Locally Advanced Oncocytic Carcinoma of the Nasal Cavity Treated With Surgery and Intensity-modulated Radiotherapy

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Oncocytic carcinomas of the nasal cavity are extremely rare. We report 1 patient whose primary tumor and neck lymphadenopathies were under control nearly 2 years after combined surgery and radiotherapy. An 80-year-old man with a history of nasal oncocytoma had received excision twice previously. Computed tomography demonstrated locally advanced recurrent tumor invading the paranasal sinuses and orbit with lymphadenopathies in the right neck. Skull base surgery was performed. Pathological examination revealed oncocytic carcinoma. Positron emission tomography showed hypermetabolic lesions in the surgical bed and right neck. The patient subsequently received intensity-modulated radiotherapy to the primary site and the whole neck. Follow-up computed tomography 4 months later showed marked shrinkage of the neck lymphadenopathies. There was no progression after nearly 2 years. Although these tumors have historically been regarded as radioresistant, the combined treatment of surgery followed by radiotherapy may offer the best chance for control of locally advanced disease. [*J Chin Med Assoc* 2010;73(3):166–172]

Key Words: intensity-modulated radiotherapy, nasal cavity, oncocytic carcinoma, positron emission tomography, surgery

Introduction

Oncocytomas are tumors composed of epithelial cells with a large, granular and eosinophilic cytoplasm rich in mitochondria. These tumors comprise less than 1% of all salivary gland tumors.[1] They occur most commonly in patients between the ages of 55 and 70, without sex predilection.[2] Oncocytic carcinomas are even rarer and estimated to represent 5%[3] to 11%[4] of all oncocytic salivary gland neoplasms. Bauer and Bauer reported the first case in 1953.[5] The mean age at occurrence of these malignancies is similar to that of benign oncocytomas, with a male-to-female ratio of approximately 2:1.[3,6]

From a search of the available literature on MEDLINE and PubMed, only 13 cases of oncocytic carcinomas arising from the nasal cavity have been reported in the English, French and German literature.[7–20] Most of the cases were treated with surgery alone. In contrast, only 4 cases[12,13,19,20] received radiotherapy as adjuvant treatment following radical surgery or salvage treatment for recurrence. Due to the rarity of this disease, what constitutes optimal treatment remains unclear. Whether or not surgery plus adjuvant radiotherapy can procure durable local control is not known.

In this article, we report our experience of treating a patient whose locally advanced primary tumor and neck lymphadenopathies were controlled for nearly 2 years with combined surgery and intensity-modulated radiotherapy (IMRT) of 66 Gy. To our knowledge, this is the first report of oncocytic carcinoma that received a high dose of radiation with the IMRT technique.

Case Report

An 80-year-old man, with a Karnofsky performance status of 80, had no history of radiation exposure. He had received surgical intervention twice at the otorhinolaryngology department of Taipei Veterans General Hospital for oncocytoma (Figure 1) of the right inferior

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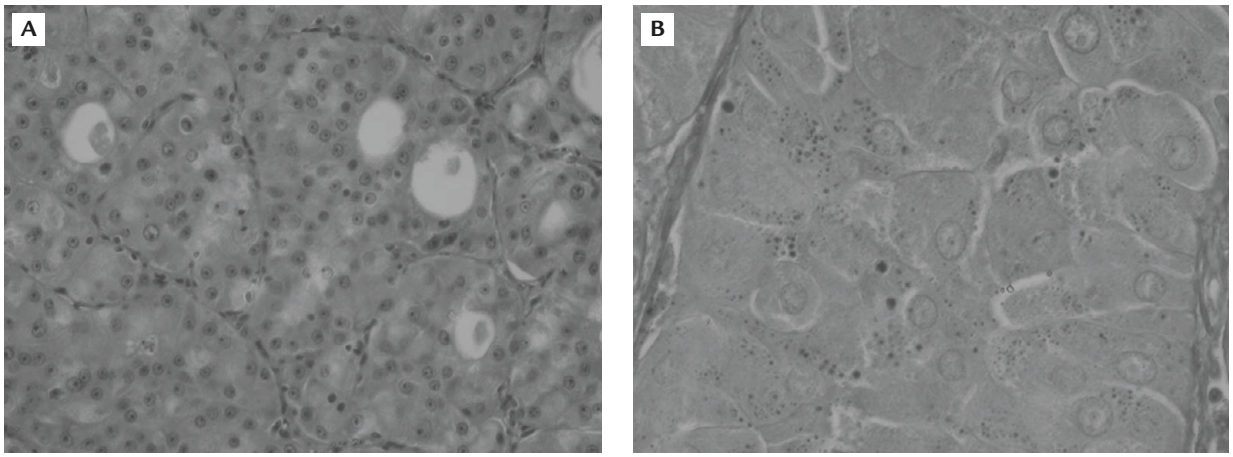

