research

The ratio of weight loss to planning target volume significantly impacts setup errors in nasopharyngeal cancer patients undergoing helical tomotherapy with daily megavoltage computed tomography

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Background. Changes in head and neck anatomy during radiation therapy (RT) produce setup uncertainties of nasopharyngeal cancer (NPC) irradiation. We retrospectively analyzed image guidance data to identify clinical predictors of setup errors.

Patients and methods. The data of 217 NPC patients undergoing definitive RT on a helical tomotherapy (HT) unit were analyzed. Factors including tumor stage, body mass index, weight loss, and planning target volume (PTV) were assessed as predictors of daily megavoltage computed tomography (MVCT) setup displacements, which were automatically registered using software.

Results. Mean daily setup displacements (in mm) were 1.2 ± 0.6, 1.8 ± 0.8, 3.4 ± 1.4 in the medial-lateral (ML), superior-inferior (SI), and anterior-posterior (AP) directions, respectively. Mean weight loss was 4.6 ± 3.3 kg (6.8 ± 4.9%). Patients with weight loss > 5% had significantly larger setup displacements in the AP (3.6 ± 1.5 *vs.* 2.9 ± 1.1 mm, $p < 0.001$) and SI (1.6 ± 0.7 *vs.* 1.9 ± 0.9 mm, $p = 0.01$) direction, but not in the ML direction ($p = 0.279$). The AP setup error increased 0.06 mm ($y = 0.055x + 2.927$, x: percentage of weight loss/PTV, y: AP displacement) per one percent increase in weight loss normalized to PTV.

Conclusions. Patients with weight loss > 5% and smaller PTVs, possibly because of small body frame or neck girth, were more likely to have increased setup errors in the AP direction.

Key words: nasopharyngeal cancer; intensity-modulated radiotherapy; setup errors

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant neoplasm of mucosal origin.[1] It has unique racial and geographic distribution with higher incidence in Southeast Asia, North Africa, and the Middle East.[2] Since the nasopharynx is located posterior to the nasal cavity and surrounded by critical structures, radical surgical resection of NPC is very challenging.[1] Radiation therapy (RT) is the mainstay of treatment for NPC due to its radiosensitivity.[3,4] Compared to three-dimensional conformal

TABLE 1. Patient characteristics (n = 217)

Variable	Number (%)	
Age		
Median	46	
Range	17–76	
Sex		
Male	160	(73.7)
Female	57	(26.3)
T stage		
1	97	(44.7)
2	32	(14.7)
3	50	(23.0)
4	38	(17.5)
N stage		
0	51	(23.5)
1	67	(30.9)
2	67	(30.9)
3a	18	(8.3)
3b	15	(6.9)
AJCC stage		
I	29	(13.4)
II	47	(21.7)
III	76	(35.0)
IVA	32	(14.7)
IVB	33	(15.2)
Chemotherapy		
No	27	(12.4)
Yes	190	(87.6)
Fraction		
33 (2.12 Gy/fraction)	182	(83.9)
35 (2 Gy/fraction)	35	(16.1)

AJCC = American Joint Committee on Cancer

radiation therapy, intensity-modulated radiation therapy (IMRT) yields superior parotid gland sparing and reduces xerostomia.[5-7]

IMRT delivers a conformal and steep dose gradient. Precise target localization is critical for IMRT delivery. During the course of RT to NPC, the primary tumor and surrounding anatomy commonly undergo significant volume changes secondary to tumor shrinkage and weight loss.[8,9] Changes in head and neck anatomy during treatment can potentially compromise the accuracy of radiation delivery.[8] The aim of image-guided radiation (*i.e.*, image-guided radiotherapy; IGRT) is to detect and correct the set-up errors prior to treatment of head and neck cancers, including NPC.[10-13]

No set-up error study with large patient numbers has identified factors affecting set-up errors in radiation delivery to patients with NPC. Among IGRT modalities, helical tomotherapy with daily megavoltage computed tomography (MVCT) is the one most frequently used to evaluate and correct daily online interfraction setup errors.[11,14] Using daily MVCT setup data, our aim was to determine which clinical and treatment factors (including tumor stage, body mass index [BMI], weight loss, and planning target volume [PTV]) predict setup errors in NPC patients treated with IMRT by tomotherapy.

