0.937 ~ 1.287]	0.838	1.099 [0.937 ~ 1.287]	0.444	1.065 [0.908 ~ 1.25]	0.085	1.142 [0.982 ~ 1.328]	**0.001**	1.285 [1.115 ~ 1.483]
Primary site										
Waldeyer's ring involved	0.596	0.953 [0.806 ~ 1.126]	0.26	0.909 [0.77 ~ 1.073]	0.636	0.96 [0.811 ~ 1.137]	0.901	1.01 [0.862 ~ 1.184]	0.405	1.066 [0.917 ~ 1.24]
Both involved	0.95	0.991 [0.843 ~ 1.164]	0.922	1.008 [0.859 ~ 1.183]	0.785	0.977 [0.83 ~ 1.15]	0.226	1.1 [0.944 ~ 1.281]	0.656	1.034 [0.894 ~ 1.195]
Stage										
Stage II	0.227	0.911 [0.782 ~ 1.062]	0.201	0.906 [0.779 ~ 1.053]	1	1 [0.857 ~ 1.166]	0.381	0.937 [0.811 ~ 1.083]	0.939	1.005 [0.876 ~ 1.154]
Bike stock during RT										
Yes	0.234	0.906 [0.773 ~ 1.061]	0.709	1.03 [0.881 ~ 1.204]	0.065	1.163 [0.991 ~ 1.363]	0.701	1.029 [0.886 ~ 1.197]	0.656	0.969 [0.839 ~ 1.116]
Pegaspargase-based chemotherapy regimen										
Yes	0.589	0.951 [0.725 ~ 1.247]	0.435	0.899 [0.688 ~ 1.175]	0.627	0.934 [0.711 ~ 1.228]	0.674	1.057 [0.817 ~ 1.366]	0.809	1.03 [0.808 ~ 1.315]
Chemotherapy cycles										
≥ 3	0.608	1.031 [0.84 ~ 1.266]	0.608	1.054 [0.861 ~ 1.292]	0.254	1.129 [0.918 ~ 1.388]	0.657	1.045 [0.86 ~ 1.27]	0.945	1.007 [0.837 ~ 1.21]
Immunotherapy										
Yes	0.789	1.162 [0.942 ~ 1.433]	0.71	1.04 [0.845 ~ 1.28]	0.619	1.055 [0.854 ~ 1.303]	0.117	1.174 [0.961 ~ 1.432]	0.774	1.028 [0.851 ~ 1.241]
Neck radiation										
Whole-neck radiation	0.463	1.11 [0.914 ~ 1.346]	**0.016**	1.267 [1.047 ~ 1.536]	0.887	0.986 [0.811 ~ 1.198]	0.062	1.191 [0.992 ~ 1.432]	0.118	0.87 [0.731 ~ 1.036]
Half neck radiation	0.278	1.252 [1.067 ~ 1.47]	0.086	1.149 [0.981 ~ 1.346]	0.366	1.078 [0.917 ~ 1.266]	0.191	1.107 [0.951 ~ 1.288]	0.987	0.999 [0.865 ~ 1.154]
Radiation dose (cGy)										
5460	**0.006**	1.226 [0.994 ~ 1.514]	0.558	0.94 [0.763 ~ 1.157]	0.312	0.896 [0.725 ~ 1.108]	0.338	1.103 [0.903 ~ 1.347]	0.143	1.153 [0.953 ~ 1.392]
5500	0.055	1.184 [0.946 ~ 1.481]	0.226	0.872 [0.698 ~ 1.088]	0.752	0.965 [0.769 ~ 1.209]	0.487	1.079 [0.872 ~ 1.334]	0.281	1.117 [0.914 ~ 1.368]
Time intervals (years)	0.146	1.001 [0.974 ~ 1.028]	**0.001**	0.957 [0.932 ~ 0.983]	0.122	0.979 [0.952 ~ 1.006]	**0.031**	0.972 [0.947 ~ 0.997]	0.327	0.988 [0.965 ~ 1.012]

