Int J Clin Exp Med 2017;10(2):3906-3911
www.ijcem.com /ISSN:1940-5901/IJCEM0035323

Case Report

Metachronous, solitary parotid gland metastasis of primary lung adenocarcinoma: a misdiagnosed case report and literature review

Chaogang Yang[1,2], Bin Xiong[1,2]

[1]*Department of Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China;* [2]*Hubei Key Laboratory of Tumor Biological Behaviors & Hubei Cancer Clinical Study Center, Wuhan, China*

Received July 8, 2016; Accepted September 30, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Parotid gland metastasis of lung cancer is extremely rare, especially as the only metastatic site of lung adenocarcinoma, no case has been reported. We sum up the experiences of missed-diagnosis through analyzing the diagnosis and management process of a 66-year-old Chinese male patient retrospectively who presented with parotid gland metastases of lung adenocarcinoma and reviewed related literatures. In conclusion, a potential metastases of lung cancer should not be ignored although it is extremely rare. Especially in patients with a prior history of cancer where the possibility of metastasis, even if improbable, should be kept in mind. Fine needle aspiration (FNA) is the first diagnostic procedure to be done and immunocytochemistry can provide valuable information. Superficial parotidectomy when feasible with adjuvant radiotherapy is the preferred approach for solitary metastasis of the parotid. The prognosis, however, remains poor regardless of the treatment modality used.

Keywords: Parotid gland, adenocarcinoma, lung cancer, metastasis, solitary

Introduction

Malignant tumors of the salivary glands are rare, accounting for more than 0.5% of all malignancies and approximately 3-5% of all head and neck cancers [1]. The overall incidence is estimated at approximately 1.3 cases per 100,000 per year [2]. Most malignant salivary gland tumors patients are in the sixth or seventh decade of life [3]. Primary malignancies of the salivary glands are common, and although metastatic to the salivary glands represents less than 10% of salivary gland tumors [1]. Metastatic malignancies from distant infraclavicular sites can spread to salivary glands, usually to the submandibular glands and to a lesser extent the parotids. Parotid gland as one of the three major salivary glands, metastases from distal primary is more rare, especially from primary lung cancer, only a few cases have been reported in the medical literature as isolated case reports or small series [4-9]. However, most of these cases were small cell carcinoma and accompanied with metastasis of other parts (lymph nodes, liver, bone, adrenal glands and brain). We are describing herein the case of lung adenocarcinoma which metastasize to the parotid gland as the first and single metastatic site and sum up our experience of missed-diagnosis combined with reviewing the literature.

Case report

A 66-year-old Chinese male presented with blood-stained sputum for six months and painful near the left ear for a week prior to attending our hospital. The patient had a history of heavy smoking for thirty years. On physical examination (PE), the left parotid gland could touch a small painful nodule, the size to be approximately 1×1 cm, with moderate texture and good activity, the rest of PE was normal. The patient had computed tomography (CT) of the thorax which showed a mass measuring 4.6 cm at its longest diameter in the left upper lung, with no lymph node in the mediastinum appearing enlarged (**Figure 1A**). The CT value was 40 HU and the enhanced CT value was 60 HU, meeting the CT manifestation of

