RADIOThERAPY FOR NASOPHARYNGEAL CARCINOMA: SHIELDING THE PITUITARY MAY IMPROVE THERAPEUTIC RATIO


Radiotherapy and Oncology Service, Queen Mary Hospital, Pokfulam, Hong Kong

Purpose: Nasopharyngeal carcinoma (NPC) is well known for its invasiveness and erosion of the base of the skull is not uncommon. Before the advent of computed tomography, the evaluation of the base of the skull was by plain radiography. Because of the low sensitivity of these investigations, traditional teaching has included the sphenoid sinus in the volume of irradiation. Increase in longevity of patients allows the manifestation and documentation of the long-term sequelae of irradiating the hypothalamic-pituitary axis and the temporal lobes. This study is an attempt to evaluate whether the hypothalamic-pituitary axis can be shielded from the target volume in a proportion of NPC patients.

Methods and Materials: One hundred fifty-two NPC patients with no evidence of erosion of the base of the skull and sphenoid, nor extension to the nasal fossa and ethmoid sinuses were randomized to receive standard radiotherapy covering the whole sphenoid sinus or radiotherapy using a modified technique that shields the pituitary and the anterior part of the hypothalamus. This modified technique also shields a large part of the lower temporal lobes that are otherwise covered by standard treatment portals. The characteristics and treatment of the two subgroups of patients were otherwise comparable.

Results: At a median follow-up of 31.5 months, the tumor control between the two subgroups of patients were comparable (p = 0.3928). However, 8 of the 71 patients in the unshielded group had developed symptomatic neuroendocrine complications, while none of the other group did (p = 0.0061). Two patients developed secondary hypothyroidism, one patient developed oligomenorrhea associated with raised prolactin, and five patients developed temporal lobe necrosis.

Conclusions: The protective effect on neuroendocrine complication of this shield was demonstrated at median follow-up of 31.5 months, and the local control was not jeopardized. Modification of treatment technique as presently described, which is applicable to one-third of NPC patients to improve the therapeutic ratio, is recommended for general use.

Nasopharyngeal carcinoma, Radiotherapy, Pituitary shield.

INTRODUCTION

Since Trotter described the dismal result of surgical treatment for nasopharyngeal neoplasm at the turn of the century (26), clinicians have come a long way, mainly through the use of radiotherapy, to improve the survival of patients with nasopharyngeal carcinoma (NPC). The 5-year survival of the patients with Stage I disease now ranges from 80% to more than 90% (21-23).

Nasopharyngeal carcinoma (NPC) is well known for its invasiveness. Because of its proximity to the base of the skull, erosion of base of skull and cranial nerve palsy have, for a long time, attracted the attention of the clinicians (6, 20).

Before the advent of computed tomography (CT), the evaluation of the base of the skull was by plain radiography and sometimes polytomography (8). Because of the low sensitivity of these investigations and for fear of undertreatment, traditional teaching has been to include the sphenoid sinus in the volume of irradiation (1, 4, 5, 7, 9, 14, 18, 19, 23-25). In fact, having considered the frequency of erosion of the base of the skull by NPC, Lenz (19) advised that the base of the skull must be irradiated. He cautioned that negative x-ray film did not exclude the University of Hong Kong (CRCG Grant No. 337/037/0001), the Li Ka Shing Foundation, the Hong Kong Jockey Club (Charity) Ltd., the Ho Hung Chiu Foundation, and Croucher Foundation, Hong Kong. The authors would like to thank Miss Elke Yim for assistance in preparing the manuscript. Accepted for publication 18 March 1994.
early invasion of the base of the skull and contended that the pituitary and cerebrum in the middle fossa, which were thus irradiated, support therapeutic radiation dose without much difficulty. More recent publications of improved result of radiotherapy using larger ports have probably reinforced such practice (30).

Increase in longevity of patients allows the manifestation and documentation of the long-term sequelae of irradiating the hypothalamic-pituitary axis and the temporal lobes, thus challenged the complacent attitude towards irradiation of the central nervous system. Lam et al. (12) reported on a series of patients with symptomatic hypothalamic-pituitary dysfunction, and Lee et al. (17) reported that late temporal lobe necrosis occurred in about 1% of patients following radiation therapy for NPC. In a prospective longitudinal study of 31 early staged NPC patients, Lam et al. (13) showed that the cumulative probability of endocrine dysfunction was estimated to be 62% after 5 years.

