Preliminary study of integrating pretreatment and early follow-up FDG-PET in patients with localized nasal natural killer/T-cell lymphoma receiving concurrent chemoradiotherapy

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Background: The optimal treatment modality for stage I/II extranodal nasal natural killer/T-cell lymphoma (NKTL) including radiotherapy (RT) alone, concurrent, or sequential chemoradiotherapy and radiation doses were not well-defined. We aimed to evaluate early responses to concurrent chemoradiotherapy (CCRT) via image-guided tomotherapy for patients with NKTL and utilize fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) for target delineation and response prediction.

Methods: We retrospectively reviewed stage I/II extranodal nasal NKTL patients who received CCRT as primary treatment. The RT was 56 Gy in 28 fractions to gross disease and 50.4 Gy in 28 fractions to the involved-field using image-guided helical tomotherapy with intensity-modulated radiation therapy-simultaneous integrated boost technique. The chemotherapy consisted of three courses of dexamethasone, etoposide, ifosfamide, and carboplatin. FDG-PET/CT scans were performed before CCRT for RT target delineation and at 1 month following the treatment for response assessment. Early responses to CCRT and treatment-related toxicities were analyzed.

Results: Four male patients who received CCRT were identified. After completion of CCRT, 4 (100%) patients achieved a complete response by CT and FDG-PET metabolic criteria. In FDG-PET metabolic responses between pre-CCRT and post-CCRT, the mean of maximum standardized uptake value (SUVmax) of tumors significantly declined from 18.25±3.77 to 2.38±0.34. The grade 3 toxicities of these four patients were leukopenia (50%) and oral mucositis (25%). At a median follow-up of 29 months (range, 21–33 months), 4 (100%) patients are currently alive in durable complete remission and disease-free status.

Conclusions: Our reports suggest that CCRT with modern image-guided helical tomotherapy provides durable initial complete responses and tolerable side effects for patients with localized nasal NKTL. Integrated FDG-PET-guided RT is feasible for target delineation and response assessment.

Keywords: Natural killer/T-cell lymphoma (NKTL); concurrent chemoradiotherapy (CCRT); intensity-modulated radiotherapy; simultaneous integrated boost (SIB); fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET)

Introduction

Natural killer/T-cell lymphoma (NKTL) accounts for less than 1% of lymphomas in Europe and North America, but it occurs more frequently with 6% to 15% of lymphomas in East Asia and Latin America (1-4). In Taiwan, NKTL constitutes 10.5% to 12.2% of lymphomas, and there are 350 to 380 new NKTL cases per year (5). Nasal cavity is the most common site of the extranodal NKTL, and 70% to 90% of patients with nasal NKTL present with early-stage localized disease (4,6,7).

Based on the retrospective studies before 2000s, radiotherapy alone with doses >50 Gy via conventional 2-domensional (2D) technique was the mainstay treatment for stage IE/IIE localized nasal NKTL. In the era of 3-dimensional conformal radiotherapy (3DCRT) in 2000s, combined modalities with concurrent or sequential chemoradiotherapy for localized nasal NKTL provided promising results with 80% to 90% complete response (CR) rate and 70% to 80% 3-year overall survival rate in the prospective phase I/II trials in Japan, Korea, and China (3,8-10). Because of the rarity of nasal NKTL and relative small patient numbers of these non-randomized trials, the optimal treatment strategy of the disease is still controversial (2).

Fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) scan serves as a useful tool for cancer staging, radiotherapy target volume delineation, and treatment response assessment. FDG-PET-based radiotherapy planning has been widely applied in the treatment for lung cancers, head and neck cancers. However, it is not well-defined in nasal NKTL (11,12).

Here we aimed to evaluate early responses to concurrent chemoradiotherapy (CCRT) for patients with localized nasal NKTL and integrate pretreatment and posttreatment FDG-PET/CT scans for target delineation and response assessment.

Methods

Patients and evaluations

We retrospectively reviewed patients who were histologically-diagnosed and clinically staged I/II extranodal nasal NKTL in Far Eastern Memorial Hospital from January 2014 to December 2015, with the approval of the Institutional Review Board (IRB approval no: FEMH-IRB-104171-E). Patients receiving CCRT as the primary treatment were included. Patients who had previous cancer history or second primary malignancy were excluded. Pretreatment evaluations including a complete history review, physical examination, complete blood counts, biochemistry tests, liver function tests, blood tumor markers, plasma Epstein-Barr virus (EBV) DNA loads, nasopharyngoscopy with biopsies, bone marrow aspiration, esophagoscopy, abdominal ultrasonography, and contrast-enhanced CT scans were recorded. FDG-PET/CT scans were performed before the treatment and at 1 month following CCRT. The disease was staged according to the Ann Arbor staging system. Part of the study data were based on Cancer Registry database of our hospital.