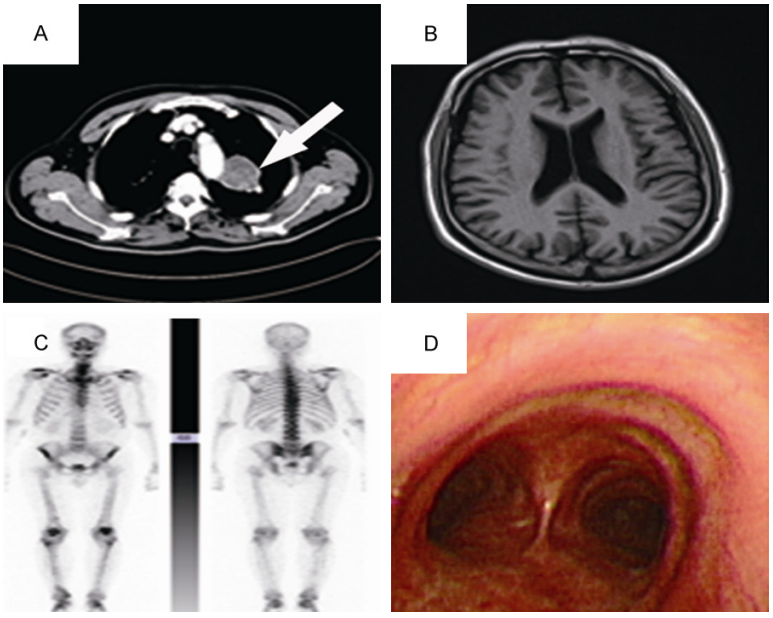

Figure 1. Preoperative assessment. A: Chest contrast-enhanced CT showing a mass with diameter of 4.6 cm in the left upper lung, with no lymph node in the mediastinum appearing enlarged. B, C: Cranial MRI and whole-body bone scanning scan are norma. D: No tumor is found through fiberbronchoscope.

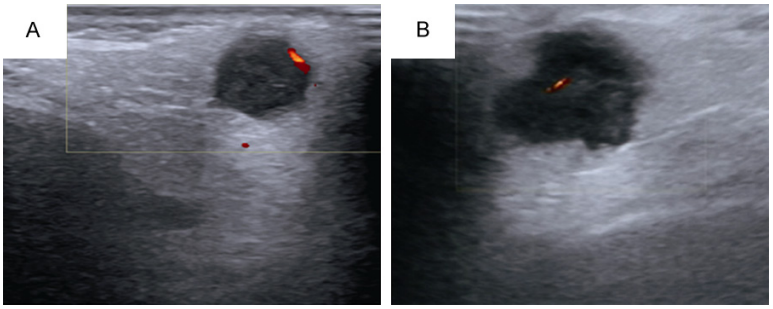

Figure 2. Ultrasound of parotid gland examination. A: Initial ultrasound of parotid gland showing a hypoechoic nodule with a size of 1.1×1.1×1.0 cm, with a little color blood flow signal displaying. B: The second ultrasound showed that the mass increased significantly compared with the previous, about 2.0×1.6×1.5 cm, and there was still a color flow signal displaying.

lung cancer. A hypoechoic nodule with a size of 1.1×1.1×1.0 cm was observed for the ultrasound of parotid gland, with a little color blood flow signal displaying (**Figure 2A**). Then, abdominal CT, cranial magnetic resonance imaging (MRI) and whole-body bone scanning were respectively performed, and no metastasis was discovered (**Figure 1B**, **1C**). The fiberbronchoscope and tumor markers were normal (**Figure 1D**). Then, CT-guided lung biopsy was operated, and pathology reported low-differentiated adenocarcinoma of lung. In light of all above findings, the patient was diagnosed with adenocarcinoma of lung (cT2bN0M0, Stage IIA) [10]. Considered that the parotid gland was a benign tumor and the patient had a strong surgical requirement, we performed an operation (left upper lobectomy + radical mediastinal lymph nodes dissection) via mini-incision [10]. Postoperative pathology reported low-differentiated adenocarcinoma of lung (**Figure 3A**), no metastasis of 5, 6, 7, 9, 10 group lymph nodes and wild type of EGFR (epidermal growth factor receptor) (**Figure 3C**, **3D**). Immunohistochemistry showed ALK (lung) (-), CgA (-), Syn (-), P40 (-), P63 (-), CD56 (-), CK5/6 (-), CK7 (+), TTF-1 (+), MOC-31 (+), Nap-A (+), Ki-67 (positive about 50%). Pathological stage was pT2bN0M0, IIA. According to the latest version of the NCCN Guidelines, the patient was put on four cycles of postoperative adjuvant chemotherapy with cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 [10], then reexamined regularly.

Five months later after operation, the patient was hospitalized again because of obvious pain and larger size of the left parotid gland nodule. PE found that the size was approximately 2×2 cm, with hard texture and poor activity. The ultrasound showed that the mass increased significantly compared with the previous, about 2.0×1.6×1.5 cm, and there was still a color flow signal displaying (**Figure 2B**). Then surgical treatment was recommended. All preoperative routine examinations and regular reexaminations were normal. After consulting with the patient and his family members, we performed superficialis parotidectomy. Postoperative pathology reported low-differentiated adenocarcinoma of lung metastases to parotid (**Figure 3B**). Immunohistochemistry showed CK5/6

