Case Report

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Hypofractionated Radiosurgery Re-irradiation in Nasopharyngeal Recurrence after Complex Treatment

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Abstract

The clinical case presented by us with locally advanced T4 nasopharyngeal carcinoma with intracranial infiltration and extensive parapharyngeal spread, despite intensity modulated radiotherapy (IMRT) up to 70 Gy, developed an inoperable local recurrence after two years.

Our goal is to track the radiobiological changes in the area of re-irradiation, which are evident both clinically and pathohistologically from biopsies after radiosurgery and from imaging studies/with and without contrast CT and PET/CT.

The conclusion is that the extremely high radiosensitivity of nasopharyngeal carcinoma requires a strict individual assessment of the dose delivered by hypofractionated radiosurgery. It is of great importance to respect the constraints of all nearby normal structures.

Keywords: Nasopharyngeal carcinoma, Local nasopharyngeal recurrence, Re-irradiation, Hypofractionated radiosurgery, PET/CT

1. Introduction

Although contemporary standard management of nasopharyngeal carcinoma (NPC) has improved local control of disease, local failure still remains a concern, especially in advanced T4 disease [1,2]. Approximately 5–15% of patients will finally experience local recurrence after primary definitive therapy [3]. For patients who are inoperable or unwilling to undergo surgery, comprehensive treatment based on radiation therapy is usually recommended [4]. The clinical case presented by us with locally advanced T4 nasopharyngeal carcinoma with intracranial infiltration and extensive parapharyngeal spread, despite intensity modulated radiotherapy (IMRT) up to 70 Gy, developed an inoperable local recurrence after two years. Currently, high-level evidence-based medical research on re-irradiation is lacking [5]. We present this rare clinical case to follow the radiobiological changes in the area of re-irradiation, which are evident both clinically and pathohistologically from biopsies after radiosurgery and from imaging studies/with and without contrast CT and PET/CT.

2. Clinical Case

In November 2023, a 64-year-old woman was diagnosed with locally advanced nasopharyngeal carcinoma- cT4N1M0. The histological result from the biopsy was non-keratinizing undifferentiated nasopharyngeal carcinoma, WHO type 2B/ lymphoepithelioma of Schminke – Regaud. MRI in November 2023 revealed a T1 iso- and T2 moderately hyperintense formation in the area of the right Rosenmuller fossa towards the roof of the nasopharynx with a suspicious small left-sided component, measuring 3.5 cm/ 3 cm/ 4 cm. Anteriorly, the lesion extends to the right choana, anteriorly and posteriorly it involves the levator muscle and the tensor veli palatini muscle, the pharyngo-basilar fascia with invasion of the parapharyngeal fat tissue, dorsocraniomedially there is involvement of the right petrous apex adjacent to the foramen lacerum. Conclusion- Nasopharyngeal carcinoma involving the right pharyngeal recess with invasion of the skull base/right petrous apex, with involvement of the levator and tensor veli palatini muscles, as well as the splenius capitis and longus capitis muscles. Metastatic upper posterior jugular ipsilateral / level II b / lymphadenopathy on the right (Fig 1-3). Mesopharyngoscopy shows an enlarged and pushed forward and medially right palatine tonsil and the right part of the soft palate. Rhinoscopy - edematous nasal mucosa with a scanty amount of blood clots. Nasopharyngoscopy - In the nasopharynx on the right, an exophytic tumor formation is visible, involving the posterior and right part of the nasopharyngeal space. Tumor spread visible from meso- and nasopharyngoscopy is clearly visible on planning CT (Fig 4). The patient is staged as cT4cN1M0 according to the 9th version of the world international TNM classification of nasopharyngeal carcinoma. From 13.12.2023 to 13.02.2024, the patient underwent combined chemoradiotherapy with weekly infusions of Cisplatin 40 mg/m2. The radiation therapy was Intensity modulated using the VMAT technique in the area of tumor growth with a safety zone up to a total dose of 70 Gy, as well as the metastatic lymph nodes on the right up to a total dose of 66 Gy. Bilateral cervical in the area of the cervical lymph nodes - Ib and II-IV level up to a total dose of 60 Gy and V level up to 54 Gy (Fig 5 and Fig 6 A/B). After 6 months of RT, a control PET/CT scan was performed, which reported local tumor control (Fig 7). The next control PET/CT scan in March 2025 detected increased metabolic activity with SUV max 14.2 in the right nasopharyngeal at the site of the previously identified tumor localization (Fig 8), therefore a biopsy was performed with data for recurrence of non-keratinizing undifferentiated nasopharyngeal carcinoma - type 2B according to WHO. From 27 05 2025 to 30 05 2025, radiosurgery was performed in the area of local tumor recurrence using 4 fractions of 6 Gy to a maximum dose of 24 Gy (Fig 9, Fig 10 and Fig 11). After 1.5 months / 14.07.25, a biopsy was performed with the following result: Material in front of the torus tubarius; from the right posterior pharyngeal wall and from the Rosenmuller fossa - chronic purulent inflammatory process with hematoma. After antibiotic therapy, a new biopsy was performed /12.08.25 with the result: Material No 1 and No 2 from an unevenness behind and above the torus tubarius on the right- Squamous epithelium with keratosis and papillomatosis, underlying stroma with fibrosis; Material No 3 from the upper edge of an ulcer - Ulcerative defect with necrotic changes. On 11. 09. 2025, PET/CT revealed data for a partial morphological response to the treated local recurrence in the nasopharynx on the right and data for regional progression of the disease with the presence of secondary cervical lymph nodes bilaterally. PET/CT after 3 months from the RS - The tumor recurrences has partially reduced dimensions /previously 32x36 mm, now 28x24 mm/ and metabolic activity is intense only in its two poles with SUV max 9.79 /previously with SUV max 14.2/ with an enlarged central hypometabolic necrotic zone and regional progression of the disease with the presence of secondary cervical lymph nodes bilaterally (Fig 12). The Oncology Committee considered continuing the treatment with polychemotherapy according to the scheme Gemcitabine 750 mg/ m2 on the first, eighth and fifteenth days together with Cisplatin 75 mg/ m2 on the first day at an interval of 21 days. On 24.10.2025 after 1 course of chemotherapy, a control CT scan was performed, which reported 30% local tumor control (Fig 13). Before entering the second course of chemotherapy, the patient reported severe headaches that were not responding to nonsteroidal anti-inflammatory medications, the presence of yellow purulent nasal discharge, and severe fatigue. After the necessary antibiotic treatment and opiate pain medication, the patient continues her prescribed chemotherapy. On 31.10.2025, after 2 courses of chemotherapy, inflammation of the middle ear was detected, which was treated with antibiotics. On 10. 11. 2025, a control CT scan with contrast was performed, which showed a large tissue necrotic defect in the area of reirradiation (Fig 14). By the end of December 2025, 4 courses of chemotherapy were performed according to the above-described scheme. On 15. 01.2026, a control PET/CT was performed, which reported data for additional morphological and metabolic reduction of the treated local recurrence of the nasopharynx on the right with the formation of a large defect and necrosis. Complete response of the secondary lymph nodes, without data for dissemination (Fig 15).