FDG-PET/CT scans

FDG was injected in the PET Center of Far Eastern Memorial Hospital. All patients fasted for at least 4 hours before FDG injection. The blood glucose levels were less than 140 mg/dL. The injected dose was adjusted according to the body weight (5 MBq/kg, 0.135 mCi/kg). A 30-minute whole-body PET scan from skull to thigh was performed on a PET/CT scanner (Discovery VCT, GE Medical Systems, Milwaukee, WI). The emission data were acquired in 3D mode, and axial field of view. The resolutions of the scanner were 15.7 cm and 4.8 mm full width at half maximum, respectively.

A low-dose whole-body CT was performed for attenuation correction of the emission data and anatomic correlation. No intravenous (IV) or oral contrast agents were given in the series. Both PET and CT scans were performed for patients under normal tidal breathing. From the raw emission data collected, the images were reconstructed by iterative reconstruction with CT-derived attenuation correction using the ordered subsets expectation maximization algorithm.

Quantitative data analyses were derived from SUV, which were normalized to body weight and calculated using data

from the attenuation-corrected images by the automatic software. The SUVmax of the lesions were then calculated and analyzed.

Radiotherapy

All patients received external beam radiotherapy with 6 MV photons via image-guided helical tomotherapy (Tomotherapy Inc., Madison, WI) at our department of radiation oncology.

To integrate FDG-PET metabolic information in the radiotherapy planning system, FDG-PET/CT simulation were performed simultaneously in the same PET/CT scanning room, with thermoplastic mask-based immobilization for the patients.

The radiotherapy dose was 56 Gy in 28 fractions to gross disease and 50.4 Gy in 28 fractions to the involved field using intensity-modulated radiation therapy-simultaneous integrated boost (IMRT-SIB) technique (2.0 Gy and 1.8 Gy per day; 5 consecutive days per week). The involved field of nasal NKTL was defined as nasal cavity, nasopharynx, adjacent paranasal sinuses for primary tumors, and involved neck nodal region(s) for stage II disease.

In the process of target volume delineation, radiation oncologists contoured the gross and clinical-biological target volumes according to the integrated fusion images of FDG-PET and simulation CT in the radiotherapy treatment planning system. The gross target volume of 56 Gy (GTV_56) was visible gross tumor contoured on simulation CT slices. The clinical target volume of 56 Gy (CTV_56) consisted of GTV_56 plus FDG-avid volumes. The clinical target volume of 50.4 Gy (CTV_50.4) consisted of the involved field, blurred FDG area and CTV_56 with a 3 to 5 mm expansion. To manage interfraction motions and setup uncertainties, the planning target volumes of 56 Gy and 50.4 Gy (PTV_56 and PTV_50.4) were designed from the CTV_56 plus a 3-mm expansion and CTV_50.4 plus a 5-mm expansion, respectively.

If setup-errors of the patient more than PTV margins were found on the helical megavoltage CT images of tomotherapy, an adaptive re-planning would be required to improve the accuracy of radiation dose distribution to the targeted areas.

All radiotherapy plans in this study were optimized with at least 95% of the PTV covered by the prescribed doses and with the maximum dose less than 110% of the prescribed dose. The dose constraints for organs at risk were as follows: (I) brainstem: a maximum dose of less than 54 Gy; (II) spinal cord: a maximum dose of less than 45 Gy; (III) optic chiasm and optic nerves: a maximum dose of less than 45 Gy; (IV) lens: a maximum dose of less than 10 Gy; (V) bilateral parotid glands: a mean dose of less than 30 Gy, and a median dose less than 26 Gy in each gland; (VI) inner ears: a mean dose less than 45 Gy; (VII) eye orbits: a maximum dose of 45 Gy and a mean dose less than 35 Gy.

Chemotherapy

The concurrent chemotherapy was delivered to patients for 3 cycles during radiotherapy, with repeated every 3 weeks. Chemotherapy regimen consisted of dexamethasone (40 mg/day intravenously on day 1 to 3), etoposide (67 mg/m^2 intravenously on day 1 to 3), ifosfamide (1.0 g/m^2 intravenously on day 1 to 3), and carboplatin (200 mg/m^2 intravenously on day 1).

