Delayed Sino-nasal Complications of Radiotherapy for Nasopharyngeal Carcinoma
Eran E. Alon, Noga Lipschitz, Lev Bedrin, Iris Gluck, Yoav Talmi, Michael Wolf and Arkadi Yakirevitch
Otolaryngology -- Head and Neck Surgery 2014 151: 354 originally published online 14 April 2014
DOI: 10.1177/0194599814530858

The online version of this article can be found at:
http://oto.sagepub.com/content/151/2/354

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
AMERICAN ACADEMY OF
OTOARYNGOLOGY--
HEAD AND NECK SURGERY

American Academy of Otolaryngology- Head and Neck Surgery

Additional services and information for Otolaryngology -- Head and Neck Surgery can be found at:

Email Alerts: http://oto.sagepub.com/cgi/alerts
Subscriptions: http://oto.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

>> Version of Record - Jul 23, 2014
OnlineFirst Version of Record - Apr 14, 2014
What is This?
Delayed Sino-nasal Complications of Radiotherapy for Nasopharyngeal Carcinoma

Eran E. Alon, MD1, Noga Lipschitz, MD1, Lev Bedrin, MD, PhD1, Iris Gluck, MD2, Yoav Talmi, MD1, Michael Wolf, MD1, and Arkadi Yakirevitch, MD1

Abstract
Objective. There are only sporadic reports of delayed sino-nasal complications associated with nasopharyngeal carcinoma (NPC) treated with radiotherapy. These include choanal stenosis, osteoradionecrosis, chronic sinusitis, and intranasal synechiae. Most likely, these complications are underestimated as in many institutions nasal endoscopies in NPC patients are not performed routinely. The aim of this study was to identify the onset and incidence of delayed sino-nasal complications in NPC patients and their effect on quality of life (QOL).

Study Design. Case series with chart review.

Setting. Tertiary medical center.

Subjects and Methods. A retrospective chart review was performed on all patients treated for NPC in our institution between 1988 through 2009. The inclusion criteria required at least a 3-year follow-up without recurrence. Included patients were contacted prospectively and asked to fill a SNOT-16 questionnaire.

Results. Sixty-two patients were included in our review. There were 42 males and 20 females. The average age at onset was 42 years. The AJCC staging for T1, T2, T3, and T4 tumors was 22 (35%), 11 (18%), 18 (29%), and 11 (18%), respectively. Eleven patients (18%) suffered from chronic sinusitis. Nine patients (15%) developed choanal stenosis. Five patients (8%) developed osteoradionecrosis. Two patients suffered from nasal synechiae. Forty-eight patients completed the SNOT-16 questionnaire. Patients with choanal stenosis had the lowest QOL scores out of the cohort.

Conclusion. The incidence of delayed sino-nasal complications after radiation treatment for NPC is not negligible and should be kept in mind when addressing the quality of life of NPC survivors.

Keywords
nasopharyngeal carcinoma, NPC, chronic sinusitis, osteoradionecrosis, synechiae, choanal stenosis, quality of life, radiotherapy

Introduction
Nasopharyngeal carcinoma (NPC) is prevalent in Southeast Asia but is encountered worldwide. This tumor is locally aggressive and highly metastasizing. Many patients are diagnosed with advanced stage of disease as most of them will present with cervical metastasis or cranial neuropathy.

Initial treatment for NPC is based on radiation therapy (with or without chemotherapy) due to its radio-sensitivity and the complexity of surgery in this location. Radiation therapy, although a very effective treatment for various malignancies, is known to have significant short- and late-term side effects. The extent of the radiation fields required to treat NPC depend on the initial tumor volume and extent, which in turn will dictate exposure of surrounding structures (ie, skull base, temporal lobes, eyes, spinal cord, carotid arteries, pituitary gland, middle and inner ears, etc) to radiation. Inevitably, it is practically impossible to spare these surrounding structures, even when using complex 3-dimensional radiation fields such as those being incorporated with intensity-modulated radiotherapy (IMRT).

Short-term side effects of radiation to the upper aerodigestive tract are well documented and include mucositis, loss of taste, burn, and so on. The late-term side effects seen after radiation to the upper aerodigestive tract may include fibrosis, xerostomia, dysphagia, trismus, Eustachian
tube dysfunction, cranial nerve palsy, carotid stenosis, temporal lobe radionecrosis, general mucosal dysfunction, and post-radiation malignancies.\(^1\text{–}^8\) Specifically, in NPC, late-term sino-nasal side effects include chronic sinusitis, endonasal synechiae, choanal stenosis, and skull base osteoradionecrosis (ORN).\(^9\text{,}^{10}\) On one hand, these complications are underestimated because their symptoms are not specific and because in endemic areas nasal endoscopy is still not a routine part of the follow-up examination.\(^9\) On the other hand, long-term survivors of NPC will continue to suffer from these potentially curable side effects long after their oncologic surveillance.

