

Late Healing Results Three Years after Radiotherapy of Local Advanced Synonasal Schwannoma with Para-Aortic Soft Tissue Metastases

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Abstract

Synonasal schwannomas are rare borderline neoplasms with a frequency of 4% of all tumors in the head and neck. We present a 60 year old woman with a locally advanced sinonasal schwannoma, originating in the sphenoid sinus and infiltrating ethmoid cells, the nasal cavity and the left retrobulbar space. In 2022 was conducted definitively intensity modulated radiotherapy (IMRT) by the VMAT method in the tumor area with a daily dose 2 Gy up to total dose (TD) 66 Gy. In 2023, para-aortic soft tissue metastases at PET/CT were diagnosed, which were also irradiated up to TD 35 Gy. The patient is monitored every year by MRI and PET/CT. We present our clinical observations on the late radiation results after 3 years since the radiotherapy (RT) of the primary local advanced synonasal schwannoma and its soft

tissue para-aortic soft tissue metastases. The local tumor undergoes less than 30 % after 3 years of radical local RT up to TD 66 Gy. Rare soft tissue metastases are relatively more radiosensitivity than the local tumor with the maintenance of low metabolic activity of PET/CT after 2 years of palliative RT.

Keywords: Synonasal schwannoma; Intensity modulated radiotherapy; Para-aortic soft tissue metastases; MRI; PET/CT; CD117

Introduction

Schwannoma is a benign, encapsulated, slow-growing and generally solitary tumour that arise from Schwann cells of the peripheral nerve sheath [1-4]. This tumor was first described by Verocay in 1910, who coined the term "neurilemmoma" to describe this benign neurogenic tumor [5].

Extracranial schwannomas in the head and neck region comprise 25–45% of all schwannomas, but only 4% involve the nasal cavity and paranasal sinuses [3,6-8]. Schwannoma is generally a benign tumour, but there are a few cases showing malignant transformation reported in the literature [9,10]. Since the radioresistance of schwannoma is known, we present our 3 years clinical observations on malignant transformed locally advanced synosal schwannoma with soft tissue paraaortic metastases after radical and palliative Radiotherapy (RT).

Case Presentation

A 57-year-old patients with headaches, progressive unilateral nasal obstruction, decrease of visual acuity of the left eye and visible left exophthalmus are presented. From CT / December 2020 -At the base of the left retrobulbar space with data on the presence of a small irregularly shaped area with a compacted and thickened medial rectus eye muscle.

The soft tissue tumor bilaterally at the base of the ethmoid sinuses and rhinobase with osteolytic changes in the clivus and complete involvement of sphenoid sinuses. Soft tissue formations at the base of the nasal cavity on the right with dimensions 8mm/ 5mm and left 5 mm/6 mm. MRI / March 2021 - Rightly, a 14 mm/6 mm soft tissue formation is visualized, destroying adjacent bones, engaging the sphenoid sinus and ethmoid sinuses bilateral, entering the two nasal passages, more in the right, and infiltrating the left retrobulbar space (Figure 1). After MRI/ 2021 an endonasal biopsy with a histological result an inflammatory myofibroblastic tumor was performed. From the Immunohistochemical (IHC) examination- spindle cells express Vimentin, do not expose ALK 1. Due to the diagnosis of a slow growing benign tumor, the patient is evaluated for active monitoring. In April 2021, the patient was reenforced to perform endoscopic medial orbital decompression.

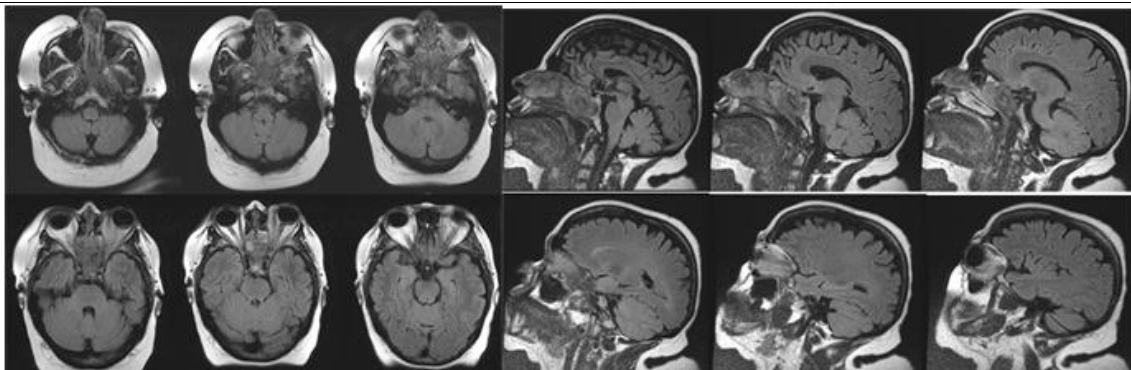


Figure 1: A/B Axial and sagittal MRI / March 2021 - The brain substance of T2- FLAIR and other sequences are with isointense signal without changes in the brain ventricles. Rightly, a 14mm/6mm soft -tissue formation is visualized, destroying adjacent bones, engaging the sphenoid sinus and ethmoid sinuses bilateral, entering the two nasal passages, more in the right, and infiltrating the left retrobulbar space.