Follow-up

All patients were evaluated every week during the courses of CCRT. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Patients received regular follow-ups by our multimodality treatment team every 3 months. Post-treatment CT or magnetic resonance imaging (MRI) of head and neck were done at 1, 3, and 6 months following completion of the 3rd cycle of CCRT. Follow-up visits included history review, physical examination, serum biochemistry, and other tests as clinically indicated. For the suspicious lesion on FDG-PET, CT or MRI images, nasopharyngoscopy with biopsies was performed to rule out any residual tumor or recurrence. Responses to CCRT and treatment-related toxicities were analyzed.

Results

Patient characteristics

Four male patients were identified in this retrospective study. Characteristics of patients and results of CCRT were summarized in *Table 1*. The median age at diagnosis of patients was 61 years old (range, 42–63 years old). Of the four patients, 2 (50%) had stage IE and 2 (50%) had stage IIE disease with multiple neck nodes. The *in situ* hybridization for EBV-encoded RNA (ISH-EBER) status was detected in four patients. The initial plasma EBV DNA loads were detectable in 2 (50%) patients, and

Table 1 Patient characteristics

Characteristics	Patient #1	Patient #2	Patient #3	Patient #4
Age (years)	63	62	60	42
Gender	Male	Male	Male	Male
Tumor involvement	Nasal cavity oropharynx	Nasal cavity oropharynx	Nasal cavity nasopharynx	Nasal cavity nasopharynx
Initial neck node(s)	Multiple	Multiple	Absent	Absent
B symptoms	Present	Absent	Absent	Absent
Elevation of serum LDH	Present	Absent	Absent	Absent
Performance status score	0	1	0	0
Immunohistochemical features	CD3+, CD30+, CD20–, CD56	CD3–, CD20–, CD56+	CD3+, CD5+, CD56+	CD3–, CD20–, CD56+
ISH-EBER status	EBER (+)	EBER (+)	EBER (+)	EBER (+)
Pre-CCRT plasma EBV DNA load	Detectable	Detectable	Undetectable	Undetectable
Post-CCRT plasma EBV DNA load	Undetectable	Undetectable	Undetectable	Undetectable

LDH, lactic dehydrogenase; NKTL, natural killer/T cell lymphoma; ISH-EBER, in situ hybridization for EBV-encoded small RNA; CCRT, concurrent chemoradiotherapy; EBER, EBV-encoded RNA; EBV, Epstein-Barr virus.

both of their EBV DNA loads became undetectable after treatment.

From the reports of the radiation treatment planning system, the mean tumor volume of these patients was 25.4 cm^3. The mean doses of GTV_56, CTV_56, and CTV_50.4 were 58.09 Gy, 58.12 Gy, and 55.30 Gy. Radiation doses to organs at risk were within acceptable tolerances. The mean doses surrounding organs were as follows: right parotid glands, 18.63 Gy; left parotid glands, 18.52 Gy; larynx 18.45 Gy; pharynx 31.02 Gy. The detailed quantitative dose indices for tumors and organs at risk of the patients were listed in *Table 2*. The representative target volume delineation and radiation dose distribution were shown in *Figure 1*.

All patients tolerated well to the IMRT-SIB (56 and 50.4 Gy) via image-guided tomotherapy and three cycles of chemotherapy without interruption during the courses of CCRT. The mean duration of radiation therapy was 39.5±2.6 days (range, 38.0–43.0 days).

Treatment responses and toxicities

At 1 month following completion of CCRT (completion of the 3rd cycle of chemotherapy), all 4 (100%) patients achieved CR by CT, MRI images and FDG-PET metabolic criteria. The treatment responses to CCRT by utilizing FDG-PET/CT were listed in *Table 3*.

In the FDG-PET metabolic responses between pre-CCRT and post-CCRT on these patients, the mean of SUVmax of the primary tumors significantly declined from 18.25±3.77 (range, 13.10–21.80) to 2.38±0.34 (range, 1.90–2.70).

Representative images of metabolic CR of nasal tumors and nodes on FDG-PET/CT scans were shown in *Figure 2A-D*.