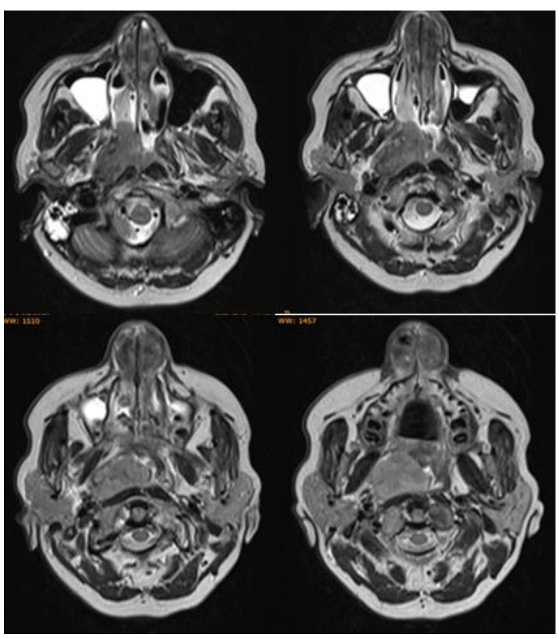

Figure 1: MRI from November 2023 - Axial scans showing locally advanced nasopharyngeal carcinoma with extensive parapharyngeal spread to the right.

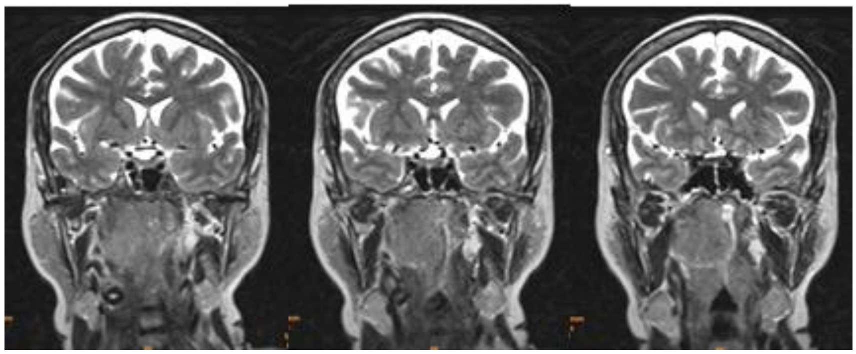

Figure 2: MRI from November 2023 - Frontal scans showing locally advanced nasopharyngeal carcinoma with extensive parapharyngeal spread to the right.

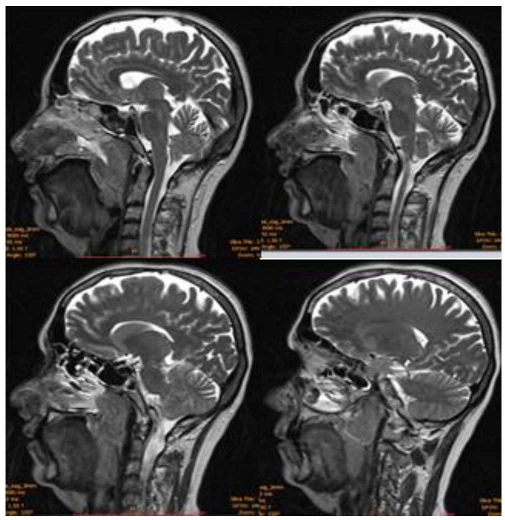

Figure 3: MRI from November 2023- Sagittal scans showing locally advanced nasopharyngeal carcinoma with extensive parapharyngeal spread to the right.