After a year of decompressive partial surgery, complaints of headaches and secretions from the nasal cavity are restored, and the vision of the left eye with exophthalm completely disappears. Sent material for histological examination from the anterior wall of the sphenoid sinus to the left and

from the periorbital tumor tissue to the left. Consultation of the histological result- The material represents bone fragments and tumor proliferation with the following characteristics: 1/ Biphasic cell proliferation; 2/ Spindel schwannoma cell (fascicular scar) and vacuolized areas; 3/ The cells

have unclearly distinguished cytoplasm, dense chromatin, without axons; 4/ No mitotic figures are observed; 5 / Degenerative changes / hyalinization (Figure 2) From Immunohistochemical (IHC) analysis - Tumor cells with positive expression to the S100 Protein and Vimentin (Figure 3 A, B), and in single atypical cells there is a positive expression to CD 117 (Figure 3C). Based on pathohistological and immunohistochemical analysis, this tumor was defined as sinonasal schwannoma. After non-radical surgery, the patient

is evaluated for active monitoring. Given the benign disease nature and its slow growth, the patient is not directed for Radiotherapy (RT). After a year, complaints of headaches and secretions from the nasal cavity are restored, and the vision of the left eye with exophthalm completely disappears. MRI January 2022 visualizes a soft tissue tumor engaging the sphenoid sinus and ethmoidal sinuses bilateral, which destroys the adjacent bones and enters the two nasal passages and infiltrates the left retrobulbar space (Figure 4).

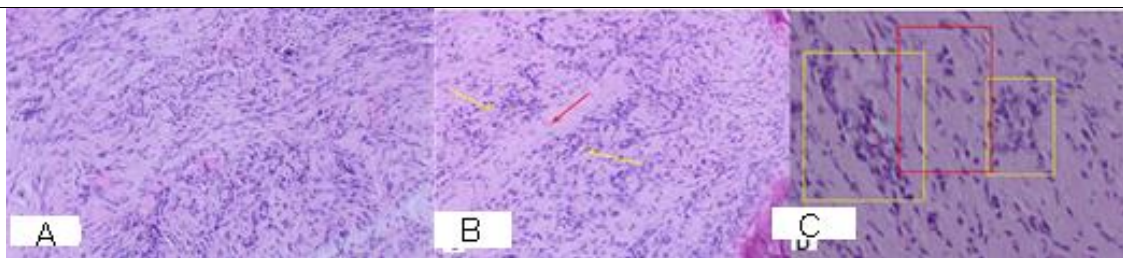


Figure 2: Microscopic histological findings – A/ Areas with many cells and a small amount of cells; Spindle cells show interlacing pattern and palisading of nuclei; whorling pattern on the right; expressed hyalinization of tumor stroma. H&E x 100; B/ At high power (H&E x 100) the palisading nuclei and Verocay bodies are evident, as well as the Antoni A and Antoni B components (the yellow arrows show Antoni A and Antoni B components, and the red arrow shows parallel arrays of nuclei forming a Verocay body); C/ At high power (H&E x 100) the palisading nuclei and Verocay bodies are evident, as well as the Antoni A and Antoni B components (the yellow rectangles show Antoni A and Antoni B components, and the red shows parallel arrays of nuclei forming a Verocay body).

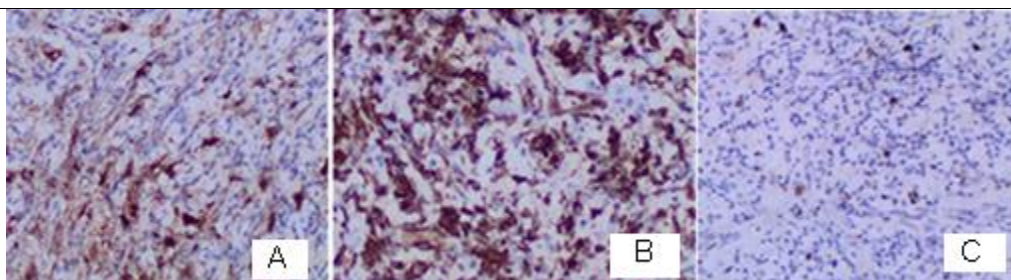


Figure 3: Immunohistochemistry – A/ Tumor cells with positive expression to S100 protein (at high power H&E x 400); B/ Tumor cells with positive Vimentin expression (at high power H&E x 400); C/ Single atypical cells there is a positive expression to CD 117 (at high power H&E x 100).