The common toxicities of these four patients were leukopenia (grade 2, n=1; grade 3, n=2) and oral mucositis (grade 2, n=3; grade 3, n=1). There were no grade 4 toxicities or treatment-related deaths during CCRT. Treatment-related toxicities of CCRT were acceptable and listed in *Table 4*.

At a median follow-up of 29 months (range, 21–33 months), four (100%) patients are currently alive in durable complete remission and disease-free status.

Discussion

The optimal treatment modality for stage IE/IIE nasal NKTL such as radiotherapy alone, concurrent, or sequential chemoradiotherapy and radiation doses were not well-defined (2). In previous studies employing radiotherapy alone for localized nasal NKTL patients, the radiation dose

Table 2 Quantitative dose indices in the radiation treatment planning

Indices	Patient #1	Patient #2	Patient #3	Patient #4
GTV_56 (cm^3)	27.85	25.69	36.05	12.04
Mean dose of GTV_56 (Gy)	58.18	57.18	58.80	58.19
CTV_56 (cm^3)	61.19	48.15	82.22	30.87
Mean dose of CTV_56 (Gy)	58.21	57.18	58.80	58.30
CTV_50.4 (cm^3)	234.60	337.09	290.35	274.53
Mean dose of CTV_50.4 (Gy)	54.98	55.03	56.24	54.95
Brainstem, maximum dose (Gy)	25.37	31.03	36.82	33.87
Spinal cord, maximum dose (Gy)	16.86	29.22	20.27	28.35
Optic chiasma, maximum dose (Gy)	25.97	20.15	20.69	13.67
Right optic nerve, maximum dose (Gy)	32.23	33.13	43.29	18.46
Left optic nerve, maximum dose (Gy)	32.85	36.73	40.05	23.81
Right lens, maximum dose (Gy)	3.14	5.77	7.44	4.03
Left lens, maximum dose (Gy)	2.90	5.03	7.05	4.35
Right eyeball, mean dose (Gy)	5.81	11.17	13.38	7.45
Left eyeball, mean dose (Gy)	5.61	12.80	10.40	7.79
Right parotid gland, mean dose (Gy)	18.10	18.76	18.63	19.03
Left parotid gland, mean dose (Gy)	20.08	17.80	17.25	18.94
Larynx, mean dose (Gy)	16.18	24.17	14.60	18.85
Pharynx, mean dose (Gy)	32.79	33.61	25.02	32.64

GTV_56, gross target volume of 56 Gy; CTV_56, clinical target volume of 56 Gy; CTV_50.4, clinical target volume of 50.4 Gy.
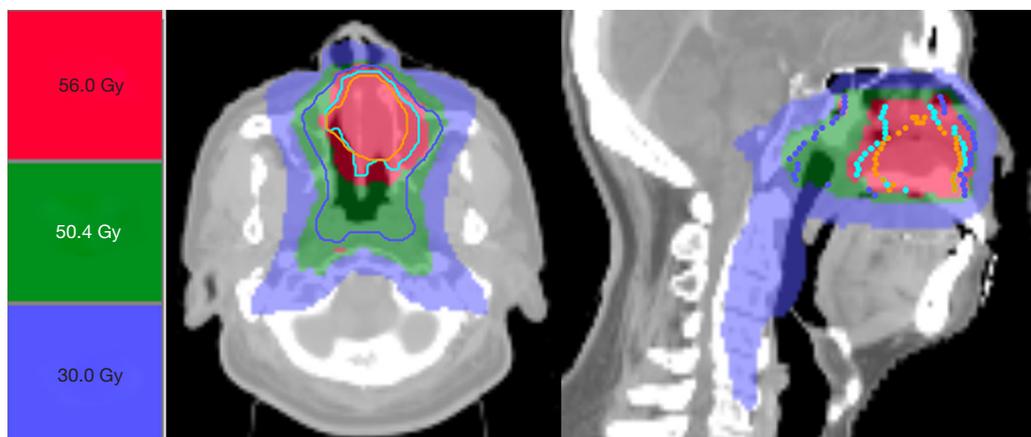
Figure 1 The radiation dose distribution of patient #2 on the radiotherapy treatment planning. The clinical target volume of 56 Gy (CTV_56, cyan line) was delineated according to the gross tumor volume and the FDG-avid volumes. The clinical target volume of 50.4 Gy (CTV_50.4, blue line) consisted of the involved field and blurred FDG area. FDG, fluorine-18-fluorodeoxyglucose.

