

Original Article

Prospective memory and retrospective memory impairment in patients with nasopharyngeal carcinoma after radiotherapy

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Abstract: The aim of this present study was to investigate prospective memory (PM) and retrospective memory (RM) impairment and their correlation with quality of life (QOL) in patients with nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiotherapy (IMRT). Forty-eight patients with newly diagnosed NPC, treated with primary IMRT, participated in the study. Patients completed several neuropsychological tests, including mini-mental state examination (MMSE) and PM and RM memory questionnaires, before and after IMRT. Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) was used for estimating quality of life (QOL) in NPC. This study compared MMSE, PM, RM and QOL scores, before and after IMRT, and analyzed correlation between PM, RM and QOL scores after IMRT. PM, RM and QOL scores after IMRT were poorer than those before IMRT (PM: before, 10.50 ± 2.2 vs. after, 11.50 ± 2.35 , $t = 5.31$, $P < 0.01$; RM: 10.40 ± 2.18 vs. 13.67 ± 2.68 , $t = 13.250$, $P < 0.01$; QOL: 67.10 ± 7.65 vs. 41.50 ± 4.01 , $t = -19.50$, $P < 0.01$). There was a significant negative correlation between RM and PM scores and QOL, respectively ($r = -0.53$, $P < 0.01$; $r = -0.43$, $P < 0.01$, respectively). Results of this present study indicate that IMRT could have deleterious effects on PM and RM. These could, in turn, affect QOL in patients with NPC.

Keywords: Nasopharyngeal carcinoma, intensity-modulated radiation therapy, prospective memory, retrospective memory, quality of life

Introduction

Cases of nasopharyngeal cancer in China account for 38.29% of its incidence worldwide [1]. Radiotherapy (RT) is the main therapeutic strategy for nasopharyngeal carcinoma (NPC). It has prolonged the 5-year estimated disease-specific survival to 84.7% [2]. This high survival rate makes quality of life (QOL) increasingly important. Late toxicities, including neuropathy, hearing loss, dysphagia, xerostomia, and neck fibrosis, have a negative impact on QOL in patients with NPC [3]. RT-induced cognitive impairment, including impairment of memory, attention, information processing, and executive functions [4], is a significant sequela following irradiation for intracranial tumors [5]. Research has shown that the cerebellum, inferomedial parts of the temporal lobe, brainstem, and cranial and cervical sympathetic nerves

can be damaged in patients with NPC if they are within the target volume and exposed to radiation [6]. Patients with NPC, treated with RT, may therefore be at significant risk for development of cognitive dysfunction.

Memory is one of the most significant cognitive functions of humans. Memory can be divided into retrospective memory (RM) and prospective memory (PM) based on what is remembered. RM refers to the ability to remember events that occurred in the past, while PM is the ability to execute a delayed intended action. There have been investigations into the relationship between cognitive dysfunction and irradiation in patients with NPC [7, 8]. Moreover, cognitive impairment has been associated with decreased QOL for patients with NPC after intensity-modulated radiation therapy [9]. However, features of PM and RM

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Table 1. Clinical data of patients with nasopharyngeal carcinoma

Variable	No. of patients (%)
	Mean \pm SD
Gender	
Male	35 (72.9)
Female	13 (27.1)
Age	50.94 \pm 7.55
< 65	46 (95.8)
> 65	2 (4.2)
Education (y)	7.75 \pm 3.42
< 5 y	21 (43.8)
> 5 y	27 (56.2)
Pathological pattern	
Non-keratinizing carcinoma	16 (33.3)
Squamous cell carcinoma	32 (66.7)
Stage (7 th AJCC)	
I~II	11 (22.9)
III~IVa	37 (77.1)
Karnofsky performance status	83.86 \pm 14.98
Concurrent chemotherapy	
Zero	45 (93.8)
One cycle	1 (2.0)
Two cycles	2 (4.2)

impairment in NPC after RT have rarely been reported. In addition, there is no evidence of correlation between PM, RM and QOL in patients with NPC after RT.

The current study investigated differences in mini-mental state examination (MMSE), PM, RM and QOL scores in 48 patients with NPC, before and after RT. Further, this study explored whether there was correlation between PM, RM and QOL after RT.

Materials and methods

Patients

A total of 48 NPC patients, hospitalized between January 2016 and May 2017, at the Department of Oncology at the Second Affiliated Hospital of Anhui Medical University, were recruited. Eligibility criteria were: (1) Primary diagnosis of NPC treated with IMRT; (2) Normal daily life activities as estimated by the Karnofsky Performance Status (KPS, score \geq 80) and no impairment of vision, hearing, intelligence, or language; (3) Ages 18 years or older; and (4) History of brainless trauma surgery.