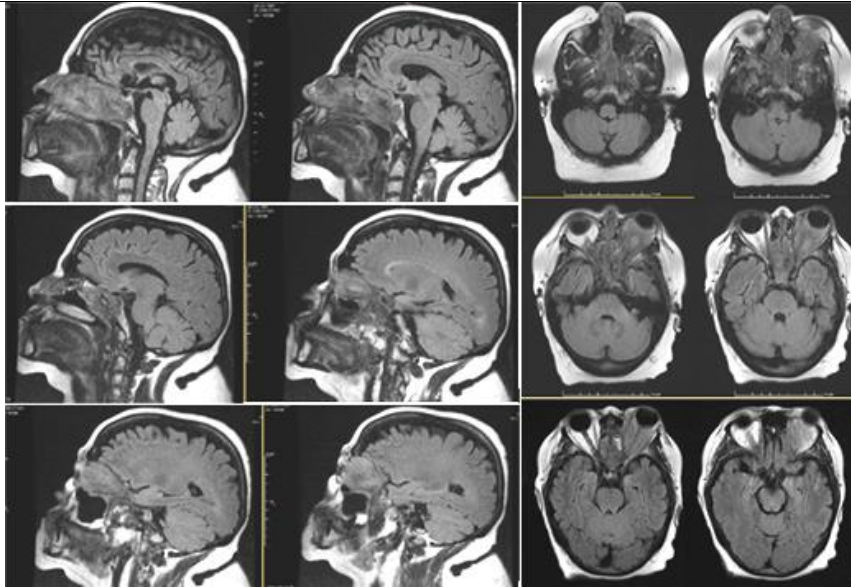


Figure 4: MRI/ January 2022- Sag T2 FLAIR and Ax T2 FLAIR visualizes a soft tissue tumor engaging bilateral the sphenoid sinus and ethmoidal sinuses, which destroys the adjacent bones and enters the two nasal passages and infiltrates the left retrobulbar space.

Due to the available symptoms, it was estimated to carry out Intensity Modulated Radiotherapy (IMRT) in the tumor area with a Daily Dose (DD) 2 Gy up to Total Dose (TD) 66 Gy. **Figure 5** shows contour the tumor volume in which this high radiation dose should be realized. After 3 months, a control MRI was conducted to establish tumor stationation, lack of visible reduction or progression (**Figure 6**). After 6 months of the RT completion, the ¹⁸F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) has reported increased metabolic activity of the tumor (SUV Max 9.2), which has proven the exceptional radioresistance of primary sinonasal schwannomas. Surprisingly, para-aortic lymph node metastases at

the level of Th 12- L2 with increased metabolic activity SUV Max 5.2-5.7 were detected (**Figure 7**). IMRT in the area of para-aortic lymph nodes from Th 10- L3 with Daily Dose (DD) 3 Gy up to Total Dose (TD) 30 Gy was carried out with simultaneous boost in metastases with DD 3.5 Gy up to TD 35 Gy. From PET/CT (May 2023) after 9 months of the RT completion, significantly reduced metabolic activity in the para-aortic and para-caval lymph nodes were established (**Figure 8**). The patient was subjected to active annual monitoring by means of a synonasal tumor MRI and PET/ CT to account for the metabolic activity of soft tissue metastases.

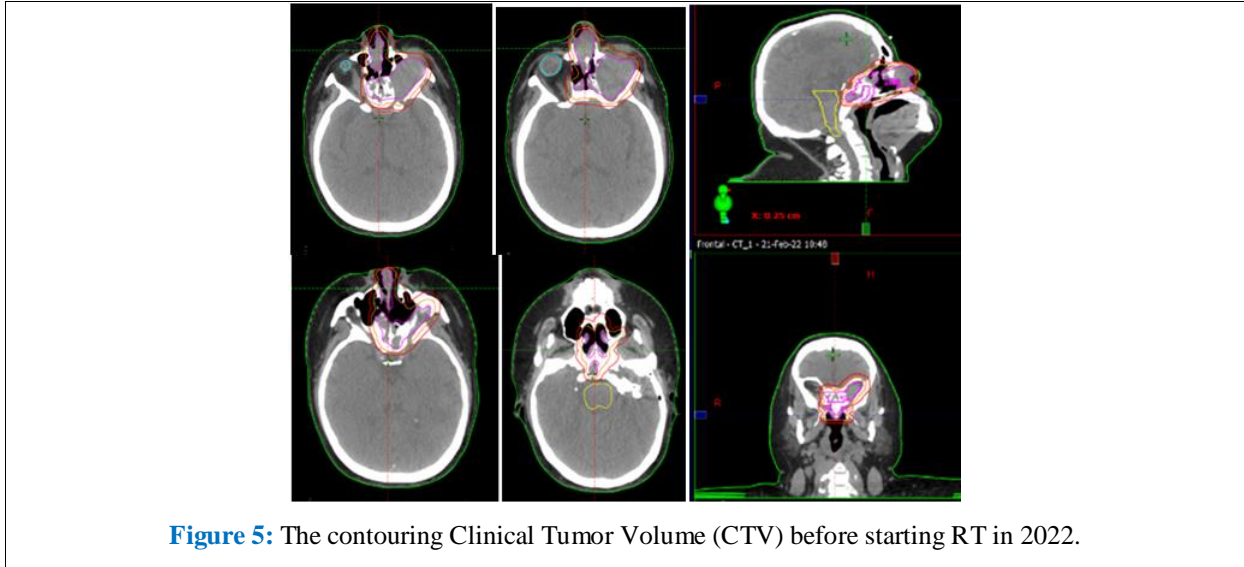


Figure 5: The contouring Clinical Tumor Volume (CTV) before starting RT in 2022.