Figure 1. (A) Tubular structures and solid cell nests formed by columnar epithelial cells with eosinophilic granular cytoplasm (oncocytes); neither cellular pleomorphism nor mitotic figures are seen (hematoxylin & eosin, 200×). (B) The eosinophilic granules in the cytoplasm of the tumor cells are positive for phosphotungstic acid hematoxylin stain (400×).

turbinate in 1999 and 2004. Two years later, he presented with intermittent epistaxis. The sinus scope revealed a soft tissue mass at the floor of the right nasal cavity with easy contact bleeding. Mobile lymph nodes were palpated at right levels II, IV and V, with the largest measuring about 1.5 cm in size. The remainder of the physical examination and laboratory data were unremarkable. Computed tomography (CT) disclosed a soft tissue mass in the right-side nasal chamber and maxillary sinus, extending to the ethmoid sinus and orbit (Figure 2A), with enlarged lymphadenopathies in the right retropharyngeal, level II (Figure 2B), IV and V regions. The largest measured 1.5 cm in diameter.

Skull base surgery via lateral rhinotomy was performed. During operation, a bony tumor was found obliterating the right maxillary sinus. The orbital floor, nasolacrimal duct, lamina papyracea, ethmoid sinus, right anterior skull base, frontal sinus, and sphenoid sinus were invaded. Grossly, all visible tumors were removed. Those specimens were labeled and sent for pathologic examination. Because of the patient's old age and his family's preference for conservative surgery, neck dissection was not done.

Sections of the specimens showed respiratory mucosal tissue and bone infiltrated by nests of large, round-to-polyhedral epithelial cells with abundant fine, granular and eosinophilic cytoplasm, and round vesicular nuclei with mild nuclear atypia and rare mitosis (Figure 3A). There were duct-like structures of variable caliber in the tumor cell nests. The features of tumor necrosis, perineural invasion, suspicious tumor emboli in angiolymphatic spaces and bone destruction (Figure 3B) were also identified. Fine purple-colored granules in the cytoplasm of tumor cells were observed on phosphotungstic acid hematoxylin (PTAH) stain. The above findings were compatible with oncocytic carcinoma. The status of the cut margins could not be determined due to pieces of tumor tissue received in this specimen.

Before adjuvant radiotherapy, whole-body positron emission tomography (PET) scan with [F18]fluoro-2-deoxy-D-glucose (FDG) was arranged to evaluate the nature of the neck lymphadenopathies. It showed several foci scattered along the right cervical chain from levels II, IV and V with maximum standard uptake values of 3.9, 3.7 and 2.9, respectively. Metastatic lymphadenopathies were highly suspected (Figure 4A). Increased uptakes were also noted in the right lobe of the thyroid gland, mediastinum and right pulmonary hilum. After comparing this PET image with neck CT and consulting nuclear medicine physicians, we considered that the increased uptakes might represent benign disease or nonspecific conditions in the above areas.

Adjuvant radiotherapy was delivered utilizing 6- and 10-MV photons via 7 intensity-modulated radiation fields from a Varian 2100CD linear accelerator (Varian, Palo Alto, CA, USA) and simultaneous integrated boost technique. The treatment planning software we used was the Eclipse® system, version 6 (Varian). The prescribed radiation doses were 66 Gy in 33 fractions to the right neck lymphadenopathies [planning target volume-66 (PTV-66)], and 59.4 Gy in 33 fractions to the whole neck plus the surgical bed of the primary tumor, including the right nasal cavity, maxillary sinus, ethmoid sinus, the floor and medial wall of the orbit, the anterior wall of the sphenoid sinus, and the lower portion of the right frontal sinus (PTV-59.4; Figure 5). Of the PTV-66, 97.9% was covered