To avoid the radiation effect on the pituitary-hypothalamic axis, individual centers and authors might have exercised caution in planning and treating early cases of NPC by shielding the pituitary, as evidenced from port films in their article (28). However, there has been no randomized studies to establish that certain subgroups of NPC patients could be treated with smaller ports or that the hypothalamic-pituitary axis could be shielded without deleterious effect, and the teaching of including the sphenoid sinus in the target volume is still frequently followed (1, 4, 5, 7, 9, 14, 18, 19, 23–25). We have conducted a prospective randomized study on the effect of shielding the hypothalamic-pituitary axis for patients with no evidence of erosion of the base of the skull, no erosion of the sphenoid sinus, nor extension to the nasal fossa or ethmoid sinus, which would indicate that the tumor has come close to the sphenoid sinus and risks being shielded from irradiation. This is a report on the result of the study.

**METHODS AND MATERIALS**

One hundred fifty-two patients seen between August 1988 and June 1991 were recruited into the present study. During this period, about 450 new patients of NPC were treated in the Department of Radiotherapy and Oncology, Queen Mary Hospital.

The criteria for recruitment into this study was the absence of erosion of the base of the skull and sphenoid sinus in CT, and no evidence of extension to the nasal fossa or ethmoid sinuses.

The lower part of temporal lobes were also assessed in the set of baseline CT. No evidence of abnormality in the temporal lobe was noted in all patients. There was no clinical evidence of endocrine abnormality at baseline evaluation, however, hormonal assays were not routinely performed. In about one-third of the patients, for whom baseline assessment was performed, their serum thyroxin, thyroid-stimulating hormone and prolactin were normal.

Patients were randomized to receive standard radiotherapy covering the whole sphenoid sinus or radiotherapy using a modified technique that shielded the pituitary and the anterior part of the hypothalamus from the lateral fields. This shield also shields a large portion of the inferior part of the temporal lobes from irradiation.

Two standard radiotherapy techniques were used in our center. The first one (technique 1) treated the nasopharynx and the neck lymphatics in two separate volumes. The nasopharynx was treated with two lateral wedged facial fields and one anterior facial field. 3.5 Gy was given three times per week to 59.5 Gy at 100%, and a large portion of the inferior part of the temporal lobes received 80–100% of the target dose (Fig. 1). For the modified version of this technique with pituitary shield (Fig. 2), the pituitary-hypothalamus received around 30% of the tumor dose, and a large portion of the inferior part of the temporal lobes, which would otherwise have been included in the 80–100% isodose volume was excluded from irradiation.

The second technique (technique 2) treated the nasopharynx and the upper neck lymphatics in one volume with lateral facio-cervical fields. 2.5 Gy was given four times per week to 40 Gy at 100%, and the inferior part of the temporal lobes received the same dose (Fig. 3). Phase II treatment used the set up of technique 1 to give another 21 Gy in six fractions over 2 weeks, when a large portion of the inferior part of the temporal lobes received 80–100% of the target volume dose. For the modified version of this technique with pituitary shield, the pituitary-hypothalamus received around 10% of the tumor dose, and a large portion of the inferior part of the temporal lobes, which would otherwise have been included in the 90–100% isodose volume was excluded from irradiation.

**Fig. 1. Isodose through the inferior part of the temporal lobes for technique 1 showing the target volume (100%) and a large portion of the inferior part of the temporal lobes received 80–100% of the target dose.**
The age, sex, and stage distribution of the patients were shown in Table 1. There were three patients with T3 disease by definition, but none of them had tumor extension close to the sphenoid: one patient had Horner's syndrome, another patient had tenth and eleventh cranial nerve palsy. Both were due to pressure effect of the neck nodes at the jugular foramen. Another patient had erosion of the inferior orbital fissure.

Thirty-five patients were treated by technique 1, and 117 patients were treated by technique 2. Seventy-one patients were treated without shield and 81 patients were treated with pituitary shield. Ninety-one patients also received booster dose to the paranasopharyngeal space with a posterior oblique field. 10.5 Gy was given in three fractions on alternate days. Twenty-one patients also received adjuvant chemotherapy for extensive nodal disease. There was no difference in the treatment received between the two groups (Table 2). One patient in the study group had died of intercurrent disease, and three patients were lost from follow-up, the other patients have been followed.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Without pituitary shield</th>
<th>With pituitary shield</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male</td>
<td>44</td>
<td>42</td>
<td>0.2749</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Age 21–40</td>
<td>19</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>41–60</td>
<td>37</td>
<td>37</td>
<td>0.6955</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>15</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>33</td>
<td>36</td>
<td>0.7431</td>
</tr>
<tr>
<td>III</td>
<td>18</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>N stage 0</td>
<td>31</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>20</td>
<td>0.7125</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>T stage 1</td>
<td>28</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>50</td>
<td>0.8227</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Treatment received

<table>
<thead>
<tr>
<th></th>
<th>Without pituitary shield</th>
<th>With pituitary shield</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>16</td>
<td>0.4061</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Boost to paranasopharyngeal space</td>
<td>No</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>42</td>
<td>57</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>67</td>
<td>0.2766</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
the temporal lobes, were being documented. Lam et al. (12) reported on a series of NPC patients with symptomatic hypothalamic-pituitary dysfunction following radiation therapy. Lee et al. (17) reported in a retrospective review late temporal lobe necrosis occurring in about 1% of patients following radiation therapy for NPC. Woo et al. (29) reported a distinct clinical syndrome of temporal lobe and hypothalamic-pituitary dysfunctions after radiotherapy for NPC.