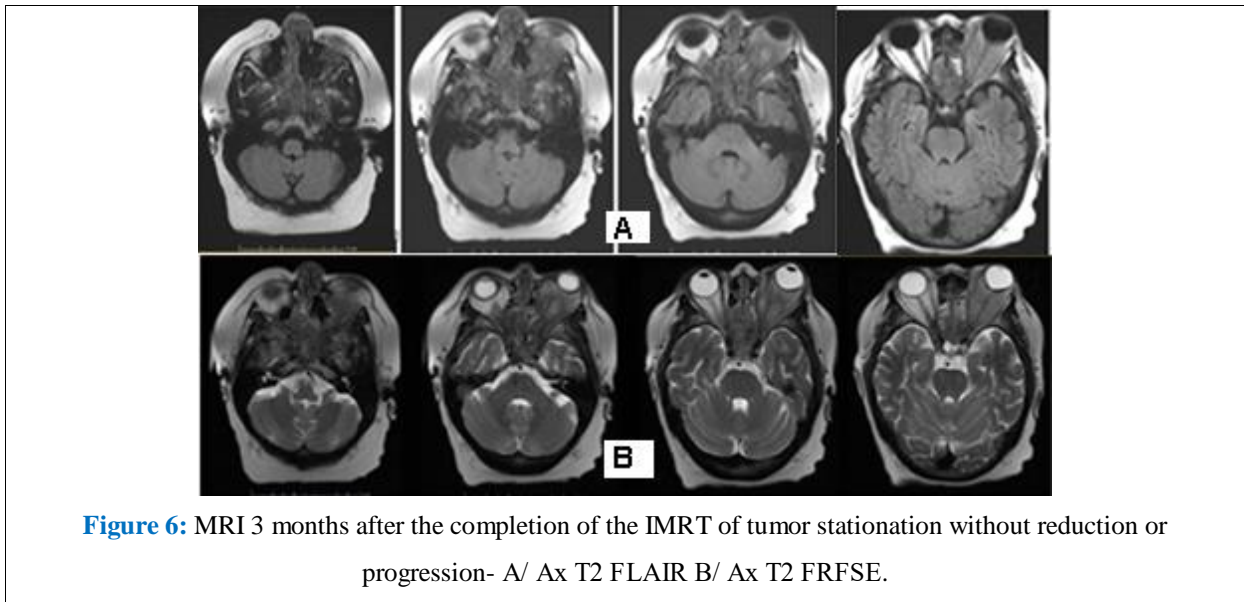


Figure 6: MRI 3 months after the completion of the IMRT of tumor stationation without reduction or progression- A/ Ax T2 FLAIR B/ Ax T2 FRFSE.