Patients and methods

Patients

We retrospectively reviewed the clinical and RT data of 217 NPC patients (160 males and 57 females; median age 46 years [range 17–76]) who underwent definitive RT by helical tomotherapy between September 2008 and May 2013 at the National Taiwan University Hospital. Patients who received RT as salvage or with palliative intent were excluded. A total of 29 (13.4%), 47 (21.7%), 76 (35%), and 65 (29.9%) patients had American Joint of Cancer Committee (AJCC 7th edition) stage I, II, III, and IV, respectively (Table 1). Concurrent cisplatin and/or tegafur-uracil (UFUR) was used in 190 (87.6%) patients at the discretion of medical oncologists.

This study followed the Helsinki Declaration and complied with the ethical standard guidelines. No patient identifying information was used or reported. Our institutional review board approved this retrospective study with the approval number 201605075RINC on 6/16/16.

Treatment planning

All patients underwent CT simulation with thermoplastic mask immobilization. CT scan images of 3-mm slices were obtained with and without intravenous contrast medium. IMRT doses were delivered to three target volumes defined for each patient in 33 to 35 treatment fractions. The primary tumor and involved lymph nodes with safety margin were treated to 70 Gy fractionated into 2–2.12 Gy daily doses. The clinical target volume (CTV) of areas at risk for microscopic involvement (nasopharynx, retropharyngeal nodal regions, skull

base, clivus, pterygoid fossae, parapharyngeal space, sphenoid sinus, nasal cavity, maxillary sinuses, and levels I through V cervical nodes) were treated with 59.4–64 Gy. Clinically negative parts of the lower neck were treated with 54 Gy. A margin of 3 mm was used for the PTV. Margins were reduced if the CTV was near critical structures including the brain stem and eyes. The prescribed dose covered 95% of the PTV. Doses to the organs at risk including brainstem, spinal cord, eyes, optic nerves, pituitary gland, parotid glands, submandibular glands, thyroid glands, cochlea, brachial plexus, and oral cavity were minimized without compromising PTV coverage.

Daily MVCT and setup error

Prior to each treatment, MVCT images were acquired after positioning the patient using wall lasers and external markings, and were reconstructed with "Normal" (4 mm) slice thickness. Setup displacements were determined with autoregistration software using the "Bone and Soft tissue" option. Setup errors of the target in the medial-lateral (ML), superior-inferior (SI), anterior-posterior (AP) directions as well as rotational errors were obtained. If a rotational displacement was larger than 3 degrees, the therapists would re-position the patient and repeat MVCT. Translational errors were corrected by automatic couch positioning.

Data analyses

Clinical and treatment factors including T and N stages, BMI, weight loss percentage, and PTV were used for data analyses. We performed the Student *t*-test and linear regression to correlate these factors with setup errors. Statistical analyses were done using the software SPSS Version 22. P values less than 0.05 were considered statistically significant.

Results

The patient cohort had an average weight (±standard deviation) before RT of 67.9 ± 13.1 kg (range: 40.0–128.8), average BMI before RT of 24.4 ± 3.5 kg/m^2 (range: 16.4–40.3), mean weight loss following 6 to 7 weeks of RT of 4.6 ± 3.3 kg (range: –3.8 to +14.5), which represented 6.8 ± 4.9% (range: –8.3 to +18.0) of weight before RT, and mean PTV of 848.0 ± 210.2 cc (range: 415.7–1584.3). A total of 7231 MVCT images were evaluated for setup errors, with a median number of 33 (range: 33–35) MVCT images per patient.

