Acta Med. Okayama, 2025
Vol. 79, No. 3, pp. 213-219

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

A Case of Chromophobe Renal Cell Carcinoma Metastasizing to the Cervical Lymph Nodes after Long-term Follow-up

Makoto Watanabe[a], Tomoyuki Ogawa[a], Kanao Kobayashi[b], Narutaka Katsuya[c], Akira Ishikawa[c], Takao Hamamoto[d]*, Hiroaki Tahara[d], Tsutomu Ueda[d], and Sachio Takeno[d]

[a]Department of Otolaryngology, Chugoku Rosai Hospital, Kure, Hiroshima 737-0134, Japan,
[b]Department of Nephrology and Urological Surgery, Chugoku Rosai Hospital, Kure, Hiroshima 737-0134, Japan,
[c]Department of Molecular Pathology, Graduate School of Medical Sciences, Hiroshima University, Hiroshima 734-8551, Japan,
[d]Department of Otolaryngology and Head and Neck Surgery, Hiroshima University Hospital, Hiroshima 734-8551, Japan

Renal cell carcinoma (RCC) can metastasize hematogenously and recur after a long dormancy. Chromophobe RCC metastasized to the cervical lymph nodes 10 years after the primary resection in a woman who underwent nephrectomy for RCC (T1aN0M0 stage I). Metastatic RCC diagnosis was confirmed by aspiration. The lymph node mass was resected, and the tumor cells matched chromophobe RCC metastasis. No adjuvant therapy was administered due to the lack of evidence regarding adjuvant therapy for chromophobe RCC. Long-term surveillance is crucial in RCC because of the possibility of late metastasis. We reviewed the clinical aspects and literature on metastatic cervical RCC.

Key words: renal cell carcinoma, cervical lymph node metastasis, late recurrence, head and neck

Renal cell carcinoma (RCC) can metastasize hematogenously to various parts of the body because of its rich renal vascular supply. A notable clinical feature of RCC is the occurrence of late recurrence and distant metastasis after extended periods of latency [1]. In this report, we present a case in which a gradually enlarging neck mass was detected during a 10-year follow-up period after the initial resection of the primary tumor. The diagnosis of metastatic RCC was confirmed after radical excision of the lesion. We also provide a comprehensive review of relevant literature.

Case Report

Present history. A 53-year-old woman with a history of urticaria and no other significant medical or familial history underwent retroperitoneoscopic right nephrectomy for right RCC (cT1aN0M0, Stage I) located close to the renal pelvis at the Department of Nephrology and Urological Surgery at Chugoku Rosai Hospital. Postoperative pathological diagnosis of the resected tissue confirmed chromophobe renal cell carcinoma pT1bN0. As the tumor was completely resected pathologically, no additional postoperative treatment was performed, and careful observation was conducted. Postoperative renal function remained within the normal range, and follow-up was conducted every six months using computed tomography (CT). Ten years postoperatively, a right cervical mass was incidentally detected during routine CT follow-up, prompting referral to the Department of Otolaryngology at Chugoku Rosai Hospital. The patient was asymptomatic, and no apparent mucosal lesions were observed in the head or

Received October 29, 2024; accepted March 6, 2025.
*Corresponding author. Phone: +81-82-257-5252; Fax: +81-82-257-5254
E-mail: takao0320@hiroshima-u.ac.jp (T. Hamamoto)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

neck region, including the pharynx. Cervical ultrasonography revealed a 2.5-cm mass compressing the bifurcation of the right common carotid artery. Although the location of the mass raised suspicion of a carotid body tumor, its isovascularity on ultrasonography led to fine-needle aspiration cytology, which suggested the possibility of metastatic RCC. Additional contrast-enhanced CT (Fig. 1A-C) and magnetic resonance imaging (Fig. 1D-F) confirmed a lesion primarily located at the right common carotid bifurcation, while positron emission tomography-CT (Fig. 2A) revealed no significant uptake outside the neck mass and no other notable findings in other organs. After multidisciplinary consultation with the nephrology and urology departments, surgical excision of the tumor was deemed necessary. However, given the potential for carotid artery invasion, the patient was referred to the Department of Otorhinolaryngology and Head and Neck Surgery at Hiroshima University Hospital for a complex surgical procedure.