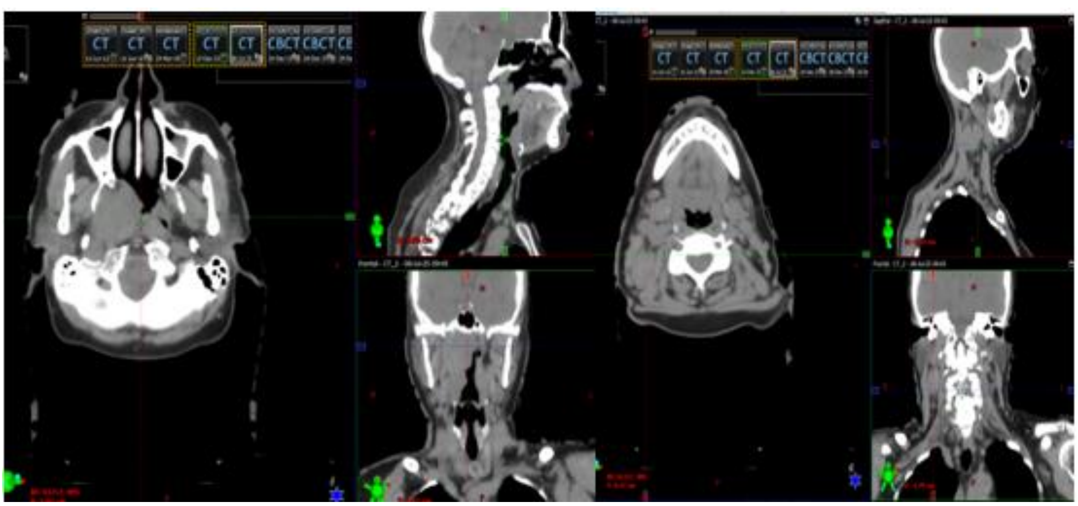

Figure 4: Planning CT scans from December 2023 before starting combined radiation-chemotherapy- nasopharyngeal carcinoma / cT4cN1M0.

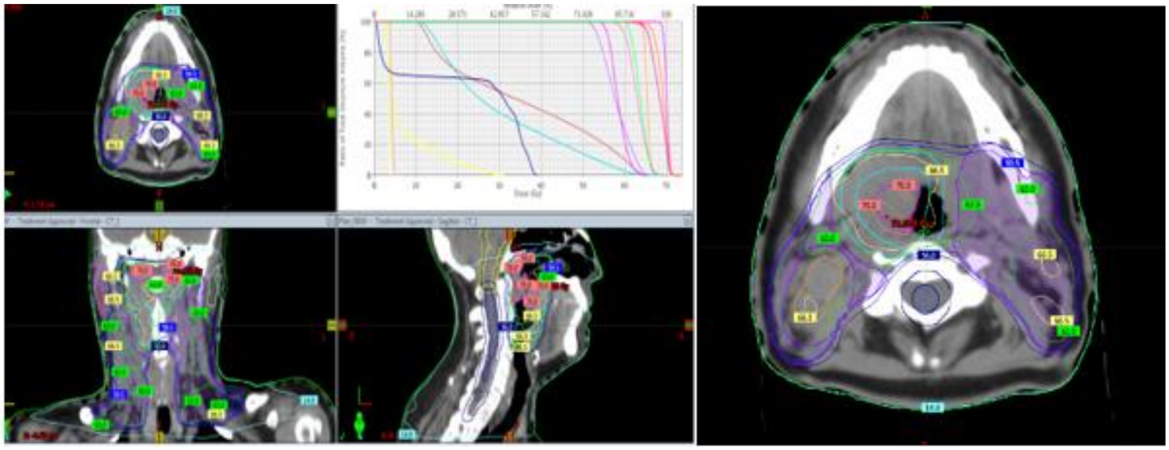

Figure 5: Intensity modulated radiotherapy using the VMAT technique in the area of tumor growth with a safety zone up to a total dose of 70 Gy -66Gy, as well as the metastatic lymph nodes on the right up to a total dose of 66 Gy. Bilateral cervical in the area of the cervical lymph nodes - Ib and II-IV level up to a total dose of 60 Gy and V level up to 54 Gy.

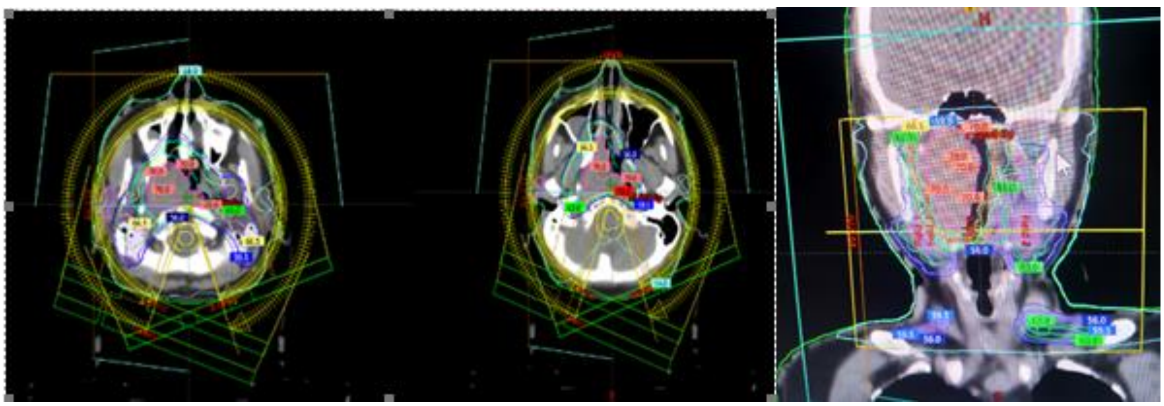

Figure 6A: Intensity modulated radiotherapy using the VMAT technique.

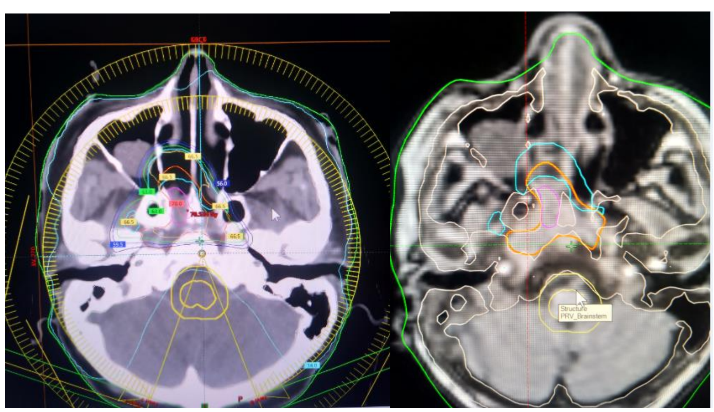

Figure 6 B: Intensity modulated radiotherapy using the VMAT technique in the area of the skull base/ CTVp 66 Gy.