Mean daily setup displacements (in mm) were 1.2 ± 0.6, 1.8 ± 0.8, and 3.4 ± 1.4 in the ML, SI, and AP directions, respectively (Table 2). The displacement was significantly larger in the AP direction than in the ML ($p < 0.001$) and SI ($p < 0.001$) directions. The displacement was also significantly

TABLE 2. Setup error by clinical factors

	ML error	SI error	AP error
Overall	1.2 ± 0.6	1.8 ± 0.8	3.4 ± 1.4
T stage			
1,2 (n = 129)	1.2 ± 0.6	1.8 ± 0.9	3.3 ± 1.5
3,4 (n = 88)	1.1 ± 0.5	1.7 ± 0.8	3.5 ± 1.3
p value	0.241	0.814	0.414
N stage			
0, 1 (n = 117)	1.1 ± 0.6	1.7 ± 0.8	3.4 ± 1.3
2, 3a, 3b (n = 100)	1.2 ± 0.6	1.9 ± 0.9	3.4 ± 1.5
p value	0.133	0.239	0.890
BMI			
< 25 (n = 138)	1.2 ± 0.6	1.7 ± 0.8	3.2 ± 1.3
≥ 25 (n = 79)	1.2 ± 0.5	1.9 ± 0.9	3.6 ± 1.5
p value	0.845	0.177	0.053
PTV			
< 850 cc (n = 113)	1.2 ± 0.7	1.9 ± 0.9	3.6 ± 1.5
≥ 850 cc (n = 104)	1.2 ± 0.5	1.6 ± 0.7	3.2 ± 1.3
p value	0.292	0.021	0.03
Weight loss			
≤ 5% (n = 84)	1.1 ± 0.4	1.6 ± 0.7	2.9 ± 1.1
> 5% (n = 133)	1.2 ± 0.6	1.9 ± 0.9	3.6 ± 1.5
p value	0.279	0.010	<0.001

AP = anterior-posterior; BMI = body mass index; ML = medial-lateral; PTV = planning target volume; SI = superior-inferior.

TABLE 3. Setup errors by the specified threshold

	ML error (%)	SI error (%)	AP error (%)
< 1.0 mm	3549 (49.1)	2471 (34.2)	525 (7.3)
1.0~1.9 mm	2315 (32.0)	2076 (28.7)	939 (13.0)
2.0~2.9 mm	925 (12.8)	1390 (19.2)	1492 (20.6)
3.0~3.9 mm	314 (4.3)	729 (10.1)	1800 (24.9)
4.0~4.9 mm	85 (1.2)	330 (4.6)	1310 (18.1)
≥ 5.0 mm	45 (0.6)	237 (3.3)	1167 (16.1)

AP = anterior-posterior; ML = medial-lateral; SI = superior-inferior

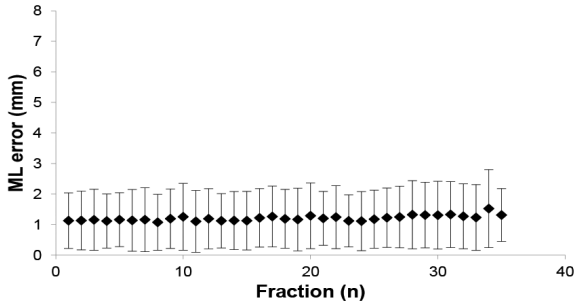

FIGURE 1. Setup error of the medial-lateral (ML) direction at each treatment fraction.

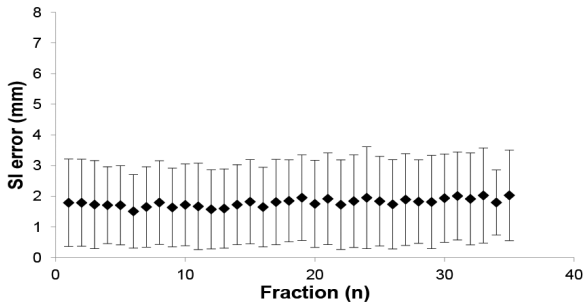

FIGURE 2. Setup error of the superior-inferior (SI) direction at each treatment fraction.

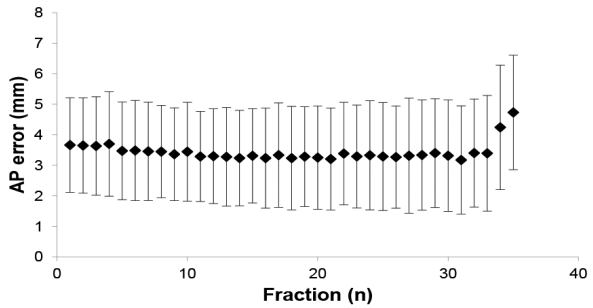

FIGURE 3. Setup error of the anterior-posterior (AP) direction at each treatment fraction.