Preoperative evaluation. The surgical plan was thoroughly explained to the patient. Informed consent for surgery was obtained, including the potential risk of massive hemorrhage due to carotid artery injury, the possibility of neurological sequelae, and the possible need for carotid artery reconstruction. Given the likelihood of intraoperative temporary carotid artery clamping, a carotid occlusion test was performed preoperatively by the Department of Cerebrovascular Surgery. Cerebral blood flow from the contralateral carotid artery and vertebral artery system was confirmed, allowing for the safe consideration of temporary clamping of the right carotid artery (Fig. 2B, C). The relationship between the tumor and nearby blood vessels was assessed using contrast-enhanced CT, and the patient was scheduled for surgical resection of the lesion for both diagnostic and therapeutic purposes (Fig. 2D-F).

Surgical plan. Given the potential need for temporary clamping of the internal and common carotid arteries and possible carotid reconstruction during tumor resection, backup support from the cardiovascular surgery department was requested. Preoperative embolization of the tumor-feeding vessels was not pursued as we planned to control any significant intraoperative bleeding by clamping the carotid arteries. Owing to the anticipated narrowing of the remaining internal carotid artery on the cephalic side, the inguinal vein and both the internal and external jugular veins were

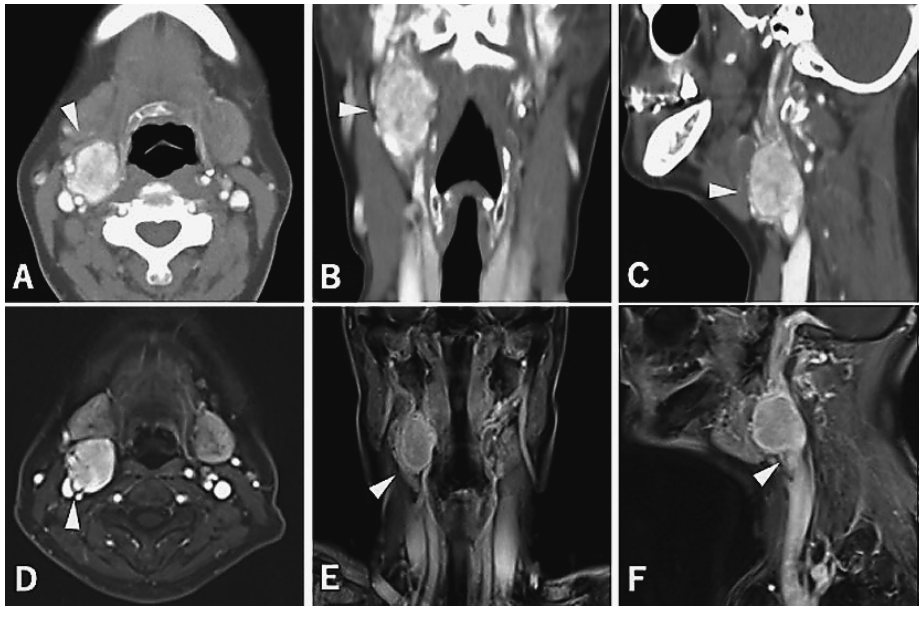

Fig. 1 Preoperative CT/MRI findings. **A**, **B**, **C**, Preoperative contrast-enhanced CT images demonstrating a mass with contrast enhancement at the carotid bifurcation (arrowhead); **D**, **E**, **F**, Preoperative contrast-enhanced MRI images showing a well-defined border between the mass and the internal jugular vein, but with signal loss at the interface with the carotid artery wall (arrowhead).
CT, computed tomography; MRI, magnetic resonance imaging.