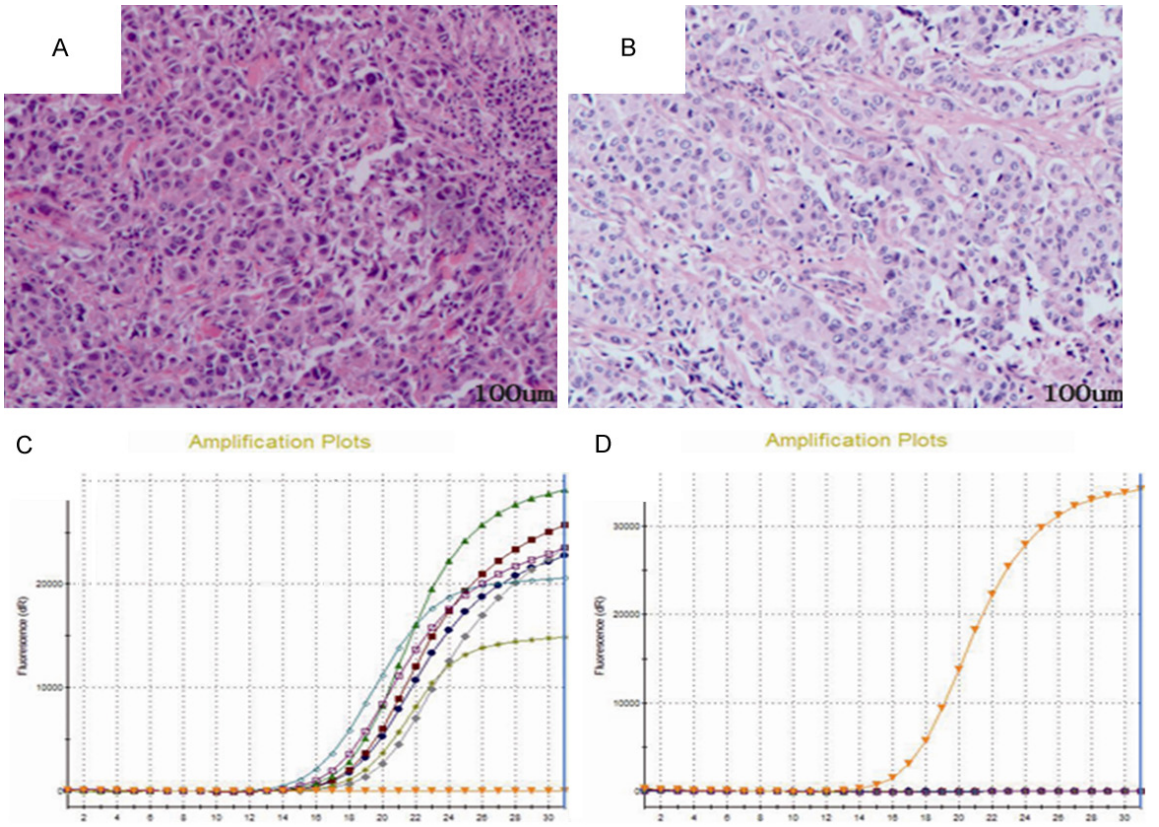

Figure 3. Histopathologic and molecular examination. A: Tumor histology of the left upper lung showing low-differentiated adenocarcinoma. B: Tumor histology of the left parotid gland showing low-differentiated metastasis adenocarcinoma of lung. C, D: Molecular examination showing wild type of EGFR.

(-), P63 (-), TTF-1 (+), MOC-31 (+), Nap-A (+), CK7 (+), CD147 (+), Ber-EP4 (+). Then, four cycles of adjuvant chemotherapy (gemcitabine 1250 mg/m^2 and cisplatin 75 mg/m^2), two courses of radiotherapy and following up (six months) were recommended, no progression was occurred.

Discussion and experiences summarize

Metastatic disease involving the parotid accounts for approximately 9E~14% of all parotid tumors [11]. As the largest major salivary glands, parotid glands are the only salivary glands with intraglandular lymph nodes, which makes it susceptible to metastases from local head and neck tumors, making up to 80% of the metastatic tumors to the parotid, squamous cell carcinoma and malignant melanomas from the upper airway and the foregut being the most common, followed by the skin, whereas metastases from distant primary is rare [12]. The reason for this is the difference in the number, anatomic relationship, and the drainage of the lymph nodes. The parotid gland is well supplied with lymphoid tissue, therefore, metastasis spreads mainly by lymphatic route [12]. So, this case with dissemination of the primary lung adenocarcinom to the parotid glands by hematogenous is a quite infrequent clinical event.