Values in bold indicate statistical significance at the $p < 0.05$ level

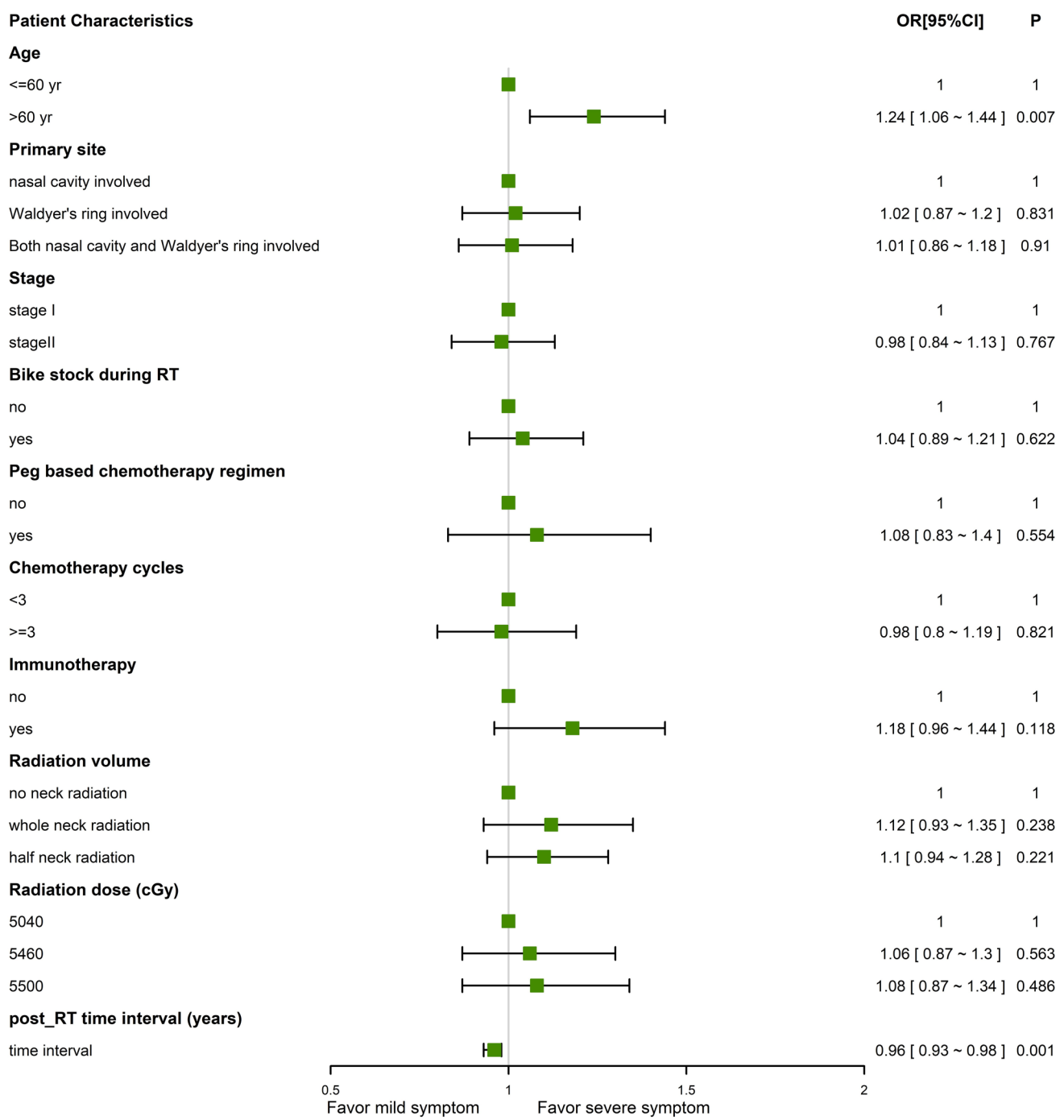

Fig. 3 Forest plot of the multivariable regression of the combined QLQ-H&N35 score. The post-RT time interval and age > 60 years were found to be protective and predictive factors, respectively