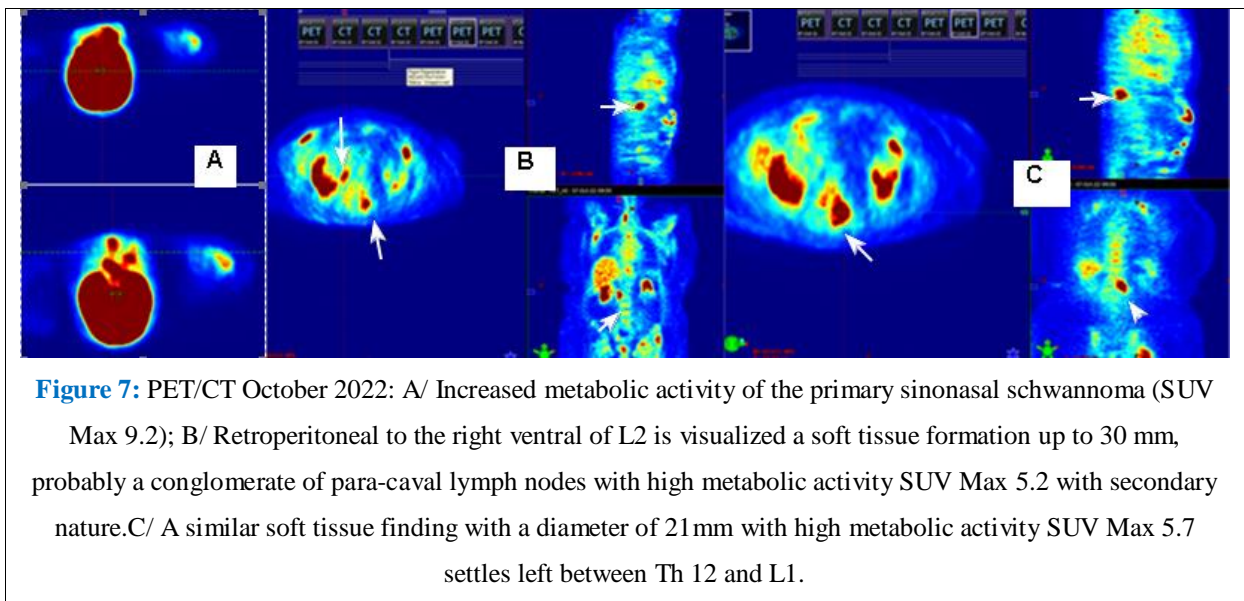


Figure 7: PET/CT October 2022: A/ Increased metabolic activity of the primary sinonasal schwannoma (SUV Max 9.2); B/ Retroperitoneal to the right ventral of L2 is visualized a soft tissue formation up to 30 mm, probably a conglomerate of para-caval lymph nodes with high metabolic activity SUV Max 5.2 with secondary nature. C/ A similar soft tissue finding with a diameter of 21 mm with high metabolic activity SUV Max 5.7 settles left between Th 12 and L1.

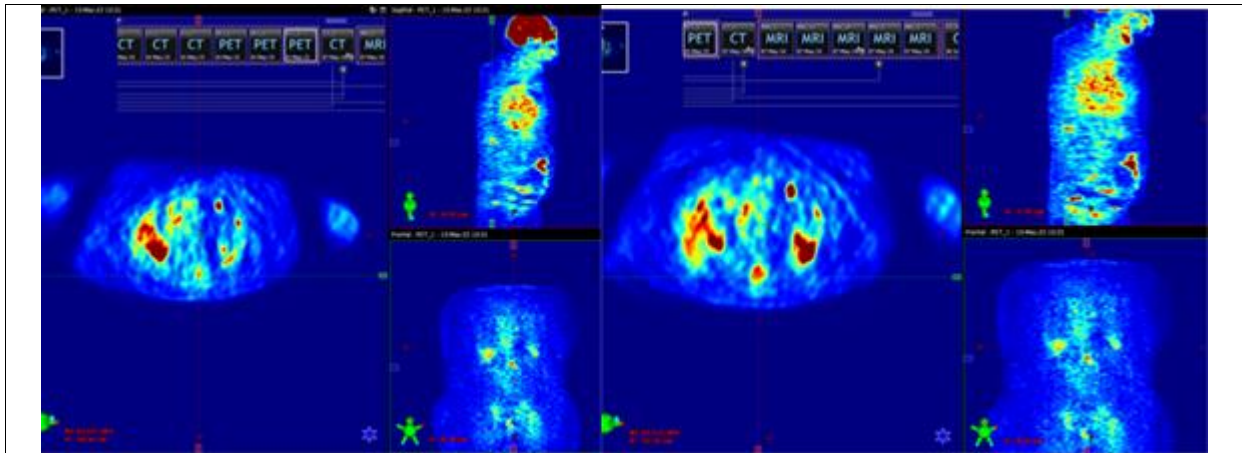


Figure 8: PET/CT (May 2023) after 9 months of the completion of RT- Retroperitoneal to the right ventral of L2 a soft tissue formation up to 27/16 mm is visualized, probably a conglomerate of para-caval lymph nodes with metabolic activity SUV Max 2,6 from SUV Max 5,2 before RT. A similar soft tissue finding with a diameter of 21mm with metabolic activity SUV Max 2,6 from SUV Max 5.7 before RT settles left between Th 12 and L1.

Discussion

Schwannomas are benign tumors usually attached to peripheral nerves, consisting of a clonal population of Schwann cells, which often undergo cystic and degenerative change [2]. These tumors can emerge from any nerve covered with a Schwann cell sheath, including the cranial nerves (with the exception of the optic and olfactory nerves), the spinal nerves, and the autonomous nervous system [11]. In sinonasal cavity, schwannomas are postulated to arise from the ophthalmic and maxillary branches of the trigeminal nerve or from autonomic nerves to the septal vessels and mucosa [12]. The ethmoid is the most common site of rhinosinusal location, followed by the maxillary sinus, the nasal cavity, and the sphenoid [13]. Sinonasal region, even though it is located in the head, has an extremely low incidence (about 4%) of Schwannomas [8,14]. Pre-operative diagnosis is difficult and further investigations are needed such as MRI, CT, US and angiography [15].

The typical features on MRI are a well-circumscribed small nodule, homogeneously isointense to muscle on T1WI and homogeneously

hyperintense on T2WI, showing homogeneous enhancement after contrast administration [16]. In the presented clinical case, MR T2 FLAIR images of the tumor are isointense to muscle tissue (Figure 1 and Figure 4). The histological diagnosis of schwannoma is usually apparent because of the presence of alternating patterns of Antoni A and B areas, nuclear palisading, Verocay bodies, and the whirling of cells, histological finding that we present in Figure 2B/C. The immunohistochemical examination revealed positivity for vimentin, S-100 and glial fibrillary acidic protein, whereas discovered on GIST-1, CD117, CD34, desmin, Smooth Muscle Actin (SMA) and cytokeratin were negative [17]. Schwannomas are characterized by strong and diffuse immunoreactivity for S-100 protein, which is the clue for the diagnosis [18-20]. The presence of S-100 protein in IHC staining is a classic marker for diagnostic confirmation and Magnetic Resonance Imaging (MRI) is the gold standard for preoperative imaging [21]. In our clinical case, we report a positive expression of tumor cells to S100 protein and Vimentin (Figure 3 AB), single atypical cells with positive expression to CD 117 (Figure 3C). As schwannomas are

typically benign, well circumscribed, and minimally invasive tumors, complete surgical excision is the standard of care for ensuring no recurrence [22-26].