Table 3 Evaluations of treatment responses to CCRT by utilizing PDG-PET/CT

Responses	Patient #1	Patient #2	Patient #3	Patient #4
Metabolic response of nasal tumor				
Pre-CCRT SUVmax	18.0	21.8	13.1	20.1
Post-CCRT SUVmax	2.7	2.4	2.5	1.9
Metabolic response of neck node				
Pre-CCRT SUVmax	5.0	19.3	N/A	N/A
Post-CCRT SUVmax	2.3	2.2	N/A	N/A
Response to CCRT	CR	CR	CR	CR

CCRT, concurrent chemoradiotherapy; PDG-PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; SUVmax, maximum standardized uptake value; N/A, not applicable; CR, complete response.
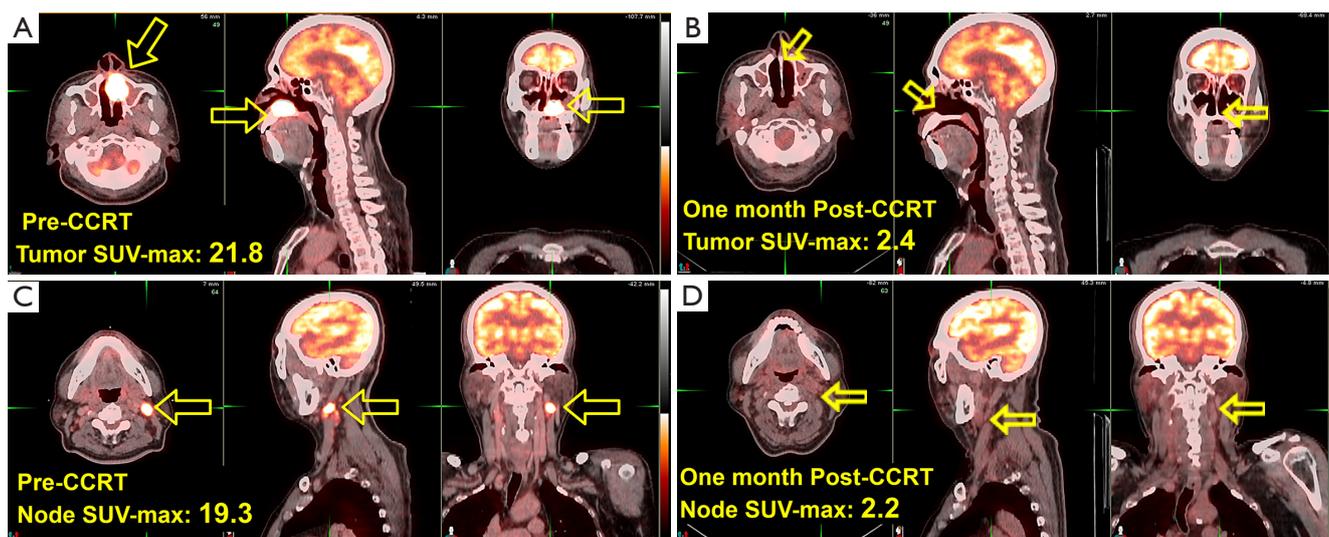
Figure 2 Metabolic responses of the tumor and node between pre-CCRT and post-CCRT FDG-PET/CT scans. Patient #2, a 62-year-old gentleman of stage IIE nasal natural killer/T-cell lymphoma with one involved neck lymph node, received CCRT via IMRT-SIB helical tomotherapy. This patient achieved a complete response at 1 month following completion of CCRT. The SUVmax of the nasal tumor (A,B) (arrows) and neck node (C,D) (arrows) between pre-CCRT and post-CCRT significantly declined from 21.8 to 2.4 and 19.3 to 2.2. CCRT, concurrent chemoradiotherapy; FDG-PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography with computed tomography; IMRT-SIB, intensity-modulated radiation therapy-simultaneous integrated boost; SUVmax, maximum standardized uptake value.

of 50 Gy or more (range, 50–70 Gy) might be required to improve in-field control and response rates. The initial CR rate and 5-year overall survival rate of radiotherapy alone were 60% and 30%, respectively. However, the incidences of local-regional and systemic failure were as high as 25% to 40% in the strategy of radiotherapy alone (2,7).

Based on phase I and II trials investigating combined modalities, including CCRT in Japan or sequential chemoradiotherapy in China and Korea, the radiation doses ranged from 40 to 60 Gy were delivered by 2D or 3DCRT techniques. Combined modalities achieved satisfactory CR rates and survivals with acceptable toxicities (3,8-10).

