 Fatal Pneumocephalus Associated with Clivus Necrosis Following Re-Irradiation for Nasopharyngeal Cancer: A Rare Complication

Meltem DAĞDELEN, Ecem DEMİR, Orkun CİVAN, Osman KIZILKILIÇ, Ömer Erol UZEL

ABSTRACT A case of recurrent nasopharyngeal cancer with osteonecrosis of clivus along with cranial nerve palsy after re-irradiation with a fatal outcome is presented. A 33-year-old female is presented with palpable bilateral enlarged lymph nodes. A mass in the endoscopy of the nasopharynx was biopsied. Histological investigation of the biopsy specimens showed non-keratinized differentiated squamous cell carcinoma. According to the American Joint Committee on Cancer 8th edition, her cancer was T1N2M0 Stage 3. Radiotherapy was delivered after the induction chemotherapy. After 4 years, she had a recurrence and 60 Gy re-irradiation in 30 fractions was delivered after 8 months from recurrence. Six months from re-irradiation; first, bulbar palsy was observed in our patient, magnetic resonance imaging revealed radiotherapy-related osteonecrosis and platybasia due to anterior compression of the cervicomedullary junction. Re-irradiation local control rates are increasing with the advancements of new radiation techniques. As the survival of re-irradiated patients increases, late complications can be fatal.

Keywords: Adverse effects; re-irradiation; cranial irradiation; radiation effects

The main treatment of nasopharyngeal carcinoma (NPC) is radiotherapy (RT). After primary intensity-modulated RT (IMRT), 10-20% of patients might experience recurrence. Local recurrence is more common in patients with advanced T stage, whereas systemic metastasis is more common in patients with advanced N stage in nasopharyngeal cancer.

Re-irradiation offers a relatively good chance of local tumor control, it carries a high probability of complication rates such as trismus, cranial nerve palsy, osteoradionecrosis, and carotid stenosis and blowout, a few of which may be fatal.

In our article, we would like to present a case of recurrent nasopharyngeal cancer which had osteonecrosis of clivus along with cranial nerve palsy after re-irradiation with a fatal outcome.

CASE REPORT

A 33-year-old female presented with palpable bilateral enlarged lymph nodes. On her physical and endoscopic examinations, there were multiple bilateral neck nodes (Largest in 3 cm) and an asymmetry in the left Rosenmuller fossa. A mass in the endoscopy of the nasopharynx was biopsied. Histological investigation of the biopsy specimens showed non-keratinized differentiated squamous cell carcinoma.

According to the American Joint Committee on Cancer 8th edition, her cancer was T1N2M0 Stage 3. Radiotherapy was delivered after the induction chemotherapy. After 4 years, she had a recurrence and 60 Gy re-irradiation in 30 fractions was delivered after 8 months from recurrence. Six months from re-irradiation; first, bulbar palsy was observed in our patient, magnetic resonance imaging revealed radiotherapy-related osteonecrosis and platybasia due to anterior compression of the cervicomedullary junction. Re-irradiation local control rates are increasing with the advancements of new radiation techniques. As the survival of re-irradiated patients increases, late complications can be fatal.

A mass in the endoscopy of the nasopharynx was biopsied. Histological investigation of the biopsy specimens showed non-keratinized differentiated squamous cell carcinoma with positivity for Epstein-Barr virus antigen and pancytokeratin.
An F-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scan was performed for staging. A 21*16 mm [standardized uptake value (SUV) maximum=16.32] lesion in the nasopharynx and multiple bilateral lymph nodes, the largest measuring 3.5 cm in diameter, in levels II, III, and IVA (SUV maximum=17.49) was found. There was no distant metastasis. According to the American Joint Committee on Cancer 8th edition, her cancer was T1N2M0 Stage 3.