In our clinical case, intraoperatively observed destroying the adjacent bones, which is also visible to MRI. This bone change is not a sign of tumor malignancy, but the result of its slow growth, leading to erosion of adjacent cranial bones. These tumours do not respond to radiotherapy [27]. In our clinical case, it is a locally advanced sinonasal schwannoma originating in the sphenoid sinus and the engagement of the clivus, which defines the tumor as an inoperable. Malignant transformation within a schwannoma usually results in an epithelioid or primitive neuroectodermal morphology [28,29]. Despite the rarity of malignant transformation, long-term monitoring is usually necessary [30,31]. Malignant change of Vestibular Schwannoma (MTVS), also called Malignant Peripheral Nerve Sheath Tumor (MPNST) of the eighth CN, firstly reported by Norén et al. [32]. In 1983, is very scarce, accounting for less than 1% of all vestibular schwannomas. Schwannoma is generally a benign tumour, but there are a few cases showing malignant transformation reported in the literature [33,34]. There are several reports [35-37] of schwannomas misdiagnosed as lymph nodes metastasis or malignant tumors detected by FDG-PET [38]. After 9 months of the local definitive IMRT completion, the 18F-Fluorodeoxyglucose (FDG). Positron Emission Tomography (PET) increased metabolic activity of the sinonasal tumor (SUV Max 9.2) has reported (Figure 7A), which has proven the exceptional radioresistance of primary schwannomas. Surprisingly, soft tissue para-aortic metastases at the level of Th 12- L2 with increased metabolic activity SUV Max 5.2-5.7 were detected (Figure 7B and C), which proves the rare possibility of malignant transformation, that

requires prolonged monitoring of patients with schwannomas [39,40]. From the immunohistochemical analysis of the presented clinical case, we have identified single tumor cells with positive expression for the SD 117 (Figure 3C), which may be a sign of a malignant transformation of the slowly increasing synosal schwannoma, which accounts for paracarcinomatous soft tissue metastases. CD117 (c-Kit) is massively involved in the process of tumorigenesis of cutaneous malignancies, being immunohistochemically undetectable in benign neural lesions, but densely expressed in dysplastic lesions (dysplastic nevi) and in situ melanoma areas [41]. Although the impact of CD117 expression on prognosis of patients with cancer has been explored recently, the prognostic value of CD117 expression in different tumor types remains conflicting because heterogeneous results were reported in studies and some of them included a small number of patients [42]. There was no association between c-kit expression and patient survival although a trend toward a worse prognosis of c-kit-positive tumors could be observed, especially in breast carcinoma and sarcoma (include the following subtypes: schwannoma, leiomyosarcomas, hemangioendothelioma, hemangiopericytoma, chondrosarcomas, fibrosarcoma, sarcomas Not Otherwise Specified (NOS), liposarcoma, myofibroblastic sarcoma, histiocytoma of the parotid gland, breast angiosarcoma) [43]. From PET/CT (May 2023) after 9 months of the RT completion, significantly reduced metabolic activity in the para-aortic and para-caval lymph nodes were established. Retroperitoneal to the right ventral of L2 a soft tissue formation up to 27/16 mm is visualized, probably a conglomerate of para-caval lymph nodes with metabolic activity SUV Max 2,6 from SUV Max 5,2 before RT. A similar soft tissue finding with a diameter of 21mm with metabolic

activity SUV Max 2,6 from SUV Max 5.7 before RT settles left between The 12 and L1 (**Figure 8**). This finding after the palliative irradiation of soft tissue metastases means that they are relatively more radiosensible than the primary synonasal tumor. We decided to compare the reduction of the local synosal tumor through the MRI image before the RT of 2022 with the one after 2 years of the local radical RT in 2024 (**Figure 9**). As this tumor reduction is not clearly visible to MRI, we decided to compare its metabolic activity of PET/ CT in

2022 before IMRT with the one in 2023 and 2024 after IMRT (**Figure 10**). **Figure 11** presented the comparison of the tumor volume through the planning CT A/ of 2022 before RT with the one of 2025/ February 3 years after the radical RT - visible reduction in the nasal part of the tumor volume with residual sphenoid and left -sided retrobulbar tumor. **Figure 12** represents the maintenance of the low metabolic activity in the area of retroperitoneal soft tissue metastases in 2024 -2 years after palliative RT.