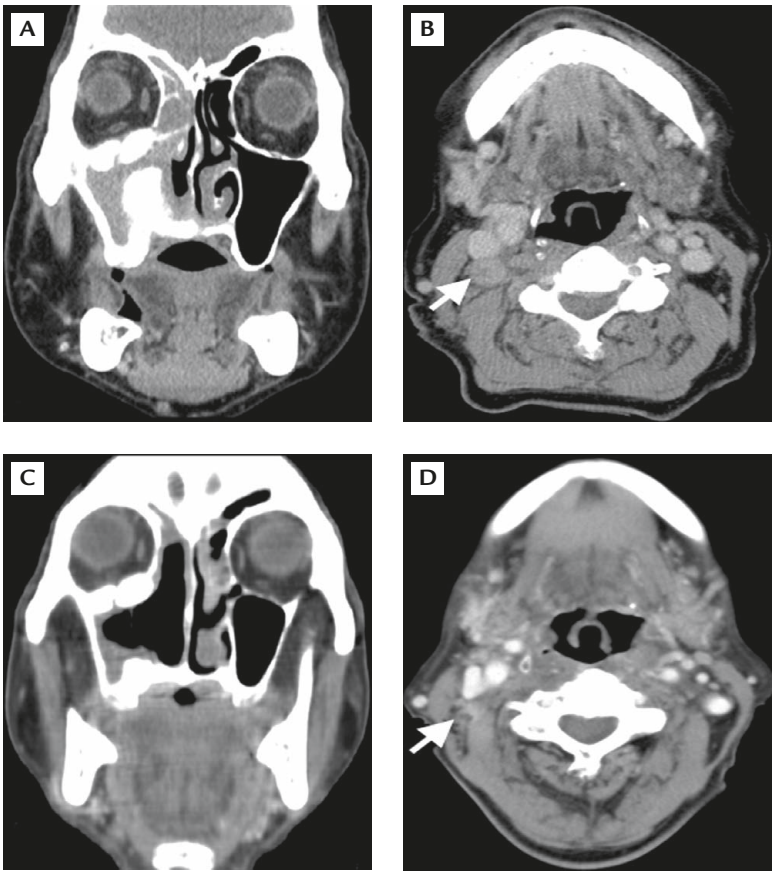

Figure 2. (A, B) Computed tomography before surgery. Coronal view demonstrates tumor invasion of the nasal floor, right maxillary sinus, ethmoid sinus and orbit. Axial view of the neck shows enlarged lymphadenopathy at right level II (arrow). (C, D) Computed tomography 4 months after surgery and 1.5 months after radiotherapy. Coronal view shows postoperative features without recurrence. Axial view of the neck reveals significant shrinkage of the lymph node (arrow).

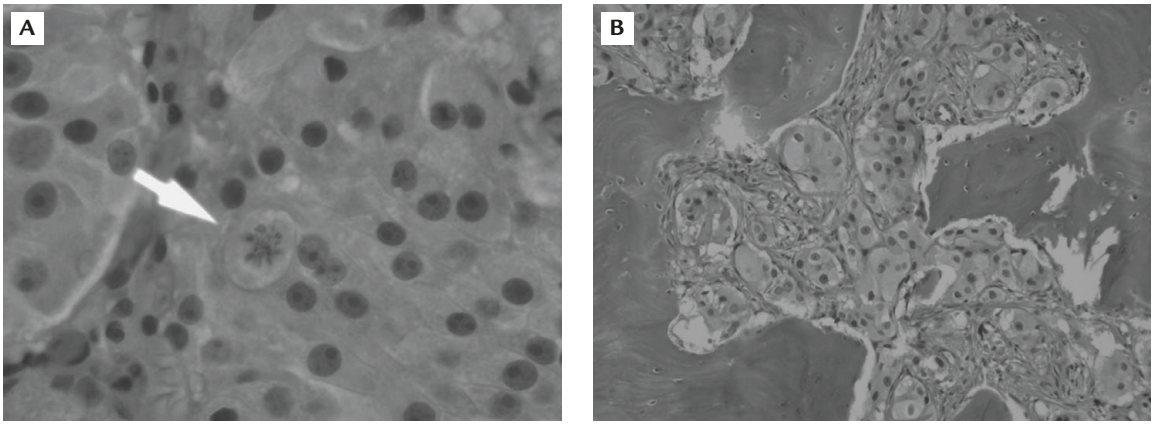

Figure 3. (A) Nuclear atypia and a mitotic figure (arrow; hematoxylin & eosin, 400×). (B) Bone destruction (hematoxylin & eosin, 200×).

by 66 Gy. Because of the proximity of the right orbital fossa to the tumor bed, the mean and maximal doses to the right optic nerve were 49.6 Gy and 61.7 Gy, respectively. The mean and maximal doses to the right eye were 27.2 Gy and 47.8 Gy, respectively. The doses to the left optic nerve, eyeball, brain stem, spinal cord and parotid gland were constrained within tolerance limits. Acute toxicities including mucositis, dermatitis and xerostomia were manageable at our outpatient department. The patient completed the treatment without interruption. Since he refused any feeding tube during radiotherapy, a loss of 9% of his original body weight was noted at the end of treatment despite supportive care.