After obtaining her informed consent for treatment, she was started on three cycles of induction chemotherapy. RT was delivered after the induction chemotherapy (cisplatin 100 mg/m²: 185 mg, docetaxel 75 mg/m²: 140 mg and 5-FU 1,000 mg/m²: 1,870 mg). The standard NPC radiation treatment dosage (70 Gy for high-risk, 60 Gy for intermediate-risk, 54 Gy for low-risk planning target volume in 33 fractions with simultaneous integrated boost technique) was used. Field verification for image-guided radiation therapy was carried out with cone beam CT every day.

Concomitant 100 mg/m²: 140 mg cisplatin chemotherapy was given for 3 cycles. Control PET/CT and MRI showed near-total regression in the nasopharynx and lymphatic lesions.

Four years later, her symptoms were bilateral impaired hearing and tinnitus. On her physical examination, palpable bilateral cervical lymph nodes were detected. PET/CT was performed which reported a lesion in the left posterolateral nasal cavity, multiple metastatic lymph nodes in the right retropharyngeal fossa, cervical level 1B-2B-3, and in the left level 4 lymphatic station. Also, in her left lung upper lobe, a new metastatic nodule was detected (Figure 1).

She was started on chemotherapy (cisplatin 75 mg/m²: 136 mg, 5-FU 1,000 mg/m²: 1,818 mg and cetuximab 400-250 mg/m²: 727 mg-454 mg) for 6 cycles. After chemotherapy, control PET/CT lung metastasis and metastatic nodes showed complete response, except the right retropharyngeal node.

60 Gy re-irradiation of the right retropharyngeal node and the primary tumor in 30 fractions was delivered after the completion of chemotherapy (8 months from recurrence) (Figure 2). Our patient’s total clivus dose was 135 Gy (Dmax). Cumulative re-irradiation cranial nerve doses were listed in Table 1.

PET/CT was performed after 3 months which reported a regression in nasopharyngeal recurrence and the right retropharyngeal lymph node. Yet, new metastatic lymph nodes were detected in the right upper and lower cervical lymphatic stations and left supraclavicular lymphatic stations. She was referred to systemic therapy again. After 4 months of chemotherapy (carboplatin 5 area under the curve: 600 mg and gemcitabine 1,000 mg/m²: 1,600 mg), she was admitted to the hospital with persistent neck pain, stinky breath, difficulty in swallowing food, speaking, and opening her jaw. In her neurological examination, right hypoglossal and facial nerve palsy was noted. In the control cervical MRI, there was no progression of a local tumor. Six months from re-irradiation; first, bulbar palsy was observed in our patient, MRI revealed RT-related osteonecrosis and platybasia due to anterior compression of the cervicomедullary junction (Figure 3).
Hemogram and biochemistry examinations showed elevated C-reactive protein (161), white blood cell count (11,900), and neutrophils (9.4). Antibiotics (amoxicillin 1,000 mg) were given to treat aspiration pneumonia for 4 weeks. The patient had Grade 3 dysphagia. When she attempted to swallow solid food particles, she aspirated them into her lungs. Nasogastric (NG) insertion or percutaneous endoscopic gastrostomy was necessary to properly feed the patient and prevent aspiration pneumonitis. She was referred to the endoscopy unit. The fluoroscopy examination showed severe impairment of swallowing. To identify the severity of stenosis, an oral contrast agent was delivered. During the procedure, due to the cranial neuropathy, the contrast agent could not progress distal to the pharyngoesophageal junction and totally aspirated into the tracheobronchial tree. A NG tube was inserted.

After 3 days from the NG tube insertion, she lost consciousness and was brought to the emergency department of our hospital. Cranial CT images revealed diffuse pneumocephalus and air in the whole ventricular system caused by the connection between the nasopharynx and the intracranial space. She died.

**DISCUSSION**

Re-irradiation is one of the main treatment options in local recurrence after curative treatment. If there is remaining chemoresistance after systemic treatment, re-irradiation can also be applied to the primary tumor or lymphatic area for patients with systemic metastases responding to the treatment. Re-irradiation is done using different techniques in these studies such as intracavitary brachytherapy, external RT, and stereotactic radiosurgery. The RT dose depends on the previous RT dose, the treatment area, and the area to be re-irradiated. Teo et al. found that the optimum dose for re-irradiation setting was 60 Gy and higher doses were associated with increased complications.