Patients with the following conditions were excluded: (1) Cachexia or distant metastasis; (2) Psychiatric symptoms, such as dysphoria, melancholia, paranoia, and so forth; (3) History of dependence on drugs that ameliorate cognitive function; (4) Clinically diagnosed dementia; (5) Intracranial metastases and other abnormalities; and (6) Other neurological diseases accompanied by cognitive disorders. This research was approved by the Research Ethics Committee of the Affiliated Second Hospital of Anhui Medical University (ethical code: 20131028). All patients provided informed consent prior to commencement of the study. All tests were conducted in a quiet environment.

Neuropsychological background tests and prospective memory and retrospective memory questionnaires

Neuropsychological tests, including the MMSE and PM/RM questionnaire (PRMQ), were performed individually for each patient within 1 week of beginning IMRT. These were followed by radical radiation therapy to determine general cognitive and memory function within 3 weeks after RT. MMSE is the most well-known and most frequently used tool for measuring cognitive function in both clinical and research contexts and comprises items concerning short-term memory, time and spatial orientation, visuospatial skills, calculation, and language. Scores can range from 1 to 30. The conventional critical point is 24, with lower scores illustrating decreased cognitive power. PRMQ consists of 16 items, 8 testing for PM disorders, and 8 for RM disorders. Patients were required to rate the degree of their memory failure on a 4-point Likert scale for each item: (4: very often, 3: sometimes, 2: rarely, 1: never). Total scores for RM or PM ranged from 8 to 32, with higher scores indicating greater memory impairment.

QOL measurement

FACT-H&N is mainly used to assess QOL of patients with head and neck tumors. The 39-item FACT-H&N comprises a supplementary head and neck cancer-specific subscale consisting of 12 questions. FACT-G includes 27 questions in 4 categories, including emotional (6), social/family (7), functional (7), and physical (7). Each item is scored on a 5-point Likert scale: 0 is almost none and 4 is very. Higher

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Table 2. Comparison of MMSE, PM, RM and FACT-H&N scores before and after radiotherapy

Group	MMSE	RM	PM	FACT-H&N
Before radiotherapy	28.06 ± 2.15	10.40 ± 2.18	10.50 ± 2.23	67.10 ± 7.65
After radiotherapy	27.92 ± 2.11 [#]	13.67 ± 2.68 [*]	11.50 ± 2.35 [*]	41.50 ± 4.01 [*]

Note: prospective memory, PM; retrospective memory, RM; FACT-H&N, QOL score; MMSE, Mini-Mental State Examination. ^{*}P < 0.05; [#]P > 0.05.

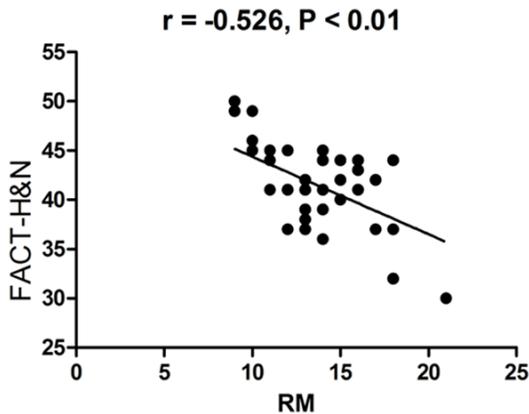


Figure 1. Correlation analysis of RM and QOL in patients with nasopharyngeal carcinoma. Higher RM scores (indicating greater memory impairment) and lower FACT-H&N scores (indicating lower QOL).

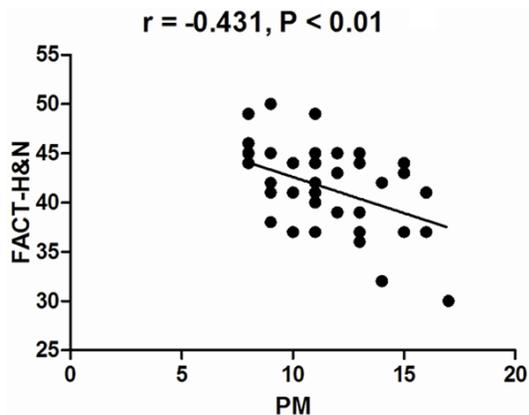


Figure 2. Correlation analysis of PM and QOL in patients with nasopharyngeal carcinoma. Higher PM scores (indicating greater memory impairment) and lower FACT-H&N scores (indicating lower QOL).

scores reflect better QOL. FACT-H&N was administered individually to each patient along with the MMSE and PRMQ, before and after radiation therapy.