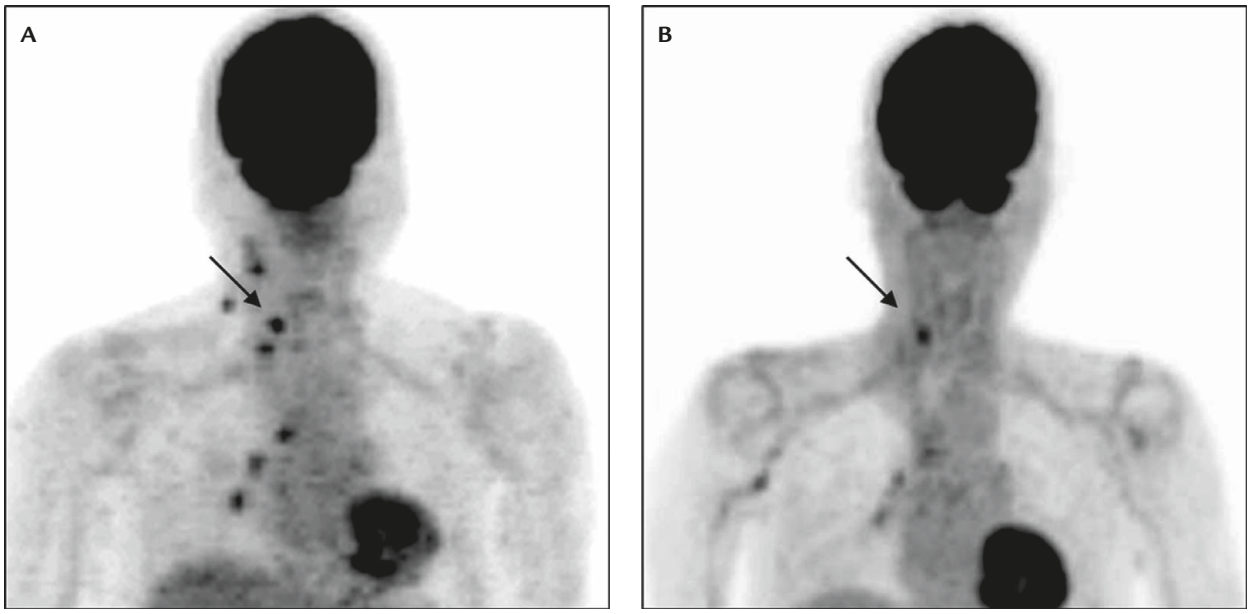

Figure 4. (A) Positron emission tomography before radiotherapy shows hypermetabolic lesions at right levels II, III and V, compatible with lymphadenopathies; benign disease or nonspecific increased uptake were also noted in the right lobe of the thyroid (arrow) and right pulmonary hilum. (B) Positron emission tomography 21 months after the completion of radiotherapy shows that the lesions with high standard uptake value (>2.5) in the right neck have disappeared, while others in the thyroid (arrow) and hilum remain unchanged. The increased uptake of the right axillary lymph nodes, with maximal standard uptake value of 2.6, was judged to be a nonspecific finding by the nuclear medicine physician.