radiotherapy. Common symptoms complained of by patients included "soft teeth, inability to bite hard objects, tooth sensitivity, tooth decay, and tooth loss," which can lead to difficulty chewing and eating solid foods. The incidences of xerostomia and sticky saliva were 44.8% and 21.6%, respectively, in this study, which may be attributed to the impairment of the salivary gland induced by irradiation [21–23]. Owing to reduced salivary gland function and damaged gums after radiotherapy, approximately 29 to 37% of patients with head and neck tumors have been reported to develop dental caries after radiotherapy[24]. Considering the lower prescription radiation dose of ENKTL compared to most other head and neck cancers, these salivary gland–related symptoms were unsurprisingly milder and easier to improve over time in our

patients, especially in the first two or 3 years after radiotherapy. Further analyses also demonstrated a significant correlation between dry mouth and dental disease, and the greater the incidence of dry mouth was, the greater the significance of the associated dental disease. However, in contrast to most head and neck cancers, ENKTL in patients with nasal primaries with or without involvement of the palate and maxillary alveolus can induce more radiation to tooth structures. This observation suggests that further efforts are needed to reduce the radiation dose to large salivary glands and tooth structures in ENKTL patients.

Sexuality is a common adverse event after RT. In our cohort, 25.8% of patients reported having hyposexuality. Compared with other time intervals, the symptoms were most significant in the first year, which may be correlated with a strong sense of weakness and sickness in the initial stage of recovery after radiotherapy. Age was identified as another vital factor for predicting hyposexuality. Additionally, due to the Chinese cultural tradition, some elderly patients refused to answer any questions about sex in public. Despite these challenges, the overall impact of this symptom on quality of life is mild, with a low score.

Other common postradiotherapy symptoms with a high incidence of more than 10% include sensory problems, trouble with social eating, and social contact. These symptoms can be significantly alleviated by long-term follow-up and symptomatic treatment.

Multivariable analysis found that radiation dose > 50 Gy and whole-neck irradiation associated with severe dry mouth after radiotherapy. Further adjustments of radiation plan may be made to deduce the occurrence of dry mouth. For patients who had achieved complete response, the prescribed dose may be reduced to 50 Gy. To preserve parotid function from neck irradiation, whole-neck irradiation may be expired for patients with low risk of lymph node recurrence. Of course, such adjustments need to be validated in further clinical practice.

In addition to IMRT, L-asparaginase-based induction chemotherapy and/or immunotherapy were used in advanced patients with high risk. Current study evaluated the impact of systemic therapy on QOL. Neither immunotherapy nor chemotherapy affects QOL, indicating the safety of systemic therapy. However, it should be carefully interpreted, as a selective bias exists that over 90% of patients in the cohort were treated with uniformed asparaginase-based chemotherapy, and only a minority of recent patients were treated immunotherapy.

To our knowledge, this is the first study to systematically report the mid-to-long-term quality of life of patients with early-stage ENKTL after definitive IMRT with uniform target volume delineations. The limitations of this cross-sectional study include the lack of continuous evaluation and information on the variation in quality of life with time in individual patients. Further studies should include dosimetry parameters to explore the correlation between symptoms and the irradiated volume and dose of organs at risk.

In summary, this cross-sectional study showed that the QOL of postradiotherapy patients was mild, and partial symptom-related QOL improved over time. Radiotherapy was correlated with specific symptoms, which necessitated further improvement.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-024-08932-2.

Author contribution Yu-Jing Zhang and Yi-Yang Li contributed to the conception and design of the study. Han-Yu Wang, Ji-Jin Wang, and Yu-Ming Ye searched the literature. Shao-Qing Niu and Yue-Tong Zhang performed the investigation and collected the data. Shao-Qing Niu and Yi-Min Li analyzed the data. Yi-Yang Li prepared the manuscript.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval statement This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center and performed in accordance with principles of the Declaration of Helsinki.

Conflict of interest The authors declare no competing interests.

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