Radiotherapy techniques have greatly advanced since previous studies of treatment for nasal NKTL after 2000s (1,7-10,13,14). IMRT or volumetric modulated arc therapy (VMAT) make it possible to deliver a higher

Table 4 Treatment-related toxicities of CCRT

Toxicities	Patient #1 (grade)	Patient #2 (grade)	Patient #3 (grade)	Patient #4 (grade)
Leukopenia	3	3	2	0
Anemia	1	0	0	0
Thrombocytopenia	2	0	0	0
Mucositis	2	2	3	2
Dermatitis	0	1	0	2
Weight loss	0	1	1	2
Nausea	0	0	1	1

Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0. CCRT, concurrent chemoradiotherapy.

radiation dose to the tumor while sparing unnecessary doses to the surrounding normal tissues (15-17). Helical tomotherapy (Tomotherapy Inc., Madison, WI) is an image-guided IMRT equipment which can further deliver highly-conformal radiation doses to the tumor precisely and minimize doses to critical organs for head and neck malignancies (18,19).

Our novel approach utilized image-guided radiotherapy with integration of FDG-PET-guidance in the radiation treatment planning and initial response assessment for patients with localized nasal NKTL. In our study, we utilized a modern IMRT-SIB technique in the setting of CCRT, with 56 Gy to gross disease and 50.4 Gy to the involved filed simultaneously. Furthermore, IMRT-SIB technique via image-guided tomotherapy provided adequate radiation dose coverage to tumors and minimized dose to normal organs. Our preliminary results of a 100% CR rate were comparable to the studies employing combined modalities. Meanwhile, the most common grade 3 toxicities such as leukopenia (50%) and mucositis (25%) in our study were also acceptable as compared to previous reports of combined chemoradiotherapy (1,3,8,10).

PET-guided delineation and dose escalation of target volumes are still not well-defined in nasal NKTL (11,12). In a previous meta-analysis of eight studies, the pooled sensitivity and specificity in the diagnosis of 135 NKTL patients were 0.95 (95% CI: 0.89–0.98) and 0.40 (95% CI: 0.09–0.78), respectively (20). Another retrospective study focused on prognostic value of the interim (n=62) and post-therapy (n=47) FDG-PET/CT in patients with NKTL, the concordance between clinical CR on CT or MRI and interim PET negativity was 89.5%; the positive predictive value (PPV), negative predictive value (NPV), and accuracy of interim PET in predicting progression-free survival (PFS) were 77.8%, 76.5%, and 77.4%. Of the post-therapy FDG-PET/CT, the concordance between clinical CR and post-therapy PET negativity was 93.5%; the PPV, NPV, and accuracy in predicting PFS were 88.9%, 58.6% and 70.2% (21). In our study, the pretreatment and early follow-up FDG-PET/CT scans served as a useful tool for NKTL staging, radiotherapy target volume delineation, and treatment response assessment. Furthermore, the integration of FDG-PET and simulation CT images in our radiotherapy treatment planning offered biological and metabolic information for delineation of FDG-avid tumor volumes. Based on the PET-guided radiotherapy treatment planning, radiation oncologists could precisely delineate the target volume of tumors and nodes. Also, the concordance of post-treatment FDG-PET, MRI and CT scans provided helpful information for assessing treatment responses. With modern radiotherapy techniques including FDG-PET-guided delineation, IMRT-SIB planning and image-guided helical tomotherapy, we could accurately deliver conformal radiation doses to the target while sparing surrounding normal organs including brain, spinal cord, nerve, parotid glands, oral mucosa and skin (15-19,22).

Although our results revealed durable initial responses and acceptable toxicities, there were some limitations including relative small numbers of patients and retrospective non-randomized nature because of the rarity of the disease. Further clinical trials and long-term survival follow-ups are required to confirm the validity and reliability of these modern tools.

Conclusions

Our results suggest that CCRT with modern image-guided helical tomotherapy provides a durable initial CR and tolerable side effects for patients with localized nasal NKTL. Integrated FDG-PET-guided radiotherapy is feasible for target delineation and response assessment. Our novel approach is worthy of further investigation, and long-term survival follow-ups are warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This work was approved by the Institutional Review Board of Far Eastern Memorial Hospital (IRB approval No. FEMH-IRB-104171-E). Informed consent was waived due to the retrospective nature of the study.

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