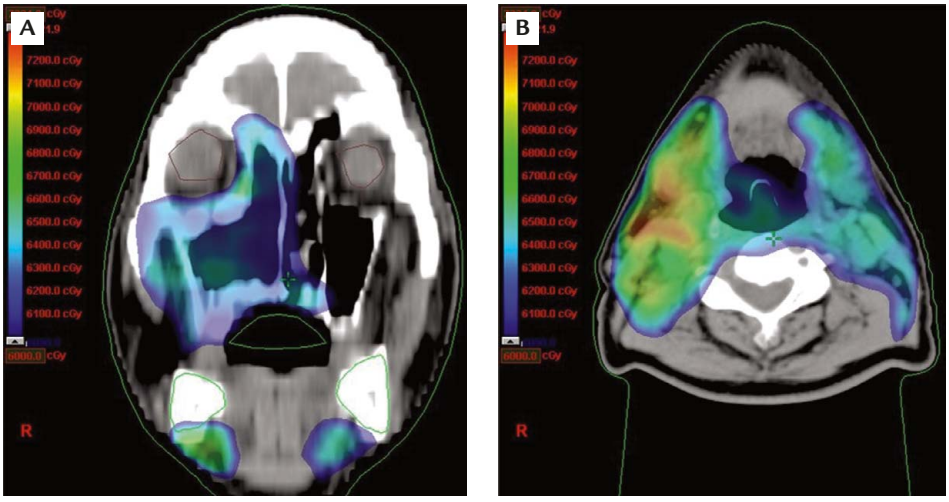

Figure 5. Dose distribution of the intensity-modulated radiotherapy plan. The spectrum from blue to red stands for doses from 60 Gy to 73.2 Gy, the maximal dose. Adequate coverage of target volume was achieved without exceeding the tolerance of critical structures. (A) Coronal view of the face. (B) Axial view of the neck, showing level Ib and II lymphatic drainage.

After adjuvant radiotherapy, the patient was regularly followed-up at our otorhinolaryngology and radiation oncology outpatient department, and sinus scope showed no evidence of tumor recurrence, but much crust over the right sinonasal cavity. The patient had nasal and oral dryness, but there were no severe late complications. Four months after surgery and 1.5 months after radiotherapy, follow-up CT revealed postoperative features in the nasal cavity (Figure 2C) and significant shrinkage of all right neck lymphadenopathies. One of them is shown in Figure 2D. At 23 months after surgery, PET-CT did not show any abnormalities in the neck (Figure 4B). Only 1 hypermetabolic spot remained in the right neck region, compatible with thyroid lesion. The number of lesions in the mediastinum and right hilum remained unchanged. At the last ENT clinical visit, sinoscopy did not show any sign of progression in the right nasal

Table 1. Reports of oncocytic carcinoma in the nasal cavity

Author	Age (yr)/sex	Treatment	RM	DM	Outcome
Hamperl, 1962[8,9]	55/M	Not specified	–	–	Unknown
Hamperl, 1962[8,9]	73/M	Not specified	+	–	Unknown
Cohen & Batsakis, 1968[10]* Johns et al, 1973[11]*	61/M	Surgery	–	–	Local recurrence at 5 yr, 7 yr; no recurrence at 8 yr
Mahmoud, 1979[12]	54/M	Surgery R/T (for 1st recurrence, 6,174 cGy over 46 d) Surgery (for 2nd recurrence)	–	–	Local recurrence at 3 yr, 13 yr; no recurrence at 14 yr
DiMaio et al, 1980[13]	32/M	Surgery R/T (incomplete, 2,600 cGy) Surgery (for recurrence) R/T (for residual recurrent tumor, 5,800 cGy)	–	–	Recurrence at 7 yr; no recurrence at 8 yr
Savic et al, 1989[14]	45/M	Surgery	–	–	Local recurrence at 1 yr and 3 mo; no recurrence at 4 yr
Fayet et al, 1990[15]	69/F	Surgery	–	–	No recurrence at 9 mo
Martin et al, 1990[16]	86/M	Not specified	–	–	Unknown
Harrison & Lund, 1993[17]	37/F	Surgery	+	–	Local recurrence at 6 mo, 1 yr and 6 mo; died of local recurrence at 2 yr
Forster & Ostertag, 1995[18]	60/M	Surgery	–	–	Unknown
Corbridge et al, 1996[7]	78/F	Surgery (without neck dissection)	+	–	Local recurrence at 7 mo; referred for terminal care
Nayak et al, 1999[19]	60/F	Surgery R/T (postoperative, 6,000 cGy in 28 fractions over 6 wk)	–	–	No recurrence at 6 mo
Abe et al, 2007[20]	47/M	Surgery (with neck dissection) R/T (postoperative, 5,000 cGy to primary site, 4,800 cGy to neck) Chemotherapy (for recurrence)	+	–	Skin recurrence at 1 yr and 4 mo; bone metastases; died of disease at 2 yr and 5 mo
Present case	80/M	Surgery (without neck dissection) R/T (adjuvant for primary tumor, definitive for lymphadenopathies)	+	–	No recurrence at 2 yr

**The case reported by Cohen & Batsakis and by Johns et al was the same case. RM = regional metastasis; DM = distant metastasis; R/T = radiotherapy.*

cavity and maxillary sinus. Magnetic resonance imaging of the brain 1 month later and 2 years after surgery also showed no sign of recurrence at the skull base and paranasal sinuses.

