# Intra-Parotid Recurrent Nasopharyngeal Carcinoma Following Intensity-Modulated Radiation Therapy: A Case Report

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## ABSTRACT

**INTRODUCTION:** Intra-parotid metastasis refers to the spread of cancerous cells from a primary tumor to the lymph nodes within the parotid gland. To our best knowledge, we report the first described case in the literature of a patient who received IMRT for nasopharyngeal carcinoma (UCNT) without sparing the parotid gland and still experienced a recurrence.

**CASE PRESENTATION:** A 57-year-old male patient of north African origin presented with a left parotid mass that had been evolving for 6 months. He was previously diagnosed with and treated for nasopharyngeal carcinoma 2 years prior to admission, with Intensity-Modulated Radiotherapy (IMRT) without sparing the parotid gland, as well as chemotherapy. Medical imaging was suggestive of recurrence of nasopharyngeal carcinoma and metastasis due to the patient's medical history. The patient benefited from a total parotidectomy; The histopathological analysis of the surgical specimen confirmed the presence of a poorly differentiated carcinoma (UCNT) with nodal metastasis.

**CONCLUSION:** Intensity-Modulated Radiation Therapy (IMRT) holds great promise as an alternative treatment option. However, it should be reserved for specific cases with minimal lymph node involvement, and always preceded by a thorough clinical and radiological examination.

**KEYWORDS:** Nasopharyngeal carcinoma, parotid neoplasms, neoplasm metastasis, lymphatic metastasis, intensity-modulated radiation therapy, IMRT

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## Introduction

In the field of otolaryngology, the management of nasopharyngeal cancers poses distinctive difficulties owing to the intricate anatomical structure and close proximity of vital elements. A notable solution that has emerged is intensity-modulated radiation therapy (IMRT), which enables precise and tailored administration of radiation doses to the tumor targets, while concurrently preserving adjacent healthy tissues,[1] hence permitting the modulation of radiation dosage to conform to the tumor's shape while minimizing exposure to surrounding healthy tissues and organs.[1,2]

"Metastasis" occurs when cancer cells detach from the primary tumor and travel through the lymphatic system or bloodstream to form secondary tumors in distant locations.[3] Intra-parotid metastasis refers to the spread of cancerous cells from a primary tumor to the lymph nodes within the parotid gland.[3]

To our best knowledge, we report the first described case in the literature of a patient who received IMRT for nasopharyngeal carcinoma (UCNT) without sparing the parotid gland and still experienced a recurrence.

## Case Presentation

A 57-year-old male patient of north African origin presented with a left parotid mass that had been evolving for 6 months. We noted a history of heavy tobacco use (30 pack year) and a previously diagnosed and treated for nasopharyngeal carcinoma 2 years prior to admission. Initially staged as T2N1M0, the nasopharyngeal carcinoma had been treated with Intensity-Modulated Radiotherapy (IMRT) without sparing the parotid gland and concurrent chemotherapy (Induction regimen with 3 cycles of cisplatin and gemcitabine, then cisplatin at 35 mg/m$^2$ weekly concomitant with radiotherapy) for 5 months

*Both authors contributed equally to this paper (co-first authors)