Intensity-modulated radiotherapy

All patients underwent RT with 6-MV photons using an IMRT technique with nine portals.

Patients were immobilized in the supine position with thermo-plastic cast and target localization was completed by a planning CT scan. Target volumes and normal tissue structures were

delineated according to recommendations of the International Commission on Radiation Units. Gross tumor volume included the nasopharyngeal gross tumor volume (GTVnx) and gross target volume of positive neck lymph nodes (GTVnd). Two clinical target volumes (CTVs) were described, CTV1 and CTV2, containing high-risk sites of microscopic extension, the whole nasopharynx mucosa, the retropharyngeal lymph node, basis crania, the pterygo-palatina fossa, and parapharyngeal space. The brainstem, spinal cord, eyeball, lens, nervus opticus, jawbone, and temporomandibular joint comprised the organs at risk. All patients were treated with 2 Gy per fraction, with five daily fractions per week for 6-7 weeks. Doses were 70 Gy to the PTV of GTVnx, 66-70 Gy to the PTV of GTVnd, 60 Gy to the PTV of CTV1, and 54-60 Gy to the PTV of CTV2 in 33 fractions.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). Mann-Whitney U-tests were used to determine if data were normally distributed. Non-normal data, such as MMSE scores, were analyzed using Wilcoxon rank sum tests. Age and other continuous variables were analyzed using Student's t-tests. All data are expressed as mean ± standard deviation (SD). Paired-sample t-tests were used to confirm the significance of differences in PM, RM and FACT-H&N scores before and after RT. Pearson's correlation analysis was used to determine linear correlation between PM, RM and QOL after RT. All tests were two-tailed and statistical significance was considered at P < 0.05.

Results

Clinical parameters of patients

A total of 48 patients with NPC (35 men and 13 women) fulfilled the eligibility criteria and were recruited. The average age of patients was 50.94 ± 7.55 years (range, 37-70 years). All

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patients had an average number of schooling years of 7.75 ± 3.42 years and had the ability to complete neuropsychological tests. Characteristics of the patients at baseline are shown in **Table 1**.

Comparison of MMSE, PM, RM and FACT-H&N scores before and after radiotherapy

As shown in **Table 2**, RM scores after RT were significantly increased (13.67 ± 2.68) compared to those before RT (10.40 ± 2.18 , $P < 0.01$). Similarly, PM scores were also greater after RT (11.50 ± 2.35) than those before RT (10.50 ± 2.23 , $P < 0.01$). The average FACT-H&N score was significantly reduced after RT (41.50 ± 4.01) compared to that before RT (67.10 ± 7.65 , $P < 0.01$). However, there were no significant changes in MMSE scores before and after RT (28.06 ± 2.15 vs. 27.92 ± 2.11 , $P > 0.05$).

Correlation analysis of RM, PM and QOL in patients with NPC

As shown in **Figure 1**, correlation analysis between RM and FACT-H&N scores demonstrated that QOL of patients was significantly negative associated with RM ($r = -0.526$, $P < 0.01$). Similarly, there was negative correlation between PM and FACT-H&N scores ($r = -0.431$, $P < 0.01$) after RT in **Figure 2**, whereby higher PM and RM scores (indicating greater memory impairment) were associated with lower QOL.

Discussion

Radiotherapy can produce excellent long-term results in patients with NPC. Consequently, keeping the memory functioning properly and performing daily activities independently is essential to maintaining QOL for these patients [10]. Increasing studies have shown that RT is associated with deficits in immediate recall, delayed recall, immediate visual recall, short-term memory, and recent memory in patients with NPC [11, 12]. Indeed, even the present results indicated that PM, RM and QOL were significantly more impaired/lower after RT. Moreover, the present study was the first to find negative correlation between PM and RM scores, respectively, and QOL after RT, whereby more severe PM and RM disorders indicated poorer QOL in patients with NPC.