Lung cancer is the most frequent malignant disease and the most common cause of cancer-related deaths in the world [13, 14]. The number of new cases of lung and bronchus cancer was 57.3 per 100,000 per year and the number of deaths was 46.0 per 100,000 per year. Approximately 6.6% of men and women will be diagnosed with lung and bronchus cancer at some point during their lifetime. The percent five-year survival rate after being diagnosed with lung cancer is just only 17.7% [11, 12]. Nowadays, lung adenocarcinoma has become the highest incidence subtype of all lung cancers, followed by squamous cell carcinoma, accounting for almost half of

all lung cancers [15], most of which belong to peripheral lung cancer and are rich in blood vessels, leading to no obvious clinical symptoms and signs in early stage. However, the local invasion and the metastasis of the blood were earlier than that of squamous cell carcinoma. Therefore, the diagnosis of lung adenocarcinoma may possibly be a result of some or even a single metastatic focus. The most common site of distant spread is the mediastinal and supraclavicular lymph nodes, liver, bone, adrenals, and brain, and it is under a propensity to metastasize to any organ theoretically, such as oral cavity, gingiva, tongue, and parotid glands [16].

On reviewing the literature, there were a few reported parotid gland metastasis cases of lung cancer in the literatures [4-9]. Of which, only one case came from lung adenocarcinoma [9], which was accompanied with metastasis of other common parts of whole body at the same time of parotid metastasis. In this case, parotid gland was the starter and the only metastatic sites, without lymph nodes, liver, bone, brain, adrenal and other common parts of transfer. It has never been reported before, which also resulted in missed-diagnosis for the patients from a certain extent.

In clinical, most patients with a parotid neoplasm characterize by a painless mass or swelling of the gland. Signs or symptoms of facial nerve involvement are suggestive of a malignant origin rather than a benign tumor. Up to 30~40% of the patients with malignant tumor in parotid gland present with the symptoms of peripheral facial nerve paralysis, decreased sensitivity to pain in the buccal region and constricted opening of the mouth [17]. However, in this case, the patient showed a painful mass without any symptoms or signs of facial nerve palsy, which affected the accurate judgment of the nature of the masse and eventually resulted in the missed-diagnosis.

Fine needle aspiration (FNA) provides surgeons with valuable diagnostic information that may influence the surgical management of parotid gland tumors. It had been proved to be the primary diagnostic procedure with high sensitivity and specificity in identifying malignant and benign lesions of the parotid and differentiate metastatic lesions from a primary neoplasm of the parotid in numerous studies. Feinstein AJ et al. studied 272 cases of parotid gland tumors, revealing a sensitivity of 75.0% and specificity of 95.1% respectively [18]. Moreover, the study also showed that the positive and negative predictive value of FNA in diagnosing parotid gland tumors were 84.9% and 91.2%, respectively. A meta-analysis by Liu et al. evaluated the sensitivity, specificity and posttest probability of parotid FNA, the results demonstrated a sensitivity of 0.882 (95% CI, 0.509-0.982) and a specificity of 0.995 (95% CI, 0.960-0.999). The probabilities of nondiagnostic and indeterminate cytology were 0.053 (95% CI, 0.030-0.075) and 0.147 (95% CI, 0.106-0.188), respectively [19]. On the other hand, Seethala RR et al. compared the relative accuracy of FNA and frozen section (FS) in the diagnosis of parotid gland lesions, and showed that both FNA and FS provided a similar accuracy (90% vs. 88%) [20]. When metastatic carcinoma is identified by parotid FNA, restaging with 6FDG-PET CT scan could assist surgeons in evaluating locoregional of tumor and detecting other distant diseases [21]. In addition, radiological examination with CT and MRI has an important role in further supporting the clinical assessment regarding the benign or malignant nature of the tumor and defining its location (intraglandular vs. extraglandular) and the extent. However, clinician could not distinguish a primary malignant tumor of the parotid from a metastasis based on imaging criteria.