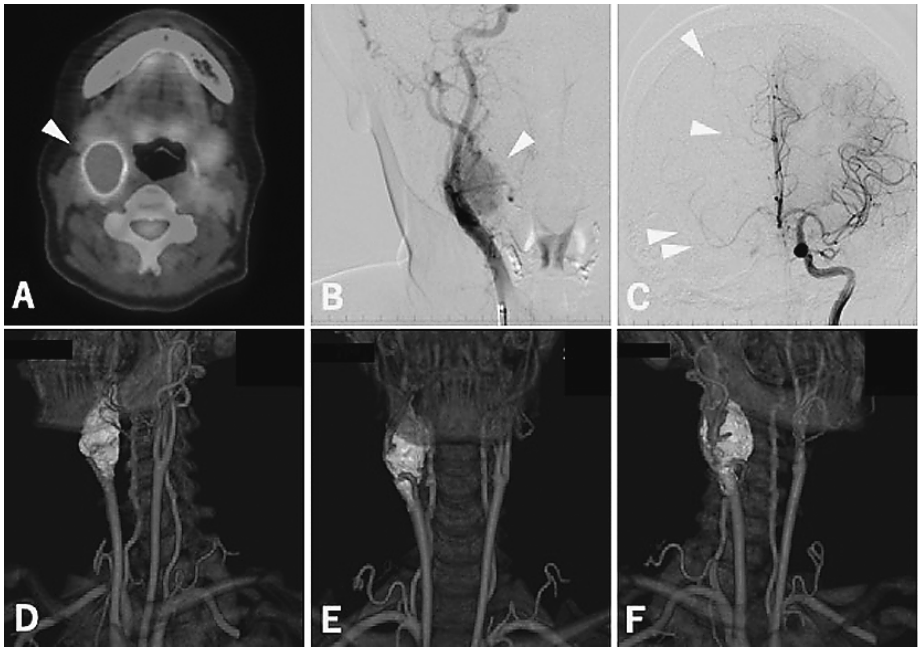

Fig. 2 Preoperative PET-CT/Angiography/3D-CT findings. **A**, A preoperative positron emission tomography-CT image showing intense uptake in the cervical lesion (arrowhead); **B**, Preoperative angiography revealing a contrast-enhanced mass originating from the right common carotid artery (arrowhead); **C**, Contrast injection from the left internal carotid artery demonstrating perfusion of the right cerebral artery system via the Circle of Willis (arrowhead); **D**, **E**, **F**, Left oblique (**D**), frontal (**E**), and right oblique (**F**): 3D-CT images illustrating the course of the artery (red) and the mass (yellow-green).
CT, computed tomography; PET, positron emission tomography; 3D, three-dimensional.

considered potential graft sites for carotid artery reconstruction. The final decision regarding the reconstruction of vessels was made intraoperatively.

Intraoperative findings. An oblique incision was made in the right neck to access the right cervical tumor. The common carotid artery, internal jugular vein, and vagus nerve within the carotid sheath were identified and preserved caudally before approaching the tumor. Lymph nodes from the inferior internal deep cervical region were sent for intraoperative frozen section analysis, which revealed no metastasis. By dissecting further, the tumor was found to compress the hypoglossal, vagus, and accessory nerves and internal jugular vein; however, no obvious invasion was observed, allowing for careful dissection and preservation of all nerves (Fig. 3A, B). The branches of the external carotid artery and surrounding vessels were meticulously ligated and dissected on the cranial side of the tumor. Upon reaching the carotid bifurcation, the tumor was found to be separable from the internal carotid artery, although adhesions were also observed at the external carotid artery bifurcation. After temporary clamping of the carotid artery, both proximally and distally, the tumor was excised en bloc, including a portion of the vessel wall, and the resulting defect was closed using continuous sutures (Fig. 3C). An artificial covering was applied to the wound, and after confirming hemostasis, surgery was concluded (Fig. 3D). The total operative time was 241 min (blood loss, 114 mL).

Perioperative course. The patient was monitored in the intensive care unit with endotracheal intubation for postoperative management, owing to the potential risks of postoperative hemorrhage, pharyngeal edema, and nerve palsy. On postoperative day 1, mild edema was noted in the right lateral pharyngeal wall; however, no vocal cord or pharyngeal paralysis was observed. Subsequently, the patient was extubated and transferred to the general ward for further observation. The postoperative course was uneventful, and the patient was discharged on postoperative day 7 without any significant complications.

