

Metastasis of genitourinary tumors to the head and neck region

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Abstract The objective of the present study is to characterize genitourinary tumors (GU) metastatic to the head and neck and to determine long-term prognoses. Using a retrospective chart review of 734 patients treated between January 1995 and May 2005 with an ICD-9 code pertaining to a metastatic head and neck cancer, we found 37 patients with primary GU tumors. There were 24 cases of prostate cancer, 10 cases of renal cell carcinoma, and 4 cases of transitional cell carcinoma. Sixteen of 24 patients (67%) with prostate cancer had a cranial metastasis while 6 of 9 (67%) patients with renal cell carcinoma had cerebral metastasis. We concluded that prolonged survival is possible in prostate cancer patients treated aggressively with radiation and

chemotherapy, indicating that early detection and aggressive screening are important in these patients.

Keywords Carcinoma of the prostate · Renal cell carcinoma · Transitional cell carcinoma · Genitourinary tumors

Introduction

Head and neck cancer is the fifth most common cancer worldwide [1]. In the United States, head and neck cancers account for 3.3% of all malignancies [2]. The cervical lymph nodes are a common site of metastasis for cancers originating in the upper aerodigestive tract. Rarely, cancers originating from sites other than the head and neck can metastasize to the cervical lymph node chain. However, genitourinary tract neoplasms make up a significant proportion of these cancers and should be considered in the differential diagnosis of neoplastic lesions of the head and neck [3]. A study reported and identified 31 (3.7%) of 845 genitourinary tumors metastasized to the head and neck and 21 tumors (2.5%) metastasized to the cervical lymph nodes [3]. Ferlito et al. [4] reported a series of genitourinary tumors and found this group to be the third most frequent tumor site to metastasize to the supraclavicular fossa.

Epithelioid tumors in the head and neck are common and include both primary and metastatic lesions [5]. Metastatic lesions, clinical factors, tumor location, and ancillary immunohistochemical studies must be taken into consideration to help the clinician and the pathologist to determine the site of origin. A group of unusual, but important, primary tumors that can metastasize to the head and neck are genitourinary tumors consisting of carcinoma of the prostate (CAP), renal cell carcinoma (RCC), which is also

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known as clear cell carcinoma, and bladder cancer, of which the most common type by far is transitional cell carcinoma (TCC) [6].

Prostate carcinoma is the second most common cause of cancer death among American men [7]. It has been established that more than 30% of men over the age of 50 will develop this devastating disease [8]. Established risk factors include age, ethnicity and family history [9]. Although most of the metastatic prostate cancers will arise in the axial skeleton or the pelvic lymph nodes, it has been reported to spread to the axillary and cervical lymph nodes of the head and neck region [3, 4]. A retrospective study identified 26 cases of metastatic prostatic carcinoma involving the supraclavicular lymph nodes, which were the most common site of invasion [4]. One study reported 26 cases in which the most common primaries with metastasis to the sphenoid sinus were prostate adenocarcinoma, with an incidence of 20% [10]. Ferlito et al. [4] reported 5 of 21 cases (24%) were normal for serum acid phosphatase, 7 of 20 cases (35%) had no evidence of metastases to bones, 8 of 19 (42%) cases had normal rectal examination and 19 of 26 cases presented with physical findings of urinary obstructive symptoms or enlarged lymph nodes despite no history of prostate cancer. This shows that the diagnosis of prostate cancer cannot rely only on clinical or serological examination. Rather it also depends highly on the combination of cytological or histological features with immunostaining using prostate-specific antigen and prostatic acid phosphatase.

Renal cell carcinoma accounts for 3% of all malignancies and can metastasize to any location in the body, and its propensity to metastasize to unusual sites has been well documented. Approximately, 30% of patients with RCC present with metastatic disease, 25% with locally advanced renal carcinoma, and 45% with localized disease [11]. It is the third most frequent neoplasm to metastasize to the head and neck region preceded only by breast and lung cancer [12]. In spite of being reported infrequently, head and neck region metastases may be linked to RCC in up to 8–15% of cases [11]. Specifically, regions in the head and neck include the paranasal sinuses, larynx, jaws, temporal bones, thyroid gland, and parotid glands [13, 14]. RCC metastases to the nose and paranasal sinuses are most commonly affected followed by the tongue [15].