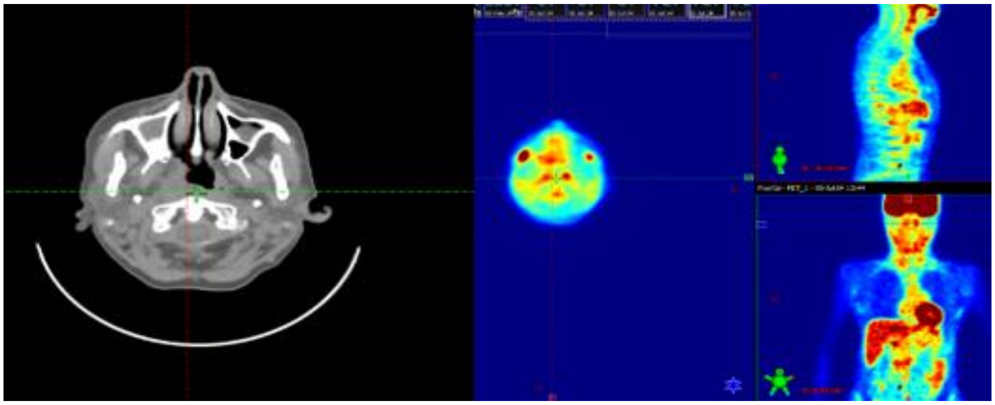

Figure 7: Control PET/CT scan after 6 months of IMRT with local tumor control without regional and distant metastases.

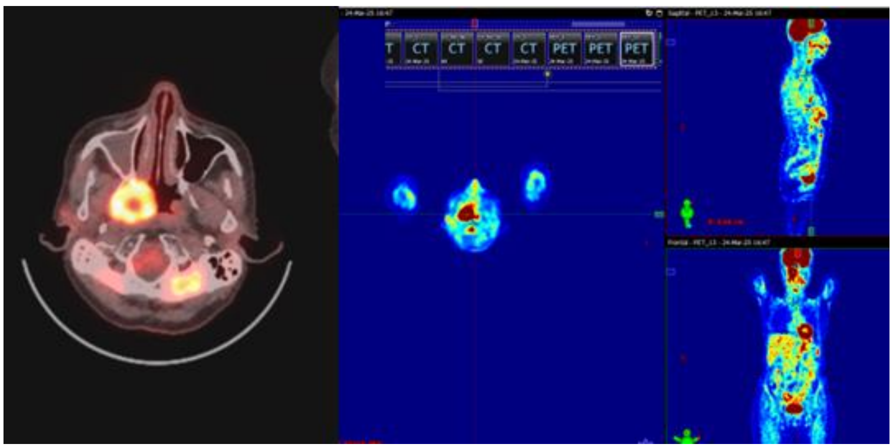

Figure 8: PET/CT scan from March 2025 detected increased metabolic activity in the right nasopharyngeal area at the site of the previously identified tumor without regional and distant metastases.

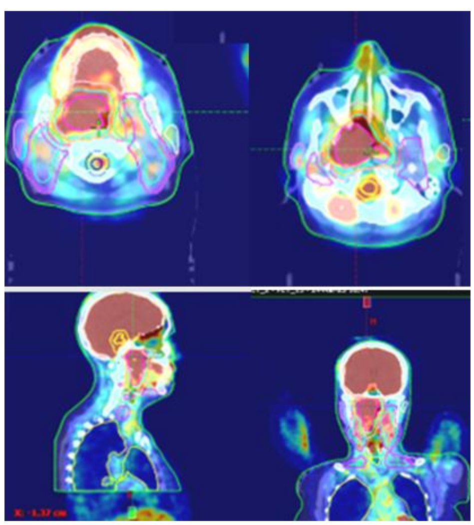

Figure 9: Fusion between PET/CT with local recurrence and planning CT with target tumor volumes from definitive IMRT, where 2 years ago we irradiated with 70 Gy.

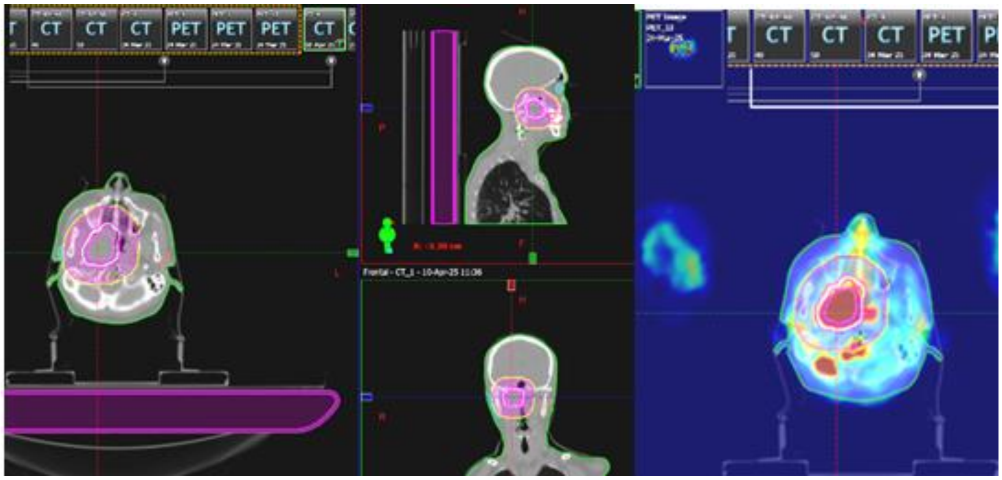

Figure 10: Contouring of the target volumes GTV and PTV, after overlaying the planning CT with the actively accumulating area/local recurrence from PET/CT.