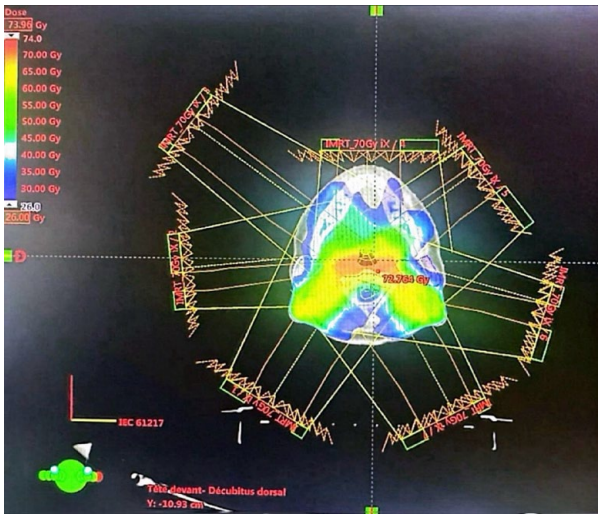


**Figure 1.** The Color-wash Image of the radiotherapy planning, demonstrating the non-sparing of the target parotid.

(last radiotherapy session 18 months prior to admission). The external radiotherapy doses reach up to 70 Gy in 35 fractions (One fraction a day, 5 fractions per week), delivered in static IMRT mode, in 7 weeks, without interruption [DVH details: Mean dose to left parotid 25.9 Gy; Mean dose to right parotid 25.7 Gy; Max dose L parotid 54 Gy; Max dose R parotid 69.3 Gy]. The Color-wash Image of the radiotherapy planning, demonstrates the non-sparing of the target parotid (Figure 1).

The patient was considered to be in complete remission until February 2023 and remained asymptomatic for 8 months until consulting for a slowly progressive parotid mass, which he had noticed a few weeks prior.

Upon clinical examination, a visible, non-painful, and firm mass was observed in the left pre-auricular region. The mass was adherent to the skin and showed signs of inflammation. The patient was classified based on Karnofsky performance status of 90%, and WHO performance status of 1.

Cervical ultrasound revealed 2 hypoechoic images in the left parotid gland suggestive of lymph nodes, and a hypoechoic upper left parotid image (26 mm × 14 mm) with a vascular signal on Doppler mode. While magnetic resonance imaging (MRI) showed no abnormalities in the nasopharyngeal area, a striking hypertrophy of the left parotid gland is evident, characterized by the presence of a nodular formation exhibiting indistinct and lobulated contours. This formation demonstrates discreet hyposignal on T1-weighted imaging, discreet hypersignal on T2-weighted imaging, and pronounced hypersignal on diffusion-weighted imaging, enhancing homogeneously following gadolinium injection (Figure 2). The diffusion restriction indicated a low Apparent Diffusion Coefficient (ADC) value (0.814, where a value below 1.2 suggests restriction, with a calculated rADC of 0.73). The lesion enhances uniformly and intensely, presenting a characteristic "*type C enhancement curve*."

At the admission, positron emission tomography (PET) revealed intense hypermetabolism in the left parotid gland (SUV = 47.73), as well as lymph node involvement in the cervical, mediastinal, and to a lesser extent the axillary regions (Figure 3a and c).

Based on these findings, 3 potential diagnoses were considered: recurrence of nasopharyngeal carcinoma (secondary parotid location), primitive parotid cancer, and a secondary location of another cancer. During the multidisciplinary meeting, it was decided to surgically approach the tumor with recurrent nerve monitoring, to facilitate a total parotidectomy with lateral neck dissection of IIA/IIB, III and IV regions.

Following the surgery, the patient's postoperative condition was considered stable, although a salivary fistula was present and managed with a compressive dressing. The histopathological analysis of the surgical specimen confirmed the presence of a poorly differentiated carcinoma (UCNT) with nodal metastasis.

The patient received a total of 6 courses of chemotherapy (Carboplatin-paclitaxel), 2 months after surgery. A follow-up positron emission tomography (PET) scan performed 6 months after surgery revealed regression of left parotid and mediastinal/axillary lymph node hypermetabolism (SUV < 6; Figure 3b and d).

## Discussion

To our knowledge and up to date based on the Medline and Scopus databases, this is the first case report about a patient who had a recurrence of a carcinoma after IMRT without sparing the parotid gland.