At present, the effect of IMRT on cognitive function in patients with NPC remains controversi-

al. Hsiao et al. found cognitive impairment in patients with NPC by administering neurocognitive tests at least 12 months after completion of IMRT [13]. Another study by Qingmin et al. found that Montreal Cognitive Assessment scores of patients without RT were significantly higher than those for patients that had completed 6 months of RT, suggesting that RT may induce cognitive deficits in patients with NPC [14]. Yan et al. found no acute cognitive deficits within 1 week before and after IMRT in patients with NPC, as measured by the Das-Naglieri cognitive assessment system [15]. However, some Chinese researchers believe that cognitive dysfunction occurs within 6 months after RT, in patients with NPC, but is restored to pre-RT levels with 12 months. Consequently, cognitive function of NPC after RT requires longitudinal investigation. There were no statistical differences in MMSE scores before and after RT in the present study. This is not surprising considering the following factors. First, the time between neurocognitive tests, before and after IMRT, may be short. Second, MMSE shows insufficient sensitivity, as do other tests, since no test is a perfect measure of its construct.

Specific mechanisms of RM and PM disturbances in NPC after RT remain unclear. However, brain damage in the temporal lobes and hippocampus after irradiation can be found by the presence of dysmnnesia [16, 17]. RM is defined as the ability to look back upon events that have happened in the past and is one of the cognitive features that supports future activities. As people formulate future plans or behaviors, they intentionally or unconsciously draw upon past experiences or acquired knowledge as a guideline [18]. A number of studies have suggested that a wide range of brain networks underlie RM, including the hippocampus, thalamus, cerebellum, parietal lobe, medial temporal lobe, and striatum, with the hippocampus and temporal lobe playing particularly important roles [19]. Radiation can directly affect proliferation and migration of neurons [20], with damage thresholds as low as 5 Gy found in animal experiments for neuronal stem cells in the hippocampal subgranular zone, which is particularly sensitive to radiation [21]. At present, the hippocampus is not taken into consideration as OARs to dose limited when designing radiotherapeutic plans in patients with NPC [22]. Khodayari et al. assessed per-

missible radiation doses for the hippocampus in NPC patients undergoing IMRT, reporting that the average mean permissible dose for the hippocampus was 30.27 Gy [23]. The hippocampus is thus highly susceptible to damage. Disruption of hippocampal neurogenesis may also affect memory functions such as RM [6, 24]. Hsiaoky et al. found that patients with NPC, receiving an average dose greater than 36 Gy or with V60 of the temporal lobes (i.e., the percentage of the temporal lobe volume that had received > 60 Gy) greater than 10%, had a greater reduction in cognitive functioning scores [13]. Chances of temporal lobe injury in patients with NPC remain high, as the total dose of RT in this study was 70 Gy. As a result, temporal lobes were inevitably exposed to considerable dosages of irradiation. Subjective RM complaints of patients with NPC seem to be consistent with objective impairment, as previously described.

PM is defined as the ability to remember to perform intended actions at a certain time in the future and is the core competency to maintaining daily life activities [25, 26]. Neuropsychological studies have reported that PM is associated with the prefrontal cortex, thalamus, cingulate gyrus, and ventral frontal lobe [27]. Duan et al. observed white matter damage, including occipital, bilateral temporal, right occipital-temporal junction, left parietal, left centrum semiovale, and left frontal-parietal junction damage, by employing diffusion tensor imaging to compare the white matter microstructure in patients with NPC within the first 6 months after RT [28]. In a functional magnetic resonance imaging study to explore radiation-induced brain functional alterations in patients with NPC, Peter identified five altered functional connections following RT, including the vermis and hippocampus, cerebellum lobule VI and dorsolateral prefrontal cortex, precuneus and dorsal frontal cortex, cuneus and middle occipital lobe, and insula and cuneus [14]. This present study revealed that PM has different degrees of impairment in patients with NPC. This may be related to the variability of RT-induced injuries in brain regions such as the prefrontal lobe.

The present study found negative correlation between PM, RM and QOL, respectively, after RT, whereby more severe PM and RM disorders indicated poorer QOL. Occurrence of memory

impairment can, therefore, affect QOL of patients. Indeed, similar results were found by Woods et al., whereby higher self-reported PRMQ failures in daily life were significantly associated with lower QOL in community-dwelling older adults [29]. These findings highlight the importance of assessing dysmnnesia and QOL of patients with NPC after RT. The present study was a relatively small cross-sectional study of specific features of memory impairment in patients with NPC after RT. Further longitudinal studies with greater sample sizes are needed to clarify these findings.

In conclusion, based on PRMQ memory questionnaires, this present study found that RT could have deleterious effects on PM and RM, especially RM. Furthermore, these impairments were correlated with QOL of patients, post RT, highlighting these memory impairments as important factors affecting QOL.

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Disclosure of conflict of interest

None.

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