The end point of this study was to identify the onset and incidence of delayed sino-nasal complications in NPC patients and their effect on quality of life (QOL).

**Methods**

An institutional internal review board for human and animal trials reviewed and approved the prospective and retrospective aspects of the study. We performed a retrospective chart review of all patients diagnosed and treated for NPC in our institution between 1988 through 2009. Only patients with no evidence of disease on their last follow-up examination at least 3 years after completion of radiotherapy were included in the study group. Demographics, age at time of diagnosis, American Joint Committee on Cancer (AJCC) staging, radiotherapy dose and modality (2-dimensional/3-dimensional or IMRT), date of its completion, chemotherapy regimen, and onset of clinical and radiological evidence of delayed sino-nasal complications (chronic sinusitis, endonasal synechiae, choanal stenosis, and skull base ORN) were compiled. Of note, nasal and nasopharyngeal endoscopy is a common practice in NPC patients’ follow-up in our institution.

For the purpose of this study, chronic sinusitis was defined as facial pain and/or anterior/posterior purulent nasal discharge persistent above 3 months. Choanal stenosis was defined as narrowing of the naso-pharyngeal passage that obscures the endoscopic view of the nasopharynx. Diagnosis of ORN was based on complaints (foul odor, headache, epistaxis), endoscopic findings of exposed bone or sequestration in the nasopharynx, characteristic radiological signs (bony erosive changes on computed tomography, increased fluorodeoxyglucose uptake on positron emission tomography), laboratory data (elevated C-reactive protein, erythrocyte sedimentation rate and white blood cell count), and histological exclusion of NPC recurrence.

Sino-nasal outcome tool, SNOT-16 questionnaire, accompanied with an explanation letter was sent to eligible patients in order to assess current symptomatology. For the purpose of this study, the questionnaire was translated to Hebrew and validated. Then, correlation between subjective data received by means of the questionnaires and objective data retrieved from the files was analyzed. For the purpose of survey analysis, chronic sinusitis, choanal stenosis, and ORN were deemed as the main complications while intranasal synechiae as a secondary one. Thus, patients having chronic sinusitis and synechiae were grouped with the patients with chronic sinusitis only.

Statistical analysis was performed with a 2-tailed Fisher’s exact test and Cochran-Armitage trend test (GraphPad InStat Software, version 3.10). A value of \(P < .05\) was considered significant.

**Results**

Sixty-two patients were eligible for the study. The male-to-female ratio was 42:20. The patients’ age at time of NPC diagnosis ranged from 11 to 74 years (average 42, mean 43). The AJCC staging of the primary tumor was T1 in 22 (35%), T2 in 11 (18%), T3 in 18 (29%), and T4 in 11 patients (18%). Eighteen patients (29%) received radiotherapy as a single modality treatment and 44 (71%) in combination with concurrent chemotherapy (cisplatin and 5-fluorouracil). Forty patients were treated with 2-dimensional/3-dimensional irradiation while the other 22 received IMRT. Radiation dose for the primary site ranged from 6600 to 7240 rad.

### Delayed Sino-nasal Complications of Radiotherapy

Follow-up for the study cohort lasted 3 to 16 years (average 7 years). Incidence of each sino-nasal complication and their combinations is demonstrated in Table 1. Chronic sinusitis was diagnosed in 11 patients (18%), in 2 of them combined with endonasal synechiae, in 3 with choanal stenosis, and in 1 patient with both of them. No correlation was found between chronic sinusitis and T-stage of NPC (Table 2). The diagnosis of chronic sinusitis was made 12 to 72 months after completion of radiotherapy. The maxillary sinus was involved in all cases and the frontal sinus in none. Choanal stenosis was found in 9 patients (15%), of those in 4 as a single complication. In all cases it was bilateral, incomplete, and had no correlation with T-staging (Table 2). It was diagnosed 12 to 84 months after completion of irradiation. Five patients developed ORN (8%), 4 of them as a single complication and 1 in combination with chronic sinusitis and endonasal synechiae. This was diagnosed 2 to 72 months after completion of radiotherapy and did not correlate with T-staging. (Table 2). No significant influence of irradiation delivery method was found for any type of complication (Table 3).