Pathological findings. The excised lymph node

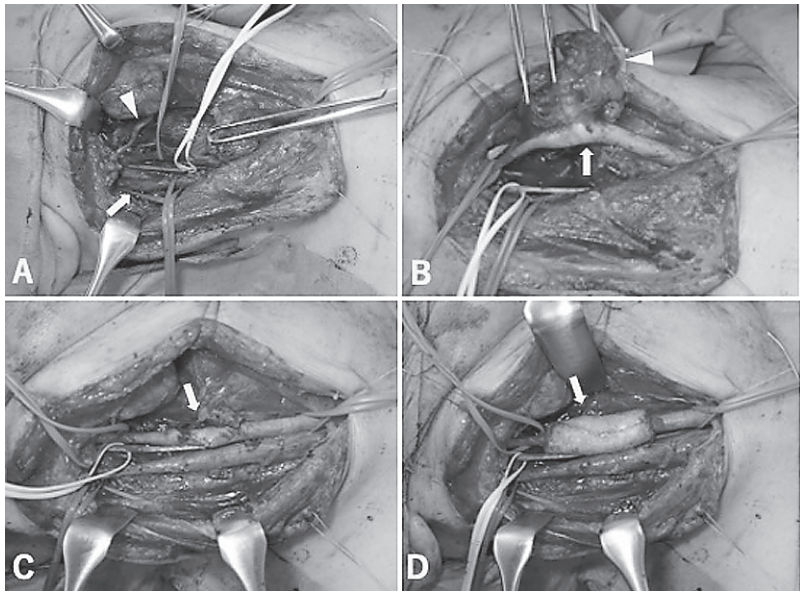

Fig. 3 Intraoperative Photographs. **A**, Identification of the common carotid artery (red tape), internal jugular vein (blue tape), vagus nerve (yellow tape), and preservation of the accessory nerve (yellow arrow) and hypoglossal nerve (yellow arrowhead); **B**, Carotid artery adhesion (yellow arrow) and the tumor (yellow arrowhead) before tumor resection; **C**, Continuous suture closure of the resected area following resection of the external carotid artery bifurcation (yellow arrowheads); **D**, Vascular closure covered with TacoSeal (yellow arrowheads).

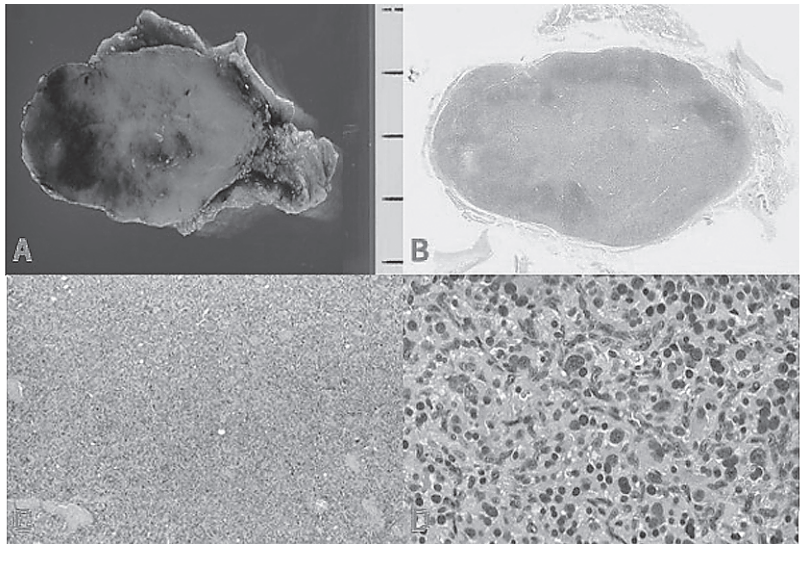

Fig. 4 Pathological Findings. **A**, Gross appearance of the tumor. The lymph node specimen was enlarged to 2 cm, revealing a grayish-white tumor on the cut surface; **B**, Low-power view of the tumor: the follicular structure of the normal lymph node has disappeared; **C**, Weakly magnified image of the tumor site: tumor cells with acidophilic cytoplasm are densely hyperplastic within the lymph nodes; **D**, Highly magnified image: at higher magnification, the tumor cells exhibit marked nuclear atypia, with large irregularly shaped nuclei and sporadic raisin-like nuclei.