Discussion

According to the World Health Organization classification, oncocytic lesions are classified into 3 categories: (1) oncocytosis or nodular oncocytic hyperplasia; (2) oncocytoma; and (3) oncocytic carcinoma. Diagnosis of malignancy in oncocytomas depends on the criteria defined by Gray et al:[21] destructive, infiltrating growth; cellular pleomorphism with scattered mitoses; lymphovascular or perineural invasion; regional or distant metastasis. Most of these carcinomas develop *de novo*, although malignant transformations of preexisting oncocytomas after a long interval have been reported.[3] Lymph node metastases occur in about 50–60% of patients with oncocytic carcinoma of the head and neck, but they may not play a critical role in overall prognosis.[3]

Surgical excision is the widely accepted method of treatment. Goode and Corio emphasized that aggressive surgical intervention at initial presentation seems to offer a more favorable prognosis.[22] Due to the rarity of oncocytic carcinomas, the role of radiotherapy is controversial.[6] Based on a case report of recurrence after radiotherapy, Mahmoud suggested that these tumors are radioresistant.[12] In Mahmoud's case, however, the radiotherapy was applied as salvage treatment for the first recurrence, which developed 3 years after the initial surgery. The radiation dose of 6,174 cGy is now considered inadequate, even for a malignant tumor with "average" radiosensitivity; yet, the patient remained free of disease until 10 years later. Goode and Corio reported a case in which rapid and widespread metastatic disease developed after conservative surgery and radiotherapy, and suggested that radiation does not appear to favorably alter the biologic behavior of this tumor.[22] In contrast, Chu and Strawitz recommended postoperative radiotherapy for oncocytic carcinoma of the parotid gland.[23] In an analysis of 36 cases with the same disease, Ardekian et al stated that patients receiving combined surgery and radiation therapy had less local recurrence than those who had surgery only.[6]

In the 13 cases of oncocytic carcinomas arising from the nasal cavity (Table 1), 4 received radiotherapy. In the 2 cases who received radiotherapy for gross recurrent disease, 1 had a further 10-year disease-free period, and another had complete response with no recurrence after 1 year by clinical examination and biopsy. Radiotherapy was prescribed in postoperative settings in the other 2 cases. Although the number of cases is too small to draw any conclusions, postoperative radiotherapy seems to be a reasonable choice for gross or suspicious microscopic residual disease. In addition, radiotherapy may be an alternative treatment when surgery is not feasible. IMRT can direct a high dose of radiation to the tumor bed while sparing normal tissue. The tumor control rate may be improved by using this technique. Our case is the first of an oncocytic carcinoma patient to receive a high dose of radiation (66 Gy) using the IMRT technique. The acute toxicities were tolerable in this old patient, and no severe late complications were seen. Though the follow-up time is not long (he is still alive at 25 months), we consider that surgery plus aggressive radiotherapy might provide the best chance of cure for locally advanced oncocytic carcinoma of the nasal cavity.

PET is a useful tool for staging of head and neck tumors and for detecting recurrence. Its role in the evaluation of malignant salivary gland tumors, however, is more limited because of a relatively high false-positive rate (approximately 30%). These PET-positive benign tumors are most commonly Warthin's tumors or pleomorphic adenomas. It is worth mentioning that Warthin's tumors are composed of oncocytic cells, and pleomorphic adenomas are frequently associated with oncocytic change. In the literature, the experience of FDG-PET in benign parotid oncocytoma is limited to only 1 case, with a high standard uptake value.[24] The present case may be the first description of PET results in a patient with oncocytic carcinoma of the nasal cavity with neck lymphadenopathies.

In conclusion, we have reported a case of locally advanced oncocytic carcinoma of the nasal cavity with clinically suspicious lymphadenopathies. After skull base surgery combined with high-dose IMRT to the surgical bed and neck, there was no local recurrence or distant failure at 2 years. Radical surgery followed by adjuvant radiotherapy might provide durable local control for such disease.