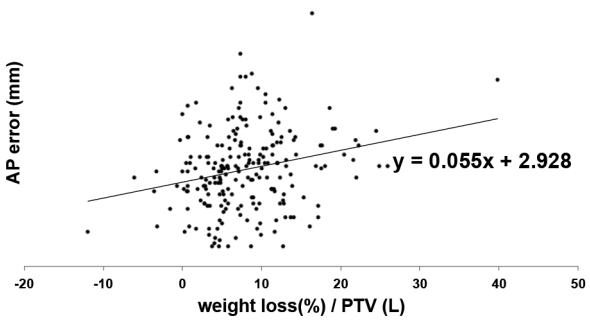

FIGURE 4. Linear regression graph of anterior-posterior (AP) setup error and weight loss normalized by planning target volume (PTV) ($R^2 = 0.059$, $p < 0.001$).

larger in SI direction than in the ML direction ($p < 0.001$). Setup errors greater than 3 mm occurred for 6.1%, 18.0%, and 59.1% of treatment fractions in the ML, SI, and AP directions, respectively (Table 3). There was a trend of increased setup errors toward the end of treatment course, especially in the AP direction (Figures 1–3).

Next, we determined whether T stage, N stage, BMI, PTV, or weight loss were factors affecting setup errors using the Student *t*-test. Setup displacements in all directions were not significantly different between patients with different T stage (1–2 *vs.* 3–4) and N stage (0–1 *vs.* 2–3). There was a strong trend indicating that patients with larger BMI (≥ 25) before RT had an increased setup displacement in the AP direction (3.6 ± 1.5 mm *vs.* 3.2 ± 1.3 mm, $p = 0.053$) during treatment. Smaller PTV (< 850 cc) was associated with larger setup displacement in the ML direction (1.9 ± 0.9 *vs.* 1.6 ± 0.7 $p = 0.021$) and AP direction (3.6 ± 1.5 mm *vs.* 3.2 ± 1.3 mm, $p = 0.03$). Patients with weight loss > 5% had a significantly larger setup displacement in the AP (3.6 ± 1.5 mm *vs.* 2.9 ± 1.1 mm, $p < 0.001$), and SI (1.9 ± 0.9 mm *vs.* 1.6 ± 0.7 mm $p = 0.01$) directions but not in the ML ($p = 0.279$) direction.

Treatment volume strongly depended on gross disease volume, neck girth, and target margins. To control the effect of treatment volume on weight loss, we normalized the amount of weight loss to PTV. We calculated the normalized weight loss by the ratio of the percentage of weight loss over PTV (cc). As shown in Figure 4, normalized weight loss correlated significantly with setup displacement in the AP direction ($R^2 = 0.059$, $p < 0.001$). For every one percent increase in weight loss normalized to PTV, AP setup error was increased by 0.06 mm ($y = 0.055x + 2.927$, x: percentage of weight loss/PTV, y: AP setup displacement).

Discussion

Setup uncertainties greatly impact the accuracy of intensity-modulated radiation delivery. CT image guidance is routinely used to correct setup errors prior to radiation delivery. A prior small study of ten nasopharynx and nasal cavity cancer patients treated with RT has shown a large setup error of 3.6 ± 1.0 mm without daily CT image guidance.[11] In our study, the daily set-up variations were assessed in NPC patients treated with definitive IMRT delivered by helical tomotherapy. A large setup displacement in the AP direction with error greater than 3.0 mm occurred for 59.1% of treat-

ment fractions. The nasopharynx is situated immediately anterior to the clivus and brainstem. For nasopharyngeal cancer with clival involvement, the posterior margin and PTV expansion was often small or absent in order to avoid the brainstem. Therefore, our study suggests that daily IGRT is crucial in ensuring adequate coverage of nasopharyngeal gross tumor volume and protection of the brainstem.