tissue measured up to 4.5 cm in size. Grossly, the lymph node specimen was enlarged to 2 cm, and a grayish-white tumor was observed on the split surface (Fig. 4A). Histologically, the follicular structure of the lymph node was absent in the loupe image (Fig. 4B), and tumor cells with acidophilic cytoplasm densely populated the lymph nodes (Fig. 4C). Strongly magnified images of the tumor cells showed conspicuous nuclear atypia with scattered, large, malformed, and raisin-like nuclei (Fig. 4D). Immunohistochemically, the tumor cells were positive for vimentin, partially positive for c-Kit, negative for CA9, and negative for CK7. The morphological features were similar to those of a previously resected specimen of right renal carcinoma, and the diagnosis was consistent with lymph node metastasis from anaplastic RCC. Cancer cells were found in only one lymph node, and no malignant cells were found in the other lymph nodes.

Postoperative course. Following multidisciplinary consultation with the nephrology and urology teams and considering the clinical course, preoperative imaging, and postoperative pathology findings, a decision was made not to administer adjuvant postoperative therapy. The patient is currently being closely monitored, and no evidence of recurrent metastasis has been observed approximately one year postoperatively.

Discussion

This case represents a rare clinical course of RCC, characterized by metastasis to a right cervical lymph node after an extended period of disease-free survival following primary tumor resection. As the CT scans were limited to the range up to the supraclavicular region during the monthly CT follow-up, the tumor grew and eventually entered the imaging field, leading to its incidental detection.

Late recurrence has been reported more frequently in RCC than in other carcinomas and is considered a unique biological characteristic of RCC [1].

In this case, the tumor size was evaluated as less than 4 cm using ultrasound, leading to a clinical classification of cT1aN0M0. However, because the tumor was located close to the renal pelvis, a nephrectomy was performed. As a result, the pathological diagnosis was confirmed as chromophobe renal cell carcinoma. Based on the size of the tumor size and absence of extension into the renal vein, the tumor was classified as pT1bN0M0. Although the tumor was completely resected, its classification as T1b indicated a slightly larger size, warranting a more frequent follow-up to monitor for potential recurrence or metastasis. Over the first 5 postoperative years, blood examinations and CT scans (chest and abdomen) were performed every 6 months. Annual blood examination and CT scans were also performed for 5 years postoperatively, considering that RCC has the potential to recure even after more than 10 years, and in this case recurrence was detected despite our patient being asymptomatic. Efrain *et al.* described a mechanism by which microscopic metastases may remain dormant for extended periods without proliferation, eventually becoming active and clinically apparent and often triggered by a decline in immune function [2]. Similarly, microscopic cancer cells may undergo distant metastasis and later reactivate through immune evasion to develop into overt malignancies [3]. In the present case, recurrence occurred approximately 10 years after initial treatment, suggesting the possibility of latent metastasis progressively enlarging over time.

Malignant tumors from other organs may metastasize to the head and neck region through several mechanisms, including direct invasion of intracranial lesions into the nasal cavity; direct extension of esophageal, pulmonary, or mediastinal lesions into the neck; lymphatic spread; or distant hematogenous metastasis [4]. Hematogenous metastasis is typically associated with distant organ involvement, whereas lymphatic metastasis often involves the regional lymph nodes. Cervical lymph node metastasis from intra-abdominal organs is most frequently observed in the left supraclavicular lymph node via the thoracic duct, as exemplified by Virchow metastasis [5].