References

1. Blanck C, Eneroth CM, Jakobsson PA. Oncocytoma of the parotid gland: neoplasm or nodular hyperplasia? *Cancer* 1970; 25:919–25.
2. Barnes L. *Surgical Pathology of the Head and Neck*, 1st edition. New York: M. Dekker, 2000.
3. Nakada M, Nishizaki K, Akagi H, Masuda Y, Yoshino T. Oncocytic carcinoma of the submandibular gland: a case report and literature review. *J Oral Pathol Med* 1998;27:225–8.

4. Guclu E, Oghan F, Ozturk O, Alper M, Egeli E. A rare malignancy of the parotid gland: oncocytic carcinoma. *Eur Arch Otorhinolaryngol* 2005;262:567–9.
5. Bauer WH, Bauer JD. Classification of glandular tumors of salivary glands; study of one-hundred forty-three cases. *AMA Arch Pathol* 1953;55:328–46.
6. Ardekian L, Manor R, Peled M, Laufer D. Malignant oncocytoma of the parotid gland: case report and analysis of the literature. *J Oral Maxillofac Surg* 1999;57:325–8.
7. Corbridge RJ, Gallimore AP, Dalton CG, O'Flynn PE. Oncocytomas of the upper jaw. *Head Neck* 1996;18: 374–80.
8. Hamperl H. Benign and malignant oncocytoma. *Cancer* 1962; 15:1019–27.
9. Hamperl H. Oncocytoma of the salivary glands. *Z Krebsforsch* 1962;64:427–40. [In German]
10. Cohen MA, Batsakis JG. Oncocytic tumors (oncocytomas) of minor salivary glands. *Arch Otolaryngol* 1968;88:71–3.
11. Johns ME, Batsakis JG, Short CD. Oncocytic and oncocytoid tumors of the salivary glands. *The Laryngoscope* 1973;83:1940.
12. Mahmoud NA. Malignant oncocytoma of the nasal cavity. *J Laryngol Otol* 1979;93:729–34.
13. DiMaio SJ, DiMaio VJ, DiMaio TM, Nicastri AD, Chen CK. Oncocytic carcinoma of the nasal cavity. *South Med J* 1980;73: 803–6.
14. Savic D, Djeric D, Jasovic A. Oncocytoma of the nose and ethmoidal and sphenoidal sinuses. *Rev Laryngol Otol Rhinol (Bord)* 1989;110:481–3. [In French]
15. Fayet B, Bernard JA, Zachar D, D'Hermies F, Janot F, Pigeau I, Pouliquen Y. Malignant nasal oncocytoma disclosed by mucocele of the lacrimal sac with hemolacrimia. *J Fr Ophtalmol* 1990; 13:153–8. [In French]
16. Martin H, Janda J, Behrbohm H. Locally invasive oncocytoma of the nasal cavity. *Zentralbl Allg Pathol* 1990;136:703–6. [In German]
17. Harrison DFN, Lund VJ. *Tumours of the Upper Jaw*, 1st edition. Edinburgh: Churchill Livingstone, 1993.
18. Forster C, Ostertag H. Oncocytoma of the nose. A case report and review of the literature. *Pathologe* 1995;16:431–3. [In German]
19. Nayak DR, Pillai S, Balakrishnan R, Thomas R, Rao R. Malignant oncocytoma of the nasal cavity: a case report. *Am J Otolaryngol* 1999;20:323–7.
20. Abe T, Murakami A, Nakajima N, Inoue T, Ohde S, Miwa M, Ueda Y, et al. Oncocytic carcinoma of the nasal cavity with widespread lymph node metastases. *Auris Nasus Larynx* 2007; 34:393–6.
21. Gray SR, Cornog JL Jr, Seo IS. Oncocytic neoplasms of salivary glands: a report of fifteen cases including two malignant oncocytomas. *Cancer* 1976;38:1306–17.
22. Goode RK, Corio RL. Oncocytic adenocarcinoma of salivary glands. *Oral Surg Oral Med Oral Pathol* 1988;65:61–6.
23. Chu W, Strawitz JG. Oncocytoma of the parotid gland with malignant change. *Arch Surg* 1978;113:318–9.
24. Shah VN, Branstetter BF. Oncocytoma of the parotid gland: a potential false-positive finding on 18F-FDG PET. *AJR Am J Roentgenol* 2007;189:W212–4.