<table>
<thead>
<tr>
<th>Complications/Combination of Them</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic sinusitis</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Chronic sinusitis + synechiae</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chronic sinusitis + choanal stenosis</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Chronic sinusitis + synechiae + choanal stenosis</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Chronic sinusitis + synechiae + osteoradionecrosis</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Choanal stenosis</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Choanal stenosis + synechiae</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>32</td>
</tr>
</tbody>
</table>

*Each patient appears only once in the table.*
Forty-eight patients filled out the SNOT-16 questionnaire. The total SNOT-16 scores for the whole cohort and for subgroups suffering from each kind of sino-nasal complication are summarized in Table 4. Figure 1 demonstrates the distribution of the SNOT-16 scores averaged according to each item of the questionnaire. It can be seen that QOL of patients with choanal stenosis is significantly worse than of the whole group of responders, mainly due to general functioning and sleep problems. Additionally, they suffer more frequently from postnasal drip. QOL of patients with chronic sinusitis is similar to the whole group average except for a higher frequency of ear fullness among them. As reflected by responses of the ORN patients, their QOL might seem similar to that of the whole group. Nevertheless, it should be kept in mind that ORN develops almost always after re-irradiation for local NPC recurrence and is potentially life-threatening by itself. Hence, poorer long-term survival in this group of patients may bias the survey results.

### Table 2. Correlation between Primary Tumor Stage and Type of Complications.

<table>
<thead>
<tr>
<th>T stage</th>
<th>Total N</th>
<th>Chronic Sinusitis N (%)</th>
<th>Choanal Stenosis N (%)</th>
<th>Osteoradionecrosis N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>6 (27.2)</td>
<td>3 (13.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>3 (16.8)</td>
<td>4 (22.4)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>P</td>
<td>.14</td>
<td>.9137</td>
<td>.2917</td>
<td></td>
</tr>
</tbody>
</table>

*By Cochran-Armitage Trend Test.

### Table 3. Correlation between Radiotherapy Modality and the Type of Complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Total</th>
<th>Standard Radiotherapy n (%)</th>
<th>Intensity-modulated Radiotherapy n (%)</th>
<th>P-value (2-sided)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic sinusitis</td>
<td>9</td>
<td>5 (12.5)</td>
<td>4 (18.2)</td>
<td>.7086</td>
</tr>
<tr>
<td>Choanal stenosis</td>
<td>8</td>
<td>4 (10)</td>
<td>4 (18.2)</td>
<td>.4381</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>5</td>
<td>4 (10)</td>
<td>1 (4.5)</td>
<td>.6473</td>
</tr>
</tbody>
</table>

*By Fisher exact test.

### Table 4. SNOT-16 Survey Results.

<table>
<thead>
<tr>
<th>Number of Patients Who Filled out the Questionnaire</th>
<th>Total Score (average of all items)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group</td>
<td>48</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>6</td>
</tr>
<tr>
<td>Choanal stenosis</td>
<td>3</td>
</tr>
<tr>
<td>Osteoradionecrosis</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Discussion

In the past few decades, growing attention has been given to the quality of life of cancer patients, and rightfully so. In years past we, at times, neglected the QOL of the patient and only hailed survivorship. Nowadays, we attempt to embed the QOL as an integral part of our practice. NPC, although it is of an aggressive nature, is a curable disease with 75% expected 5-year survival with contemporary treatment practices.1 Previous works highlighted NPC patients’ QOL using various questionnaires, none of which specifically addressed sino-nasal disease.2-6 Addressing the unique issues of QOL in NPC patients, Tong et al7 published and validated in 2009 a functional assessment of cancer therapy nasopharyngeal cancer subscale (FACT-NP). In their newly developed subscale the patients were asked to address specific concerns such as eating, swallowing, mouth dryness, appetite, taste, voice quality, communication, appearance, pain, neck movement, tinnitus, hearing, vision, smell, and nasal blockage. Although this new questionnaire was validated, specific data on sino-nasal complaints were not presented.7

In an attempt to shed light on late sino-nasal complications, we utilized retrospective data together with a survey based on a validated sino-nasal questionnaire (SNOT-16). This tool was chosen to assess the possibility of delayed sino-nasal complications because, to our mind, it sufficiently reflects the expected symptoms of delayed sino-nasal complications of radiotherapy and is short enough to gain the responders’ compliance. Reliability and validity of the SNOT-16 was demonstrated by Anderson et al in 1998,8 and since then it was used in multiple studies for evaluation of sino-nasal pathology and its treatment results. Routine fiberoptic nasal
endoscopy is the standard of care in our practice allowing for a collection of long-term follow-up data. Surprisingly, in some regions endemic for NPC endoscopy is not performed routinely, which may be one of few explanations why there is underreporting of these complications. Even with the routine use of endoscopies we took into consideration that there is underreporting of choanal stenosis in our series, as when one side of the nasal cavity is somewhat narrowed we, naturally, would use the contralateral side to visualize the nasopharynx.