The management of parotid metastasis of lung origin is still a matter of debate. The treatment is planned according to radiological staging. With the different degree of disease transfer, treatment is consistently different. For diffuse metastatic disease, a combination of chemotherapy, immunotherapy and radiation therapy is practiced, however, the results is dismal. On the other hand, it is well known that management for metachronous, single metastasis is aggressive surgical resection. For the tumor totally restricted to the parotid without nodal involvement, a R0 parotidectomy whilst preservation of the facial nerve followed by radiotherapy to the parotid and neck is preferred by most authors [3-9, 22]. Bumpous reviewed related cases and concluded that a combination of surgical management with postoperative radiation could decrease locoregional recurrence [23]. Some authors suggested ipsi-

lateral neck dissection, however, only limited data exists regarding the benefit of such procedure. Nuyens et al. advocate the use of an ipsilateral neck dissection when the metastasis was from head and neck primaries as spread occurred predominantly via the lymphatic system, whereas, in cases of hematogenous spreading from distant sites, neck dissection was thought to be unnecessary [24]. Moreover, some reports favored adjuvant chemotherapy, the reason for that may be the coexistence of occult and microscopic metastasis.

Although metachronous solitary parotid metastases with longer disease-free survival are considered as favourable prognostic factors [25], some authors consider that radical parotid surgery has little effect on improving life expectancy and the management of a parotid metastasis is palliative, regardless of the therapeutic modalities used as the prognosis of such patients is dismal with a 5-year survival rate of only 10% [25]. Combining the experience and review of the literatures, surgical resection followed by postoperative radiotherapy, in our opinion, is a correct approach to cure the patient when parotid metastasis is only a metachronous, single metastasis, not extending to the surrounding tissue, which could improve local control. In the patient described herewith, parotidectomy with preservation of facial nerve was enlarged to the superficial lobe, without ipsilateral neck dissection because no lymph nodes were found in the preoperative imaging assessment. Then the patient was advised to receive four cycles of chemotherapy with GP (gemcitabine 1250 mg/m^2 and cisplatin 75 mg/m^2) regimen based on the fact that lung adenocarcinoma metastasized to the parotid gland by hematogenous. After the end of chemotherapy, the patients received two courses of radiotherapy to the parotid and neck. Subsequently, no progression occurred during the 6-mouth follow-up period.

In conclusion, we summarize the following experience items combining with our diagnosis and treatment process: first, when parotid mass appears, the anamnesis of the patient should be checked carefully; second, FNA is one of major importance in orientating the diagnosis; third, 6FDG-PET contributes greatly to lung cancer re-staging; fourth, surgery combined with post-operative chemotherapy and radiotherapy, should be considered as a therapeutic option for parotid gland metastases of lung adenocarcinoma, and the scope of operation should be determined according to the degree of tumor invasion; fifth, genetic testing may provide an alternative treatment option for lung adenocarcinoma patients with parotid metastasis.

All in all, for patients with a painful lump in the parotid gland in the process of diagnosis and management of lung cancer, we should be on high alert. Ignoring that may lead to misdiagnose, which will have a negative impact on the subsequent treatment, and negatively affect the lifetime survival rate and the prognosis of patient ultimately.

Disclosure of conflict of interest

None.

Address correspondence to: Bin Xiong, Department of Oncology, Zhongnan Hospital of Wuhan University, Hubei Key Laboratory of Tumor Biological Behaviors & Hubei Cancer Clinical Study Center, 169 Donghu Road, Wuchang District, Wuhan 430071, China. Tel: +86-27-67813152; Fax: +86-27-67812892; E-mail: binxiong1961@whu.edu.cn

References

[1] National Cancer Institute. PDQ Salivary Gland Cancer Treatment, National Cancer Institute, Bethesda, Md, USA, 2014.
[2] National Cancer Institute. SEER Cancer Statistics Review 1975-2011, Section 20 Cancer of the Oral Cavity and Pharynx, National Cancer Institute, 2014.
[3] Wahlberg P, Anderson H, Biörklund A, Möller T, Perfekt R. Carcinoma of the parotid and submandibular glands--a study of survival in 2465 patients. Oral Oncol 2002; 38: 706-13.
[4] Shi S, Fang QG, Liu FY, Sun CF. Parotid gland metastasis of lung cancer: a case report. World J Surg Oncol 2014; 12: 119.
[5] Boeger D, Hocke T, Esser D. Metastasis of a small cell carcinoma to the parotid gland. Laryngorhinootologie 2005; 84: 117-20.
[6] Ulubas B, Ozcan C, Polat A. Small cell lung cancer diagnosed with metastasis in parotid gland. J Craniofac Surg 2010; 21: 781-3.
[7] Shalowitz JI, Cassidy C, Anders CB. Parotid metastasis of small cell carcinoma of the lung causing facial nerve paralysis. J Oral Maxillofac Surg 1988; 46: 404-6.