In a minority of patients, the classical presentation of RCC manifests itself in the classical triad of pain, hematuria, and flank mass. Unfortunately, head and neck metastasis from RCC is usually a manifestation of widespread disease and it is often indicative of advanced disease. RCC may remain clinically occult for most of its course. The expected 5- and 10-year survival rates for these patients are 5–30 and 0–5%, respectively [11]. Approximately, 75% of patients with RCC metastasize most commonly to the

lungs, 20% to bone, 18% to liver, 36% to soft tissue and 8% to central nervous system [16].

Bladder neoplasm accounts for 2–6% of all tumors, with bladder cancer becoming the fourth most common cancer occurring in the United States, with an increase in incidence after 65 years [17]. Bladder cancer is the second most prevalent cancer for men and the tenth most prevalent cancer for women [17]. Bladder carcinoma metastases are commonly found in bone (75%), followed by lymph nodes (26%) and lung (20%) [4]. Supraclavicular lymph node metastases are rare and indicate widespread disease with poor prognosis. Metastases of the head and neck regions are also uncommon and their most frequent sites are the brain, supraclavicular nodes, neck nodes and the skull [3]. Hessian et al. [3] reported and identified 3 of 207 cases (1.4%) for cervical lymph nodes. Very few cases of TCC metastasize to the oral cavity, including one reported case in the maxilla [18] and seven reports identified in the mandible [19]. Only four cases have been described in the oral soft tissues one in the tongue [20] and one in the submandibular gland [21].

Metastatic tumors to the head and neck are extremely rare. Therefore, the literature is based largely on sporadic case reports. Possible routes of metastasis to the head and neck include arterial, venous and lymphatic circulations. These include paravertebral venous plexus (Batson's) or through the thoracic lymphatic duct. Overall, correct diagnosis is important, as these patients may achieve remission and prolonged survival with chemotherapy, irradiation and/or hormonal therapy.

Materials and methods

The Systematized Nomenclature of Medicine (SNOMED) files of the Greater Los Angeles VA Medical System (GLAVAMS) Department of Pathology were searched for cases of metastatic CAP, RCC, and TCC. SNOMED is a newer version of the widely used Decentralized Hospital Computer Program (DHCP) which is a way of classifying medical terms based on topography and morphology. Multiple searches were performed through VISTA system which is a Massachusetts General Hospital Utility Multi-Programming System (MUMPS)-based hospital database. Medical records of 14,756 patients with genitourinary cancers being treated or referred to the GLAVAMS from January 1995 to May 2005 were pulled out. Among those, 734 patients who had an ICD-9 code pertaining to a metastatic head and neck cancer were selected and their medical records were thoroughly studied. All relevant slides were examined, and clinical information was obtained from the referring physician's patient charts (Tables 1, 2 and 3).

Table 1 Characteristics of prostate cancer (CAP) cases metastatic to the head and neck

Case #	Site of mets	Gleason score	Presentation of metastasis	Age at CAP	Survival (years)	Year at mets
1	Virchow	9	Swelling	52	1	1
2	Skull (diffuse)	4+X	Pain in cranium	54	5	5
3	Temporal lobe	7	Incontinence LE weakness	69	10	8
4	Dura matter	5	Diplopia, blindness	74	9a	1
5	Dura matter	7	Confusion	56	10a	7
6	Virchow	7	Neck mass	79	3	1
7	Orbit skull base	9	Blindness	85	3	2
8	Temporal lobe	8	HA	59	5	3
9	Virchow	8	Neck mass	80	15	14
10	Virchow	6	Neck mass	57	13	9
11	Midbrain, cavernous sinus	NA	Right hand weakness	75	4	3
12	Brain (diffuse)	7	Disequilibrium	62	9	1
13	Virchow	9	Neck mass	57	7	7
14	Orbit frontal lobe	NA	Proptosis, ptosis redness	70	7	6
15	Brain (diffuse)	7	Confusion, seizure	63	2	2
16	Temporal lobe	7	Left side weakness	52	5	4
17	Parotid	9	VII cranial nerve palsy	62	1	1
18	Clivus	NA	XII cranial nerve palsy	59	5	5
19	Brain (diffuse)	NA	NA	58	10	10
20	Sphenoid	7	Left side hyperreflexia, anisocoria	71	10	10
21	Orbit dura matter	NA	Blindness and headache	63	3	2
22	Virchow	NA	Neck mass	75	4	2
23	Virchow	8	Neck mass	59	2	1
24	Skull (fronto temporal)	NA	Confusion	75	4	4