Parotid gland tumors are abnormal growths that develop within the largest salivary gland, located near the ear. MRI is particularly valuable due to its ability to provide detailed images of the soft tissues in and around the parotid gland. However, the gold standard for definitive diagnosis remains anatomopathological findings.[4]

Nasopharyngeal tumors are a group of neoplasms that develop in the nasopharynx; One type of the nasopharyngeal tumors group is the Undifferentiated Carcinoma of Nasopharyngeal Type (UCNT), which is a highly aggressive and poorly differentiated malignancy.[5] Despite being localized initially, UCNT has a strong tendency to metastasize to regional and distant sites. The most common predilection sites for metastasis in UCNT include regional lymph nodes, such as the cervical lymph nodes, as well as distant sites like the bones, liver, and lungs.[5] Although the metastasis of nasopharyngeal tumors to the parotid gland, along with its lymph nodes, is a relatively infrequent occurrence, it is important to acknowledge that these tumors have the capability to spread to distant sites. This metastatic involvement can potentially result in the infiltration of the gland's parenchyma, connective tissue, or the adjacent lymph nodes.[6]

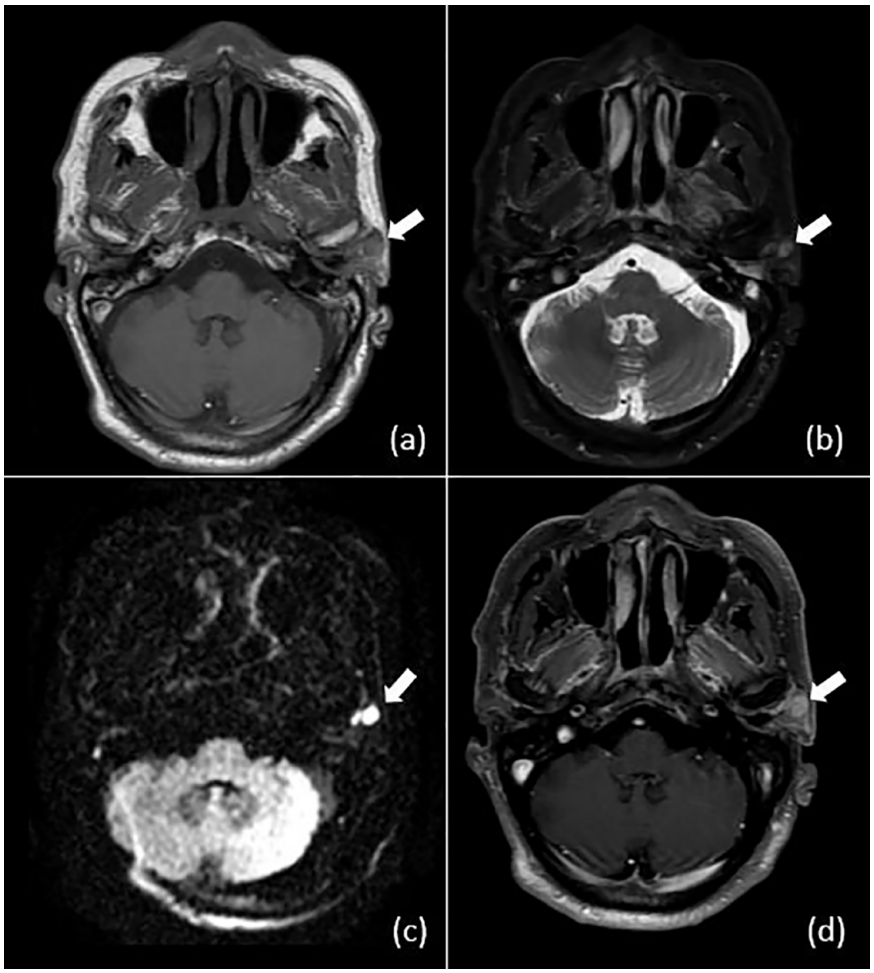


**Figure 2.** An axial section passing through the base of the skull of a patient undergoing treatment for nasopharyngeal carcinoma, showcasing various imaging sequences: T1 fast spin-echo (a), T2-weighted (b) with fat signal saturation, diffusion-weighted imaging (c), and T1-weighted with fat saturation post-gadolinium injection (d).