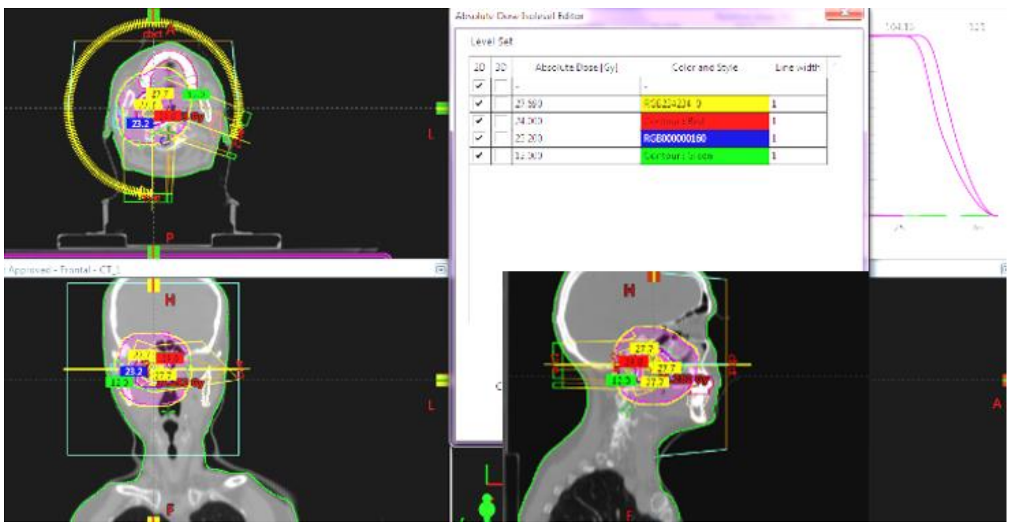

Figure 11: Radiosurgery of recurrence using the VMAT method using 4 fractions of 6 Gy. In PTV the dose distribution is as follows - from 115% (27.6 Gy) - 100% (24 Gy) to 88% (21.2 Gy).

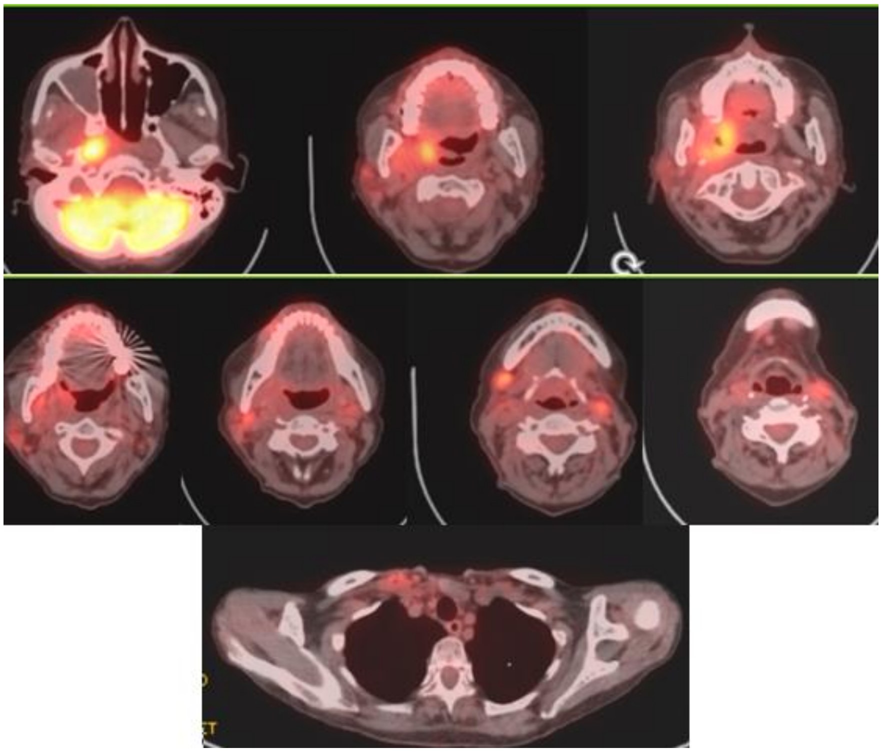

Figure 12: PET/CT 3 months after radiosurgery with partial response to the treated local recurrence in the nasopharynx on the right and data for regional progression of the disease with the presence of secondary cervical lymph nodes bilaterally.

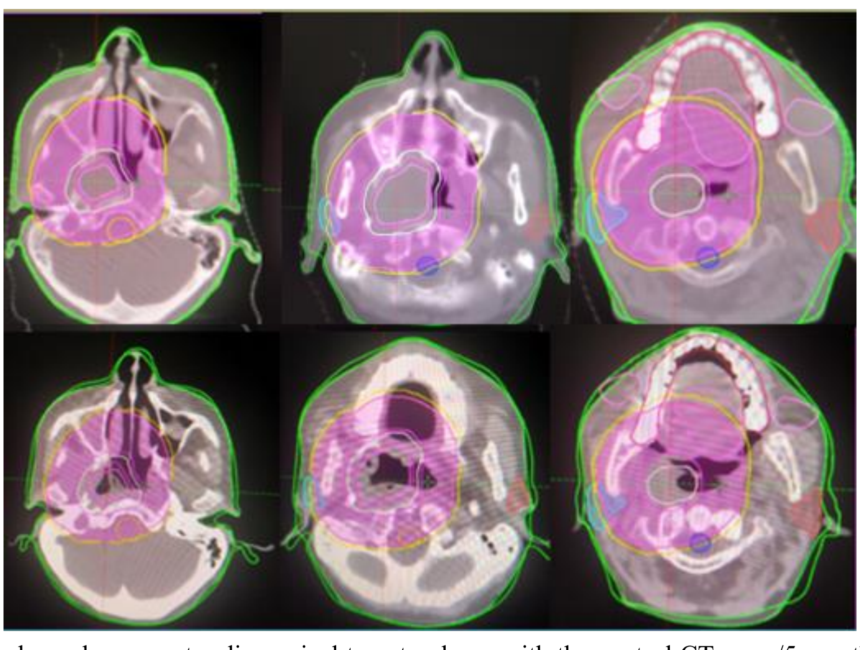

Figure 13: Fusion of the planned recurrent radiosurgical target volume with the control CT scan /5 months after reirradiation/, which reported a 30% reduction in recurrence.