RCCs are highly vascularized and frequently metastasize. The predominant route of metastasis to the head and neck region is believed to be hematogenous [2, 6]. Among malignancies from other regions that metastasize to the head and neck, RCC ranks third after breast and lung cancers, with > 10% of distant RCC metastases involving the head and neck, particularly the nasal sinuses [6]. Hematogenous metastasis of RCC to the head and neck is thought to occur via Batson's venous plexus (paravertebral venous plexus), which bypasses the pulmonary circulation [7]. The paravertebral venous plexus is connected to the superior and inferior vena cava, pterygoid venous plexus, and cavernous sinus. Owing to the absence of valves in this venous system,

increased thoracic or abdominal pressure may drive tumor cells into the vertebral venous system, allowing direct access to the head and neck without passing through pulmonary circulation [8].

Anja *et al*. reviewed 671 cases of RCC with head and neck metastases and found 13 cases of cervical lymph node metastasis, primarily involving a Virchow node. These cases were believed to be either Virchow metastases or secondary to hematogenous metastatic lesions in the sinuses or thyroid [9]. In the present case, the patient had solitary lymph node metastasis at the right carotid bifurcation, with no metastasis to the lower cervical lymph nodes. Pathologically, the tumor exhibited characteristics consistent with lymphatic metastasis. To date, only three reports of isolated cervical lymph node metastasis without hematogenous metastasis to other organs or Virchow metastasis have been published, making it exceptionally rare [10-12]. Based on the metastatic pattern, microscopic hematogenous metastasis may have initially occurred in the head and neck region, subsequently leading to right cervical lymph node involvement through regional lymphatic drainage.

In the treatment strategy for head and neck squamous cell carcinoma, chemoradiotherapy is recommended as an adjunctive postoperative treatment for patients with high-risk recurrent metastatic disease, particularly when extranodal extension is identified in the postoperative pathology of cervical lymph node metastases [13]. In this case, although a small portion of the metastatic lymph nodes exhibited extranodal invasion, the surgical margins were negative. As the treatment strategy typically applied to head and neck squamous cell carcinoma was not appropriate in this case, considering the potential for risk, it was determined that the applicability of postoperative treatment should be evaluated. However, standard adjuvant therapy for RCC following surgery has not yet been established.

Because chromophobe RCC is radioresistant and the efficacy of postoperative radiotherapy for this subtype has not been demonstrated, postoperative radiotherapy was not selected [14]. With regard to postoperative chemotherapy, the effectiveness of molecularly targeted therapies as adjuvant treatments has been explored in recent years. Although adjuvant therapy with sunitinib demonstrated prolonged disease-free survival (DFS) in the S-TRAC clinical trial for high-risk clear cell RCC, chromophobe RCC was not included as a target in that clinical study [15]. The efficacy of sunitinib and sorafenib as adjuvant therapies was evaluated in the ASSURE trial, which included a small number of chromophobe RCC cases. However, no improvement in DFS or overall survival was observed, and a high rate of discontinuation due to adverse effects was reported [16]. Furthermore, in regard to RCC, there are limited postoperative treatment options that have demonstrated significant efficacy when combined with chemotherapy [17]. In this case, the use of molecularly targeted therapy as an adjuvant treatment was considered. However, since the evidence for adjuvant molecular targeted therapy in chromophobe RCC is not well established, we decided not to proceed with additional treatment.

Following discussions with the nephrology and urology teams, the decision was made not to pursue additional postoperative therapy.

Although it appeared that only a short postoperative follow-up was necessary in this case, there was a possibility that metastatic lesions in the head and neck region could become apparent during ongoing surveillance. We therefore planned to conduct a CT scan of the head and neck region every six months. We also have to perform follow-up to underscore the need for careful long-term monitoring.

Conclusion

We encountered a case of chromophobe RCC presenting with solitary cervical lymph node metastasis at the right carotid bifurcation that occurred 10 years after the resection of the primary tumor. The metastasis was successfully treated with surgical excision, including combined resection of the external carotid artery. RCC is known for its potential to recur after prolonged latency, underscoring the importance of vigilance and long-term follow-ups.