Radiation therapy is a highly effective method for inhibiting tumor growth and is widely used in clinical settings. It damages the vital biomolecules (especially DNA) of cancer cells and eventually promotes them to different cellular death processes, including apoptosis, necrosis, and necroptosis, among others.[7] Meanwhile, a fraction of cancer cells exhibit resistance against the radiation effects.[8,9]

To date, the determinant factors of response to radiation have been presented as 6 terms that start with the letter R,[10,11] including Repair (DNA damage repair efficacy), Re-assortment (cell cycle stage), Repopulation (proliferation rate), Reoxygenation (the sensitivity to radiation increases in well oxygenated tissues), Radiosensitivity (intrinsic and individual radiosensitivity of cancer cells), and Reactivation (immune response after radiation).[11] An interesting study suggested that the tumor microenvironment might be the seventh R[7].

Furthermore, studies showed that tobacco products have a negative impact on fibroblasts. Oxidative stress is one of the important causes of abnormal cell function caused by these products.[9,12] On the other side, nicotine induces Human embryonic lung fibroblasts-to-myofibroblasts transdifferentiation through a mechanism involving downregulation of lipogenic human parathyroid hormone-related protein (PTHrP)-mediated, cAMP-dependent PKA signaling pathway.[12,13] Cigarette smoke containing other carcinogenic components of tobacco (NNK and NNN) can also activate surrounding epithelial cells and alter the secretion of TGF-β1 or release of extracellular vesicles to promote myofibroblasts differentiation.[12,14] Moreover, it's been observed that tobacco induced autophagy in different kinds of fibroblasts like CAFs of breast cancer and human lung fibroblasts.[15,16] Exposition to cigarette smoke extract can up-regulate the expression of autophagy-related protein (LB3 and p62) in fibroblasts and promote the secretion of IL8.[16] Also, Tobacco products affect the secretion of proteases in fibroblast, induce metabolism reprogram, affects the secretion of cytokines, chemokines and growth factor in fibroblasts.[12] For instance, the metabolism cross talk between fibroblasts and cancer cells has been considered as a potential therapeutic target. Tobacco smoke not only promotes oncogenesis, but the literature also links it