In our series, every third patient developed some form of delayed sino-nasal complication. Chronic sinusitis was the most common complication seen. Other reports have seen upwards to 73% of post-radiated NPC patients with chronic sinusitis.9 All cases of chronic sinusitis had maxillary sinus involvement and sparing of the frontal sinuses. These findings were consistent with other reports.10 Presumably, the combination of the anti-gravity mucociliary clearance and inability to shield the area of the maxillary sinus and osteomeatal complex from radiation play a significant role in the chronic sinusitis state. According to our survey, the most prominent symptom in these patients was aural fullness that can be related to permanent discharge obstructing Eustachian tube orifices. Severity of the remaining symptoms was similar to all responders’ average. We assume that intensive treatment for this potentially curable complication may lead to a meaningful improvement in quality of life.11

Ku et al12 presented their experience with 6 patients suffering from posterior choanal stenosis. Four patients suffered from bilateral atresia and 2 patients from severe unilateral stenosis. All the patients complained of severe difficulty in breathing through and discharge from the nose. The authors stress in their discussion that the patients were diagnosed only due to their significant symptoms as they do not routinely perform nasal endoscopy for follow-up in NPC patients, thus probably missing more subtle symptoms and pathology. They concluded that endoscopic evaluation of the nasal cavity and nasopharynx is thus required in all NPC patients.12 If the posterior choana is in close proximity or involved by disease, this area is most likely exposed to the maximal or near maximal radiation dose. Fibrosis follows the immediate mucosal response leading in some cases to circumferential scarring. Due to variations in patients’ mucosal response to radiation, it stands to reason that there are variations in the fibrosis and stenosis formation.

In our series, QOL of the patients with choanal stenosis was poorer than the whole cohort average, mostly at the expense of complaints that raise suspicion of sleep-disordered breathing. It should be pointed out that nasal obstruction, the most expected symptom of choanal stenosis, is not questioned in SNOT-16. In most patients, diagnosis was made late in their follow-up, although they were examined routinely with an endoscope. Only when the patients had formed bilateral stenosis and more significant symptoms was the diagnosis made. We suspect there are certainly more patients with mild stenosis that are not diagnosed.

Osteoradionecrosis is an uncommon but potentially serious complication. Known risk factors for ORN include...
radiation dose, gender, trauma/inflammation, poor oral hygiene, tobacco/alcohol consumption, and re-irradiation. The exact mechanism that causes ORN is not well known; Marx’s theory of hypoxia—hypovascularity and hypocellularity as the process leading to ORN—has been cited. A study by Hua et al described ORN as the end stage of postradiation nasopharyngeal necrosis (PRNN). In their cohort, most of the patients who developed PRNN were re-irradiated for recurrent disease. They emphasized that although there are patient factors that increase the chance for ORN, the most important factor is likely the radiation dosage. Previous studies have reported the incidence of ORN to be from 4.74% to as high as 37.5%. In a recent review, Nabil et al demonstrated that approximately 2% of all irradiated head and neck cancer patients will develop ORN with current radiotherapy techniques. In their study there were no specific data on skull base ORN after treatment of NPC. In our cohort 8% of the patients developed ORN, a much higher number, possibly due to the inability to spare the skull base from maximal/near maximal radiation doses. The higher expected rate of ORN was also reported by Lee et al. In their cohort ORN was diagnosed in 10% of patients. Huang et al describe their experience treating 15 patients with ORN of the skull base in the setting of NPC. The latency of ORN diagnosis of 8 patients treated with radiation alone in their cohort was between 3 to 15 years. The latent course for patients treated with multiple courses was 7 months to 2 years. In our series, patients with ORN were diagnosed up to 6 years from completion of treatment. The relatively prolonged latency in diagnosis emphasizes the need to be aware of the very late onset of these complications. Similar to our experience they noted that exposed bone after removal of crusts in the nasopharynx was the most important sign for diagnosis. Although, according to our survey results, the ORN process can be indolent, we still advocate active evaluation for this potentially life-threatening complication.

Conclusion

Treatment of nasopharyngeal cancer may lead to long-term quality of life impairment. The treating clinicians should be minded of potentially treatable long-term sino-nasal complications. They should be aware of these complications in their occurrence, especially when patients do not require further oncologic follow-up.

Author Contributions

Eran E. Alon, design, acquisition of data, analysis and interpretation, drafting of the article, revision and final approval; Noga Lipschitz, data analysis, drafting, final approval; Lev Bedrin, data analysis, drafting, final approval; Iris Gluck, data analysis, drafting, final approval; Yoav Talmi, data analysis, drafting, final approval; Michael Wolf, data analysis, drafting, final approval; Arkadi Yakirevitch, design, acquisition of data, analysis and interpretation, drafting of the article, revision and final approval.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

References