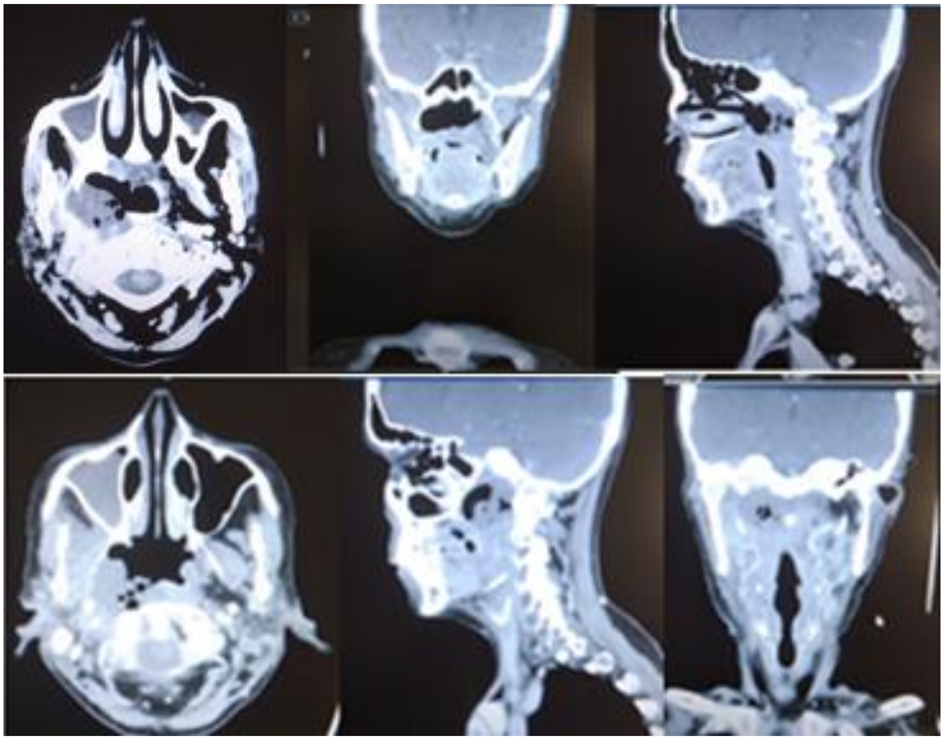

Figure 14: Control computed tomography with contrast from 10.11. 2025 with a large tissue necrotic defect in the area of re-irradiation.

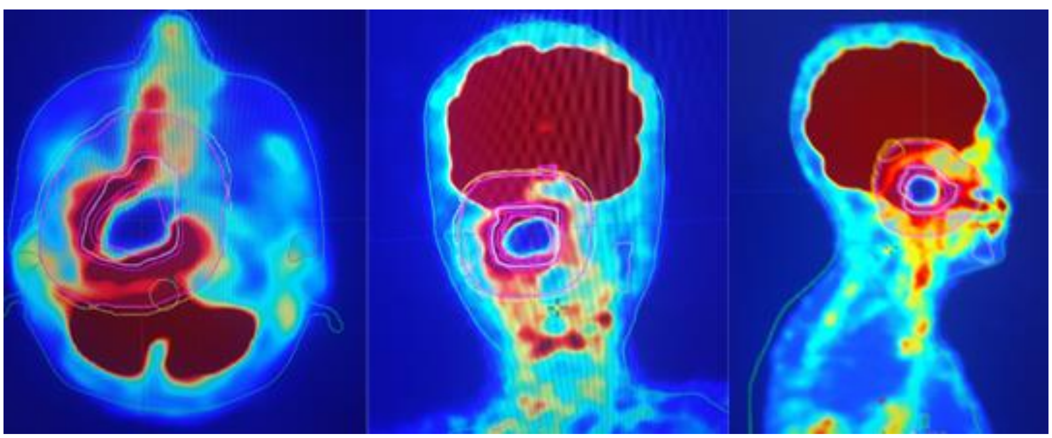

Figure 15: Control PET/CT from 15.01.2026 after 8 months from radiosurgery with data for additional morphological and metabolic reduction of the treated local nasopharyngeal recurrence on the right with the large defect and necrosis. Complete response of the secondary lymph nodes, without evidence of dissemination.

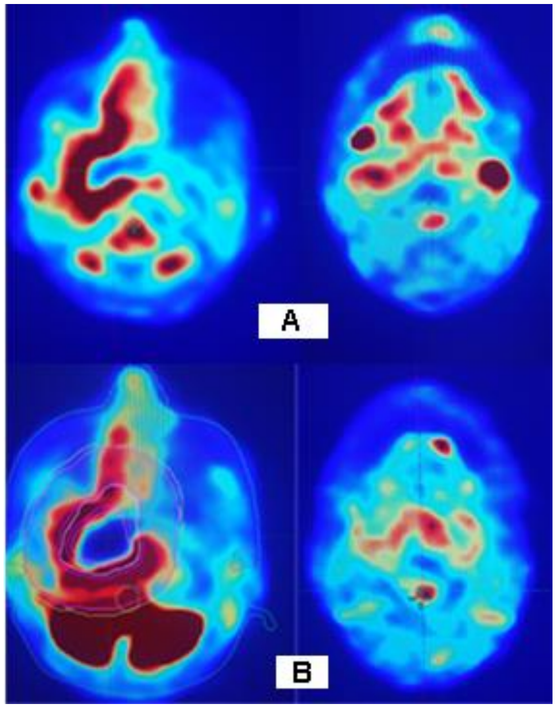

Figure 16: Comparison of PET/CT images A/ after 3 months of re-radiosurgery and B/ after 8 months of re-radiosurgery in the area of local recurrence and adjuvant chemotherapy in the area of metastatic cervical lymph nodes.