Acknowledgments. We thank Akira Taguchi, a cerebrovascular surgeon, and Taiichi Takasaki, a cardiovascular surgeon at Hiroshima University Hospital, for their assistance.

References

1. Park YH, Baik KD, Lee YJ, Ku JH, Kim HH and Kwak C: Late recurrence of renal cell carcinoma >5 years after surgery: Clinicopathological characteristics and prognosis. BJU Int (2012) 110:

E553-558.
2. Castillo E and Martinez K: Late Recurrence of Renal Cell Carcinoma in Unusual Sites 23 Years After Nephrectomy. Cureus (2023) 15: e45707.
3. Qin Z, Xu Q, Hu H, Yu L and Zeng S: Extracellular Vesicles in Renal Cell Carcinoma: Multifaceted Roles and Potential Applications Identified by Experimental and Computational Methods. Front Oncol (2020) 10: 724.
4. Mastronikolis NS, Delides A, Kyrodimos E, Piperigkou Z, Spyropoulou D, Giotakis E, Tsiambas E and Karamanos NK: Insights into metastatic roadmap of head and neck cancer squamous cell carcinoma based on clinical, histopathological and molecular profiles: Mol Biol Rep (2024) 51: 597.
5. Adler C, Lubner MG, Menias CO, Lubner SJ and Dahiya N: What's in a node? The clinical and radiologic significance of Virchow's node: Abdom Radiol (NY) (2022) 47: 2244-2253.
6. Sountoulides P, Metaxa L and Cindolo L: Atypical presentations and rare metastatic sites of renal cell carcinoma: a review of case reports: J Med Case Rep (2011) 5: 429.
7. Brook RC, Tung K and Oeppen R: Batson's plexus and retrograde venous spread of malignancy - a pictorial review: Cancer Imaging (2014) 14: 40.
8. Closca RM, Nicoara A, Rakitovan M, Mot IC and Baderca F: Unpredictable Metastasis in the Head and Neck Region: A Diagnostic Immunohistochemical Challenge: Diagnostics (Basel) (2023) 13: 3513.
9. Lieder A, Guenzel T, Lebentrau S, Schneider C and Franzen A: Diagnostic relevance of metastatic renal cell carcinoma in the head and neck: An evaluation of 22 cases in 671 patients: Int Braz J Urol (2017) 43: 202-208.
10. Garje R, Elhag D, Yasin HA, Acharya L, Vaena D and Dahmoush L: Comprehensive review of chromophobe renal cell carcinoma: Crit Rev Oncol Hematol (2021) 160: 103287.
11. Alain R, Rovert JM, Hardev SP, Daniel JG, Allan JP, Anup P, Yen-Hwa C, Bernard E, Frede D, Ahmed M, Giacomo C, Brigitte L, Piort T, Jan N Paola G, Mariajose L, Xun L, Jean-Francois M, Krishnan R, Michelle C, Michael S and Jean-J P: Adjuvant Sunitinib in High-Risk Renal-Cell Carinoma after Nephrectomy: N Eng J Med (2016) 375: 2246-2254.
12. Haas NB, Manola J and Uzzo RG: Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomized, phase 3 trial: Lancet (2016) 387: 2008-2016.
13. Tzanakakis GN, McCully KS and Vezeridis MP: Solitary cervical node metastasis in renal cell carcinoma: RI Med J (1990) 73: 113-115.
14. Savaş MC, Çelik I, Benekli M, Güllü IH and Tekuzman G: Renal Cell Carcinoma Presenting as Solitary Cervical Node Metastasis Compressing the Brachial Plexus: Nephron (1998) 79: 107-108.
15. Nakadai J, Ide H, Hirasawa Y, Ito Y, Uchida Y and Masuda T: Isolated cervical lymph node metastasis of renal pelvic squamous cell carcinoma: A case report: Can Urol Assoc J (2013) 7: E344-346.
16. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK and Lefèbvre JL: Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501): Head Neck (2005) 27: 843-850.
17. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M and Mafakher L: Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment: G Ital Nefrol (2022) 39: 2022-vol3.