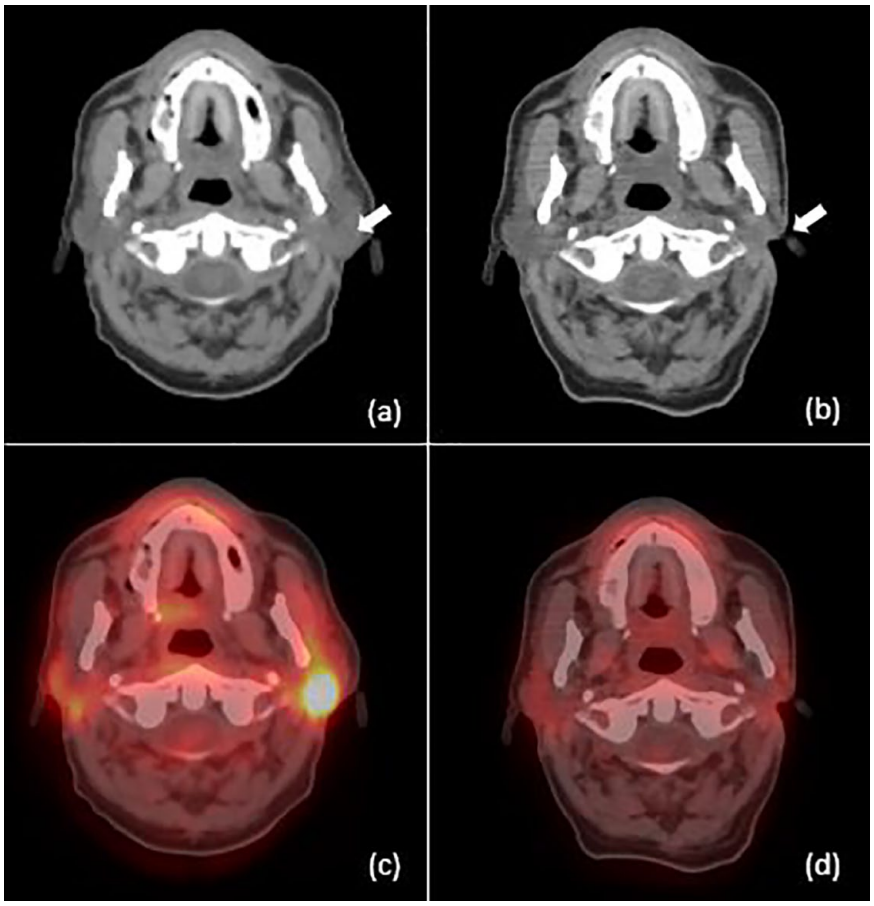


**Figure 3.** Pre and postoperative positron emission tomography (PET), showing the evolution of left parotid hypermetabolism. (a) Preoperative CT axial section. (b) Postoperative CT axial section. (c) Pre-operative PET-CT image. (d) Post-operative PET-CT image. [white arrow = left parotid mass].

with different other areas like mitochondrial function, oxidant production/signaling, mtDNA copy, and mtDNA mutagenesis impact tumorgenicity, metastasis and resistance to anti-cancer drugs.[8,9,17-19]

In the literature, several articles have shown a recurrence of nasopharyngeal cancer with IMRT (intensity-modulated radiation therapy) when the parotid gland was spared, they showed a recurrence of nasopharyngeal cancer when the parotid gland was spared, and the presence of multiple N2 lymph nodes increases the risk of microscopic lesions. The data suggests that radiation should perhaps be broader and include the parotid gland.[20,21] Interestingly, in another study it was shown that among the patients' sample, the reduction of doses to protect the parotid gland was questioned, and thus it was hypothesized that it could be responsible for an inadequate dosage for microscopic tumor cells.[22]

In our case, IMRT included irradiation of the parotid gland. The initial imaging did not show any changes in the structure of the parotid gland, which posed a diagnostic problem between a recurrence of nasopharyngeal cancer or a primary parotid cancer. This necessitated a total parotidectomy, which revealed a recurrence of nasopharyngeal cancer.

Given the evolving landscape of radiation oncology and the potential implications for treatment outcomes and patient well-being, the question arises: should we continue to spare the parotid glands as organs at risk in IMRT for nasopharyngeal cancer? This question prompts further investigation into the optimal balance between tumor control and sparing critical structures, taking into account individualized patient factors and long-term functional outcomes. We believe that while the debate surrounding parotid sparing in IMRT for nasopharyngeal cancer continues, evidence suggests that sparing the parotid glands benefits the majority of patients by reducing radiation-related morbidity.

## Conclusion

In conclusion, Intensity-Modulated Radiation Therapy (IMRT) holds great promise as an alternative treatment option. However, it should be reserved for specific cases with minimal lymph node involvement, and always preceded by a thorough clinical and radiological examination. It is imperative to ensure rigorous evaluation and patient selection to maximize the benefits of IMRT while minimizing potential risks. This approach ensures that IMRT is utilized effectively and efficiently, offering improved outcomes for patients in need of precise and targeted radiation therapy.

## Author Contributions

Abderrahim Bourial, Zineb Dahbi, Amal Hajjij took part in taking care of the patient, researching the bibliography, the design, and writing the article. Othmane Nourallah Laraqui

took part in researching the bibliography, the design and writing the article. Chirwa Abdillahi Mahamoud contributed in the creation and analysis of medical images. All authors approved the final manuscript.

## Availability of Data and Material

On request, email the corresponding author.

## Ethical Approval

Not applicable.

## Consent to Participate

Written and informed consent taken.

## Consent for Publication

Written and informed consent taken.

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## Code Availability

Not applicable.

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