Osteonecrosis was observed in our patient when an MRI was performed. Cranial nerves were damaged, especially in the 9th and 12th cranial nerves motor deficits were detected. When cranial nerves were contoured in the planning system, we evaluated the cumulative radiation doses of irradiated nerves. Cranial nerve doses were listed in Table 1. For cranial neuropathy; hypoxia and radiation factors such as dosage and dose rates are important. Cranial nerves

![Table 1: Irradiated cranial nerve total Dmax doses and presumed recovered Dmax doses.](image)

<table>
<thead>
<tr>
<th>Right cranial nerve</th>
<th>Dmax (Gy)</th>
<th>Presumed recovered Dmax (Gy)</th>
<th>Left cranial nerve</th>
<th>Dmax (Gy)</th>
<th>Presumed recovered Dmax (Gy)</th>
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<tr>
<td>1R</td>
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<td>11-12R</td>
<td>77.2</td>
<td>56</td>
<td>11-12L</td>
<td>66.3</td>
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</tr>
</tbody>
</table>

![Figure 3: A) Clivus necrosis in T2-weighted magnetic resonance imaging; B) Cranial computed tomography images of pneumocephalus.](image)
are radioresistant, however, cranial nerves were affected due to the high cumulative dose after re-RT. The lower cranial nerve was affected in bulbar palsy, the most common symptoms presented were difficulty in swallowing, speaking, and chewing. These symptoms occurred due to the hypoglossal nerve (XII) and vagus nerve (X) damage.\textsuperscript{7} Firstly, bulbar palsy was observed in our patient, then necrosis was detected. The other side effect was necrosis. MRI has high sensitivity to detect necrosis. Before new MRI techniques, radiation-related cranial nerve palsy was difficult to diagnose. Nowadays, diffusion-weighted imaging MRI separates recurrence from radiation-related cranial neuropathy.\textsuperscript{8}

Skull base osteoradionecrosis was detected in our patient, causing platybasia, compression of the cervicomедullary junction, and cranial nerve deficits, particularly the 9\textsuperscript{th} cranial nerve, nervus glossopharyngeus. The patient was referred to the endoscopy unit, after 3 days from the NG tube insertion, osteonecrosis, fracture of clivus, and diffuse pneumocephalus were detected. We assume that the fracture might have been provoked during the insertion of the NG tube. In a review, 23 cases of intracranial NG tube placements were examined. Most of these patients were trauma patients with evident or suspected skull base fractures; so, in trauma patients, orogastric tube insertion is advised, not nasogastric.\textsuperscript{9}

For patients who received RT, the accumulating prescribed dose for the nasopharynx was more than 120 Gy. For the patients treated with IMRT, the dose for the nasopharynx was more than 80 Gy. Our patient’s cumulative clivus doses were 135 Gy (Dmax). Radiobiologically 40\% restitution of the first irradiation doses were accepted. Extrapolating from the study of Ang et al., the presumed new recovered doses are listed in Table 1.\textsuperscript{10} In the light of this literature, re-irradiation cumulative doses should be evaluated during planning.

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\textbf{Conflict of Interest}

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

\textbf{Authorship Contributions}

\textit{Idea/Concept: Ömer Erol Uzel; Design: Meltem Dağdelen, Ecem Demir; Control/Supervision: Meltem Dağdelen, Osman Kızılkılıç; Data Collection and/or Processing: Ecem Demir, Orkun Civan; Analysis and/or Interpretation: Ömer Erol Uzel, Osman Kızılkılıç; Literature Review: Meltem Dağdelen, Ecem Demir; Writing the Article: Ecem Demir, Meltem Dağdelen; Critical Review: Ömer Erol Uzel, Osman Kızılkılıç; References and Fundings: Meltem Dağdelen; Materials: Ecem Demir, Orkun Civan.}
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