To our knowledge, our study produced the largest dataset of daily setup errors by helical tomotherapy during NPC RT. Helical tomotherapy-based MVCT uses the same X-ray source for image acquisition and treatment.[15] No surrogate telemetry systems are required to register image space to treatment space. In contrast, the kilovoltage (kV) cone-beam computed tomography (CBCT) on a linear accelerator can produce systematic errors due to misalignment. Compared with MVCT, kV CBCT offers superior spatial and contrast resolution because of less Compton scattering and pair production interaction with its kV photon source.[16] Nevertheless, helical tomotherapy MVCT can provide sufficient contrast to delineate many soft tissue structures.[17] The cone beam geometry of CBCT systems can generate a larger scattered radiation component affecting image quality indices including homogeneity, contrast, and noise in the reconstructed CBCT images.[18] Furthermore, MVCT scan contrast is linearly related to the electron density of the material imaged and is not associated with scatter artifacts produced by dental prosthesis.[17] Given these potential shortcomings of kV CBCT, helical tomotherapy MVCT might be a more suitable choice for daily IGRT.

NPC is a lymphoid-rich neoplasm that is radiation-sensitive and undergoes dramatic shrinkage in response to radiation.[19] Shrinkage of the gross tumor volume can lead to anatomy shifts and increased setup errors. A previous study using electronic portal imaging in 20 patients undergoing definitive IMRT showed setup displacements of > 3 mm occurred more frequently in patients with bulky nodal disease.[13] In contrast to the previous finding, our data indicated no worsening of setup errors in patients with advanced T stage or N stage NPC. Furthermore, weight loss greatly impacts setup error magnitude, and is consistent with previous findings in patients treated with head and neck RT.[13,20,21] Weight loss during RT for head and neck cancers is multi-factorial. Ionizing radiation, along with concurrent systemic chemotherapy, induces acute mucositis and taste change.[6] Radiation-induced xerostomia contributes to swallowing difficulty. Inadvertent radiation dose to the brainstem and vestibule as well as platinum-based chemotherapy can induce intractable nausea.[22] These factors combine to contribute to severe malnourishment and weight loss during NPC RT.

Several potential strategies can minimize weight loss-induced setup errors during RT. Rigorous weight monitoring and nutrition support with enteral feeding can ameliorate malnutrition and help preserve head and neck muscle mass and subcutaneous fat.[23] Aggressive management of mucositis and nausea with supportive care can alleviate discomfort during food intake.[24] Optimization of radiation treatment planning can help reduce mucositis and nausea by minimizing the dose to the mucosal surface and brainstem.[22,25] As observed in our study, there is a trend toward enlarged setup errors with increasing number of fractions. The use of a shorter radiation treatment course with altered fractionation scheme may also help reduce setup errors. Adaptive RT can potentially decrease radiation dose to normal organs and thereby reduce xerostomia and nausea.[26-30]

Volume of irradiated normal tissue is correlated with RT toxicity. Size of the PTV can be a crude predictor of acute RT toxicity.[31,32] However, we found that patients with larger PTV actually had smaller setup errors in the SI and AP directions. Our image guidance procedure allows the observers to apply additional shifts to ensure adequate target coverage following automatic correction of setup displacements. It is possible that the larger PTV achieves smaller setup error by reducing these shifts. In our study, weight loss normalized to PTV accounts for the observed effect of PTV on setup errors. Importantly, weight loss normalized to PTV is a more precise measure of "tissue density loss" and correlates better with setup errors due to weight change.

Our study had several limitations including the absence of post-treatment images that can reveal the extent of intrafraction displacement. Nonetheless, a prior study that employs post-treatment cone-beam CTs has shown a small intrafraction motion of 1.2 mm during RT delivery to NPC with standard thermoplastic mask immobilization.[33] Our study also lacks treatment toxicity data that would further determine the causes of weight loss. The retrospective nature of this analysis poses the risks of patient selection bias and uncontrolled confounding factors. Despite these limitations, using our large daily MVCT dataset, we were able to identify weight loss as an independent risk factor for setup errors. Future prospective study is need-

ed to determine if weight loss intervention reduces interfraction setup errors in NPC RT.

In conclusion, weight loss is an independent risk factor for setup error during RT delivery to NPC. Patients with a moderate weight loss of more than 5% may be susceptible to increased interfraction AP and SI setup errors. Ameliorating weight loss during RT to NPC by close dietary monitoring and appropriate interventions may improve target coverage and reduce treatment toxicity by reducing the frequency and magnitude of setup errors.

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