3. Discussion

According to Ninth Version of the AJCC and UICC Nasopharyngeal Cancer TNM Staging Classification primary T4 carcinoma includes the following criteria: Tumor with any of the following extension/involvement:(1) intracranial extension; (2) unequivocal radiological and/or clinical involvement of cranial nerves; (3) hypopharynx; (4) orbit (including inferior orbital fissure); (5) parotid gland; (6) extensive soft tissue infiltration beyond the anterolateral surface of the lateral pterygoid muscle [6]. Based on MRI, which best defines soft tissue tumor spread, the presented clinical case is cT4 with parapharyngeal involvement (Figures 1, -3), which determines the poor prognosis with expected local recurrence. Approximately 10% of patients develop recurrent disease, and the median recurrence period is approximately 30 months, with 85% of local recurrences being detected within 5 years [7, 8]. Radiation therapy (RT) is the mainstay treatment for nasopharyngeal carcinoma, as it is highly sensitive to radiation [9]. The nasopharyngeal localisation and high doses of RT and chemotherapy (Ch) given for primary radical combined therapy make retreatment difficult [10,11]. Advanced MRI (diffusion, perfusion) plays a growing role, especially in neuro-oncology and pelvic tumours [12]. Contouring of tumor volumes in which high radiation doses of 66-70 Gy are delivered after fusion with MRI is essential. Nasopharyngectomy can be performed for only patients with T1-2 recurrences with no distant metastases [13,14]. For patients with locally recurrent head and neck cancer, re-irradiation is a feasible therapeutic option. The total dose at re-irradiation improves overall survival. Therefore, re-irradiation with curative intent should only be applied if a sufficient total dose of ≥46 Gy can be given [15]. Stereotactic radiosurgery (SRS) has been accepted as an effective model with high dose delivery option; however, high risk of toxicity remains a challenging problem [16,17]. The most of the contemporary linacs fulfill the recommendations of the ICRU 91 for SBRT treatment [18]. In reirradiation, it is necessary to consider controversies, including the definition of a clinical target volume (CTV), the addition of systemic therapy, the choice of RT regimen, and the normal tissue protection [19]. in serial-architecture tissues (spinal cord, digestive tract, peripheral nerves etc.), the destruction of an organ subunit by an excessively high dose will affectits downstream functioning (like damaging one of the links in a chain) [12]. Li et al. [20] reported the development of a prognostic model for survival in patients who undergo salvage re-irradiation (re-RT). This model uses several covariates (ie, age, rGTV, prior toxicities/ grade 3, rT stage, and re-RT EQD2) to classify patients as high or low risk [21]. According to this prognostic model, our patient appears to be at low risk with a score of 224.8 and hypofractionated radiosurgery (HF RS) is appropriate. SRT with its characteristic dose conformity and precision setup is a potentially advantageous modality with effective tumor control for low volume recurrent nasopharyngeal carcinoma [9]. Most authors applying hypofractionated re-radiosurgery (HF re-RS) use 3–6 fractions with a fraction dose of 4.25–15 Gy [17,22, 23]. After fusion between local recurrence PET/CT and planning CT with primary target tumor volumes from definitive IMRT, where 2 years ago we irradiated with 70 Gy, it is seen that the recurrence is exactly in this area (Figure 9). The first question we asked ourselves was about the cause of the recurrence, and the answer was the extensive parapharyngeal spread to the right and the tumor infiltration of the skull base, which determines the high recurrence risk (Figure 2). Figure 6 B shows the target volume in the skull base area CTVp, irradiated with 70- 66 Gy., Due to the lack of another treatment alternative, as well as a relatively small recurrence volume of 27 ml, we decided to perform re-irradiation using HFRS with 4 fractions of 6 Gy to a maximum dose of 24 Gy (Figure 10 and 11). The alpha/beta ratio in nasopharyngeal carcinoma is 10-16Gy. From the first IMRT in the primary nasopharyngeal tumor with a daily dose (DD) of 2.12 Gy, a dose equivalent to 2 Gy (EQD2) of 70.4 Gy was realized, which is biologically effective dose (BED) of 79.8Gy. Intensity-modulated radiotherapy recommends that dose–volume histograms should be used for dose reporting. Thus, it is recommended for therapeutic volumes to report D50 % (corresponding to the prescribed dose), D98 % (representative of the minimum absorbed dose) and D2 % (representative of the maximum absorbed dose). Any other relevant dose level can be used, which is often the case for D95 %. The mean dose to organs at risk should be recorded, as well as D2 % [12]. It is known that after an interval of 2 years between irradiation of the primary tumor, 50% of the realized dose is reduced, which means that the residual dose equivalent to 2 Gy (EQD2) from the primary radiotherapy is 35 Gy, which corresponds to a biologically effective dose (BED) of 39.98 Gy. From the re-irradiation with HFRS (four fractions of 6Gy) in the recurrent tumor EQD2 29.6 Gy and BED 33.6Gy were realized. The total cumulative mean doses in the recurrent tumor volume from both radiation treatments was sum. EQD2 64,6 Gy and sum. BED 73.58Gy.