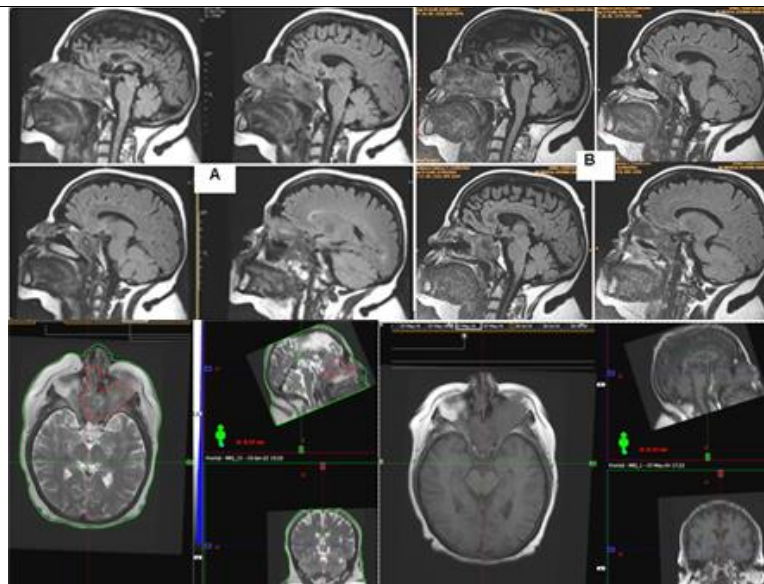


Figure 9: MRT comparison in 2022 before IMRT/A with MRT in 2024 after IMRT/B – The monitored retrobulbar formation on the left has a reduced volume with less pronounced exophthalm. The formation engaging the sphenoid and ethmoidal sinuses is also reduced at the expense of the infiltration of ethmoid cells.

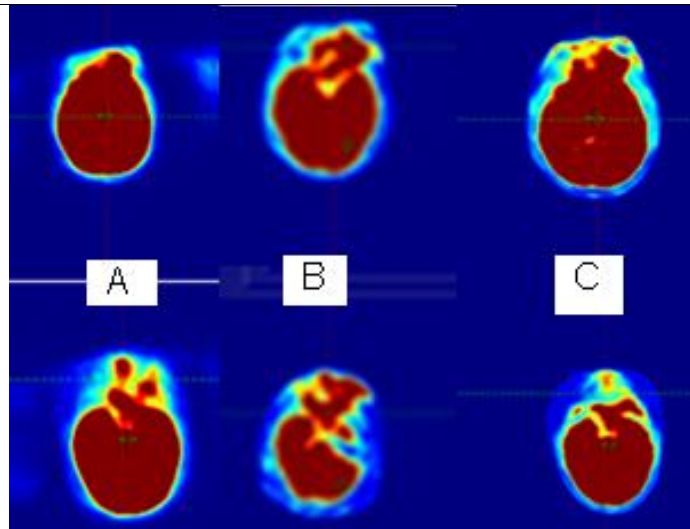


Figure 10: Comparison of the local metabolic activity of the sinonasal tumor of PET/CT in 2022 (A) with 2023 and 2024 (B) A/ Increased metabolic activity of the primary sinonasal schwannoma (SUV Max 9.2) primary sinonasal schwannoma. B/ The monitored retrobulbar tumor on the left has a reduced volume with less pronounced exophthalm. Scan is similar unevenly distributed metabolic activity now / 2024 with SUV Max 8.4 by SUV Max 8.3 / 2023. The formation engaging the sphenoid and ethmoidal sinuses is also reduced at the expense of the infiltration of ethmoid cells with SUV Max 6.96 by SUV Max 7.9. No metabolic active cervical lymph nodes.