[8] Katsurago N, Shiraishi Y, Hashizume M, Miyasaka Y. Long-term survival following multimodality treatment of metachronous metastases (parotid gland, adrenal gland, brain and mediastinal lymph node) after resection of non-small cell lung cancer; report of a case. Kyobu Geka 2006; 59: 168-71.

[9] Debnath CR, Shahjahan SM, Debnath MR, Alam MM, Moshwan MM, Khan MF, Rana MS, Himel RR, Ahmed S. Parotid gland metastasis-an unusual presentation of adenocarcinoma of lung. Mymensingh Med J 2015; 24: 175-7.

[10] Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, Cheney RT, Chirieac LR, D'Amico TA, Dilling TJ, Dobelbower MC, Govindan R, Hennon M, Horn L, Jahan TM, Komaki R, Lackner RP, Lanuti M, Lilenbaum R, Lin J, Loo BW Jr, Martins R, Otterson GA, Patel JD, Pisters KM, Reckamp K, Riely GJ, Schild SE, Shapiro TA, Sharma N, Stevenson J, Swanson SJ, Tauer K, Yang SC, Gregory K, Hughes M. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 4.2016. J Natl Compr Canc Netw 2016; 14: 255-64.

[11] Batsakis JG. Pathology consultation. Parotid gland and its lymph nodes as metastatic sites. Ann Otol Rhinol Laryngol 1983; 92: 209-10.

[12] Batsakis JG, Bautina E. Metastases to major salivary glands. Ann Otol Rhinol Laryngol 1990; 99: 501-3.

[13] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[14] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[15] Matsuda T, Machii R. Morphological distribution of lung cancer from Cancer Incidence in Five Continents Vol. X. Jpn J Clin Oncol 2015; 45: 404.

[16] Hirshberg A, Buchner A. Metastatic tumours to the oral region. An overview. Eur J Cancer B Oral Oncol 1995; 31: 355-60.

[17] Jungehuelsing M, Sittel C, Fischbach R, Wagner M, Stennert E. Limitations of magnetic resonance imaging in the evaluation of perineural tumor spread causing facial nerve paralysis. Arch Otolaryngol Head Neck Surg 2000; 126: 506-10.

[18] Feinstein AJ, Alonso J, Yang SE, St John M. Diagnostic Accuracy of Fine-Needle Aspiration for Parotid and Submandibular Gland Lesions. Otolaryngol Head Neck Surg 2016; 155: 431-6.

[19] Liu CC, Jethwa AR, Khariwala SS, Johnson J, Shin JJ. Sensitivity, Specificity, and Posttest Probability of Parotid Fine-Needle Aspiration: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg 2016; 154: 9-23.

[20] Seethala RR, LiVolsi VA, Baloch ZW. Relative accuracy of fine-needle aspiration and frozen section in the diagnosis of lesions of the parotid gland. Head Neck 2005; 27: 217-23.

[21] Stokkel MP, ten Broek FW, van Rijk PP. The role of FDG PET in the clinical management of head and neck cancer. Oral Oncol 1998; 34: 466-71.

[22] Raut V, Sinnathuray AR, Primrose WJ. Aggressive treatment of metastasis to the parotid. Ulster Med J 2004; 73: 85-8.

[23] Bumpous J. Metastatic cutaneous squamous cell carcinoma to the parotid and cervical lymph nodes: treatment and outcomes. Curr Opin Otolaryngol Head Neck Surg 2009; 17: 122-5.

[24] Nuyens M, Schüpbach J, Stauffer E, Zbären P. Metastatic disease to the parotid gland. Otolaryngol Head Neck Surg 2006; 135: 844-8.

[25] Jecker P, Hartwein J. Metastasis to the parotid gland: is a radical surgical approach justified? Am J Otolaryngol 1996; 17: 102-5.