In radiobiology, the concept of residual dose (or "dose memory") refers to the amount of biological damage that remains in tissues after a period of recovery, which must be considered if re-irradiation is required. After a radical dose of 70 Gy, the residual dose realized in the tumor and surrounding tissues in the second year following irradiation is typically estimated at 50% of the initial dose (approximately 35 Gy). In the second year, it is widely accepted in clinical models that roughly 50% of the biological effect of the first treatment remains. For the tumor specifically, "residual dose" is often a theoretical calculation used to determine the safe "top-up" dose during re-irradiation. If the tumor recurs, it is treated as having zero effective dose for the purpose of cell killing, but the 35 Gy (50%) residual limit is often applied to the surrounding healthy "stroma" to prevent necrosis. Critical normal organs and structures near this volume are right parotid gland, the mucosa of the pharynx and nasopharynx, and the right internal carotid artery. The masseter muscles and those affected by recurrence such as the levator and tensor veli palatini muscles, as well as the splenius capitis and longus capitis muscles, are also critical structures in which to expect late radiation changes due to tumor decay after RS (Table 1).

Volume of the realized dose	mean dose (Gy) from IMRT	After 2 years from IMRT residual mean dose (Gy)	HFRS mean dose (4x6 Gy) (Gy)	Total mean D of residual dose from the first IMRT + the mean D from second HFRS (4x6 Gy)	Radiobiological tissue and organ changes in the irradiated volume
right parotid gland	29,9	14,95	5,1	20,0	xerostomia - II degree
mandibular joint (masseter muscles)	48,9	24,45	2,3	26,7	trismus - II degree
right internal carotid artery	65,36	32,68	4,47	37,15	No bleeding and stenosis after 5 months of HFRS
right submandibular salivary gland	63,7	31,85	4,47	36,32	xerostomia - II degree
the levator and tensor veli palatini muscles / constrictor pharyngeal muscles	68,9	34,45	26,9	61,35	dysphagia with difficulty eating/ weight loss of over 15 kg
nasopharyngeal and pharyngeal mucosa	68,9	34,45	26,7	61,15	mucositis -III degree

Table 1: Realized mean doses from the first radiotherapy (IMRT) summed with the residual mean doses after 2 years and with those from hypofractionated radiosurgery (HFRS) that led to late radiation reactions in nearby normal tissues and organs.

It is necessary to specify that the realized high sum mean D in the pharyngeal muscles (61,35 Gy) and, pharyngeal and nasopharyngeal mucosa (61,15 Gy) are located in the volume of the primary nasopharyngeal tumor and in the volume of tumor recurrence. The right submandibular salivary gland and the right internal carotid artery (sum mean D 36.32 Gy and sum mean 37.15 Gy) are located in the primary volume of the regional metastatic lymph nodes on the right and 2 cm away from the optimal PTV from HFRS of the local recurrence. Even after the first IMRT, it was evident that due to the advanced primary T4 tumor with extensive parapharyngeal spread, the constraints for both parotid and submandibular salivary glands (Dmean < 26 Gy); for the pharyngeal constrictor muscles on the right (Dmean < 55 Gy); for the oral and pharyngeal mucosa (Dmean < 30 Gy), as well as for the right internal carotid artery (Dmean < 40 Gy) were exceeded, which caused the radiation changes - xerostomia, dysphagia and radiation mucositis (**Table 1**). After summing the residual D mean, which after 2 years is reduced by 50% from the first IMRT + max EQD2 from second HFRS (4x6 Gy) at alpha beta ratio 3 Gy for normal tissues, even higher total doses are reported in the above-mentioned critical structures, which causes the mentioned radiation reactions (**Table 2**).

Volume of the realized dose	**mean dose (Gy) from IMRT**	**After 2 years from IMRT residual mean dose (Gy)**	**HFRS max dose (4x6 Gy)**	**Total mean D of residual dose from the first IMRT + max EQD2** ***from second HFRS (4x6 Gy) at alpha beta ratio 3 Gy***	**Radiobiological radiation-induced normal tissues early and late effects**
right parotid gland	29,9	14,95	13	14,95+23,4= 38,35	xerostomia - II degree
mandibular joint (masseter muscles)	48,9	24,45	20	24,45+37,08= 61,53	trismus - II degree
right internal carotid artery	65,36	32,68	13,59	32,68+24,46= 57,14	No bleeding and stenosis after 5 months of HFRS
the levator and tensor veli palatini muscles / constrictor pharyngeal muscles	68,9	34,45	26,9	34,45+48,42= 82,87	dysphagia with difficulty eating/weight loss of over 15 kg
nasopharyngeal and pharyngeal mucosa	68,9	34,45	26,7	34,45+48,06= 82,51	mucositis -III degree

Table 2: Realized mean doses from the first radiotherapy (IMRT) summed with the residual mean doses after 2 years and with max EQD2 from second HFRS (4x6 Gy) at alpha beta ratio 3 Gy that led to late radiation reactions in nearby normal tissues and organs.

Regarding the achieved local tumor control of the local nasopharyngeal recurrence after radiosurgery, Figure 16 A/ B shows the large necrotic tissue defect after 3 and 8 months from the completion of the re-irradiation. Tumor necrosis after HFRS develops gradually over a period of 3-8 months and is combined with purulent acute inflammation of the surrounding tissues, requiring intensive antibiotic treatment. Due to lymphonodular progression, proven 3 months after completion of radiosurgery for local recurrence, against the background of pronounced radiation reactions, curative polychemotherapy was performed, which achieved regional tumor control (Figure 16 B).

4. Conclusion

From the presented rare clinical case of local recurrence after combined definitive IMRT of locally advanced nasopharyngeal carcinoma with extensive parapharyngeal spread, we can draw the following conclusions:

1. The scheme of hypofractionated radiosurgery should be evaluated individually after risk assessment according to the model of Li et al. [20].
2. After a 2-year interval of high-dose percutaneous irradiation of the primary tumor, HFRS is tolerated without problems, but is followed by radiation reactions in normal tissues and organs close to the tumor recurrence.
3. Tumor necrosis after HFRS develops gradually over a period of 3-8 months and is combined with purulent acute inflammation of the surrounding tissues, requiring intensive antibiotic treatment.

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