Frank temporal lobe necrosis was a more severe form of damage. Not unexpectedly, more subtle damage may occur with a even higher incidence. Lee et al. (16) reported on the effect of radiation therapy on neuropsychological functioning of patients with NPC. These patients were found to have significant impairment in overall IQ, non-verbal memory recall, and reported a substantially greater number of memory related complaints. They pointed out that these findings were in sharp contrast with the complacent general assumption that radiation therapy had negligible effect on adult brain functioning.

Chen et al. (2) carried out a prospective study on hypothalamic-pituitary function in patients with NPC after high dose irradiation. Although none of the patients showed any clinically recognizable symptoms or signs of hormone deficiency in the 18–33 months after completion of the radiation therapy, a significant change in the level of luteinizing hormone, growth hormone (GH), thyroid-stimulating hormone, follicle-stimulating hormone, cortisol, and prolactin were found. The decrease in GH level appeared earlier and was more sensitive than the other hormones, and they concluded that GH could prove to be a useful parameter for clinical evaluation. In another study, Huang et al. (10, 11) demonstrated impairment of the hypothalamus-pituitary-endocrine axes as early as 6 months after cranial irradiation with or without chemotherapy.

Chieng et al. (3), using single photon emission computed tomography (SPECT) studies in 34 patients, reported reduced hypothalamic blood flow after radiation treatment of NPC, thus providing an anatomical evidence for the radiation damage.

Lee et al. (15) reported on the use of magnetic resonance imaging in the clinical diagnosis of late temporal lobe necrosis following radiotherapy for NPC and found it more sensitive than CT. The use of more sensitive investigations, like hormonal assays and MR, may result in a higher pick up rate of subclinical cases of radiation damage. The long-term implications of such subclinical damage are yet unknown.

In a prospective longitudinal study of 31 early staged NPC patients, Lam et al. (13) showed, using life table analysis, that the cumulative probability of endocrine dysfunction was estimated to be 62% after 5 years with deficiencies in growth hormone, gonadotrophins, corticotrophin, and thyrotrophin found respectively in 63.5, 30.7, 26.7, and 14.9% of patients. They recommended that regular endocrine assessment should be performed in all patients following cranial irradiation.
However, it would be far better to practice prevention rather than early detection of sequelae and institution of treatment. Even though earlier authors stressed on the importance of adequately covering the base of the skull [19], more recent authors had seldom stressed such points [23]. Though not explicitly mentioned in their reports, the port films or diagrams shown in the more recent reports had indicated that the sphenoid sinus was being shielded from the radiation portal [28]. For patients with no evidence of erosion of the base of the skull and sphenoid, not extension to nasal fossa and ethmoid, data at median follow-up of 31.5 months showed that shielding of the pituitary by the present technique would not adversely affect the local control (Table 3). This should be a valid conclusion, considering the local control for previous studies had shown that 72% of NPC local relapse were diagnosed within 2 years [27]. The absence of involvement of the sphenoid sinus in all four pituitary-shielded patients at diagnosis of local relapse also gives support to this.

A major criticism of the present study is the absence of comprehensive baseline neuroendocrine assessment. However, clinical baseline evaluation, together with CT evaluation of the temporal lobes, and the absence of skull base erosion at diagnosis and recurrence (which could have contributed to the neuroendocrine abnormalities), would safeguard the validity of clinical evaluation of neuroendocrine abnormalities after irradiation in the present study.

The adding of a pituitary shield as presently practiced not only significantly reduced the radiation dose to the hypothalamic-pituitary axis, it also shields a large portion of the inferior part of the temporal lobes from irradiation. With a median follow-up of 31.5 months, the protective effect on neuroendocrine complication of this shield was demonstrated and the local control was not jeopardized. The large fractional dose employed in the present study had contributed to the high incidence of complication, and without this incidence of complication the beneficial effect of shielding the pituitary might not have been demonstrated with a median follow-up of 31.5 months. This, however, should not distract from the fact that this study demonstrated that it is safe to shield the pituitary and sphenoid sinus for this subgroup of patients. Furthermore, in South East Asia, where nasopharyngeal carcinoma is common, limitation of machines often necessitates the practice of hypofractionation. Before this situation could be rectified, such practice of shielding the pituitary-hypothalamic axis to improve the therapeutic ratio would benefit about one-third of patients.

REFERENCES