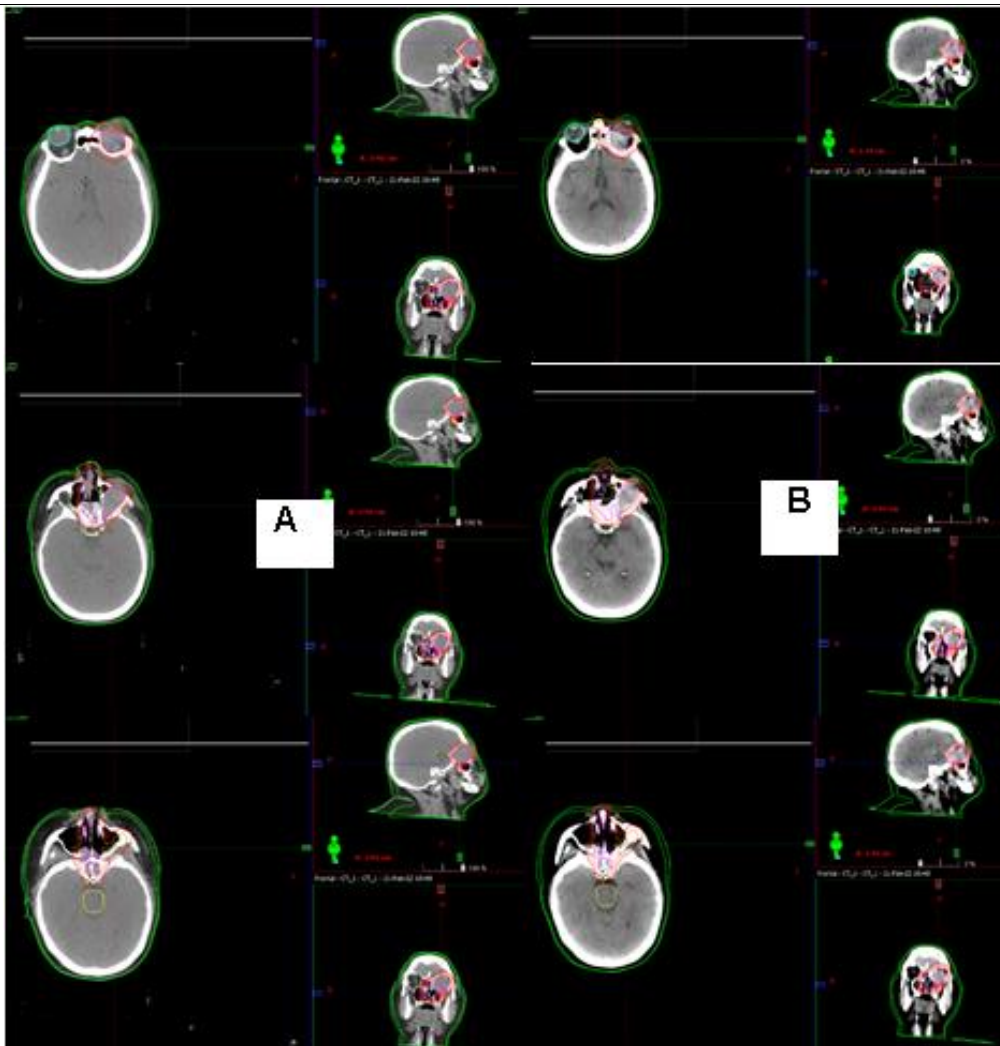


Figure 11: Comparison of the tumor volume through the planning CT A/ of 2022 before RT with the one of 2025/ February 3 years after the radical RT - visible reduction in the nasal part of the tumor volume with residual sphenoid and left -sided retrobulbar tumor.

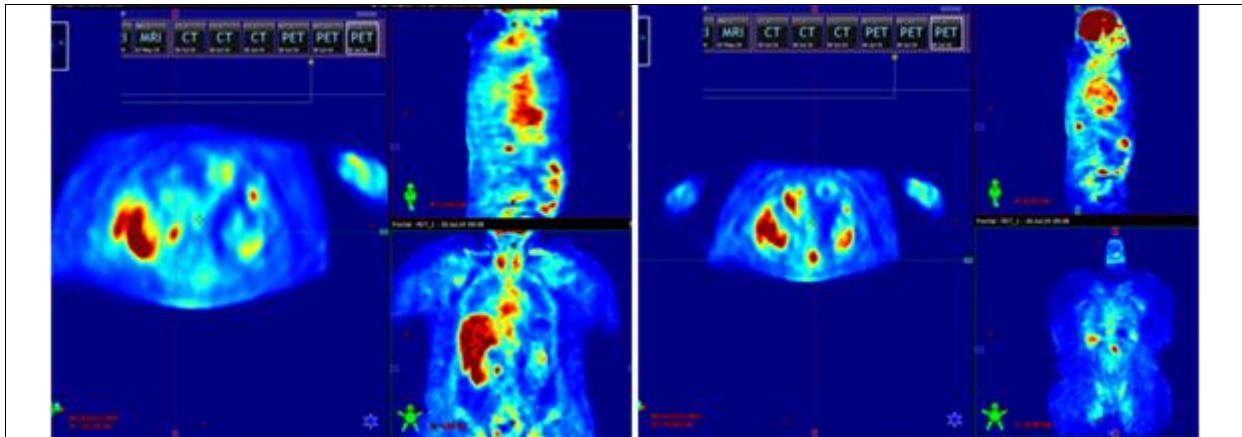


Figure 12: PET/CT (July 2024) after 18 months of the completion of RT- Retroperitoneal to the right ventral of L2 is visualized a soft tissue formation up to 24/14 mm, probably a conglomerate of para-caval lymph nodes with metabolic activity SUV Max 2,57 by SUV Max 5,2 before RT. A similar soft tissue finding with a diameter of 21mm with metabolic activity SUV Max 2,71 by SUV Max 5.7 before RT settles left between The 12 and L1.

Conclusion

Synonasal schwannomas are rare borderline neoplasms with a frequency of 4% of all tumors in the head and neck. A malignant transformation is possible in a slow growing sinonasal schwannoma, which can be predicted by single tumor cells with IHC increased expression of the CD 117. The local tumor undergoes less than 30 % after 3 years of radical local RT up to TD 66 Gy. Rare soft tissue metastases are relatively more radiosensitivity than the local tumor with the maintenance of low metabolic activity of PET/ CT after 2 years of palliative RT.

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