Case #	PSA * serum	Hormone response	Treatment
1	5,500	Ref [1]	Goserelin, bicalutamide
2	>1,000	Ref	Goserelin, flutamide, TRFP
3	4	Treatment late in the course of disease	Fronto temporal craniotomy, XRT, goserelin/flutamide, TURP
4	2522	Sen [2]	Luprolide, ketoconazole, XRT
5	938	Sen	Goserelin, bicalutimide, flutamide, ketoconazole, TURP
6	279	Sen	Goserelin, bicalutimide,
7	126	Sen	XRT, goserelin, flutamide
8	13	Ref	Prostatectomy, goserelin, flutamide, ketoconazole, estramustine, VP 16, XRT
9	7869	Ref	Prostatectomy, bicalutamide,
10	5.2	Ref	Prostatectomy, goserelin, bicalutimide, docetaxel
11	NA	Ref	Hormonal TX, XRT, vinblastine, estramustine
12	284	Sen	Orchiectomy, hormonal TX, XRT
13	14	Ref	XRT, goserelin, bicalutimide, ketoconazole, flutamide
14	1165	Ref	XRT, leperamide, bicalutamide, vinblastine, estramustine
15	51	Ref	Goserelin, flutamide
16	>100	Ref	Craniotomy, TURP, orchiectomy, chemotherapy
17	NA	Ref	XRT, estramustine
18	66	Ref	XRT, total prostatectomy, bilateral orchiectomy
19	214	NA	Lupramide
20	46	Ref	XRT, hormonal therapy
21	13	Ref	XRT, hormonal therapy
22	4	Ref	XRT, estramustin/taxotere carboplatin,
23	9	Ref	Goserelin, bicalutamide, XRT
24	NA	Ref	Lupramide, bicalutimide

Table 2 Metastatic RCC of head and neck region and their characteristics

Case #	Mets	Present	Age at Dx	Year at mets	Survival (years)	Tob.
1	Frontal lobe	HA, LUE Numbness, weakness	24	4	17 ^a	–
2	Cerebellum	HA ^b , N/V, blurry vision	51	0	5	+
3	Frontal lobe, mandible, scalp	Cystic lesions in the scalp ^b	55	0	1	+
4	Frontal lobe	Frontal HA, memory loss	53	1	3	–
5	Frontal, occipital lobes, cerebellum	Dizziness ^b , dysarthria, dysphagia	58	0	1	+
6	Parotid	Parotid mass	67	1	14 ^a	+
7	Eye	^c	55	11	14	+
8	Tongue	Tongue cyst	27	0	1	–
9	Brain	HA	62	0	<1	+

Case #	Pathology	Other mets	Para-neoplastic syndromes	Treatments
1	Poorly differentiated carcinoma, staining for GFAP	Lung	None	Right frontal lobe craniotomy, nephrectomy, immune therapy, chemotherapy
2	Poorly differentiated (grade III),	Bone marrow, liver	None	Nephrectomy, posterior fossa craniotomy, hepatic wedge resection, chemotherapy, XRT
3	^c	Adrenal, lungs, liver, skin	Hypercalcemia	IL-2, IFN a, XRT
4	Clear cell type (grade II)	None	Hypercalcemia	Nephrectomy, craniotomy
5	Clear cell (not graded)	Lungs	Hypercalcemia	XRT
6	Moderately well differentiated (grade II)	Colon	Polycythemia, hypercalcemia	Nephrectomy, colectomy
7	^c	Bone	None	Nephrectomy, XRT, eye enucleation
8	Grade III	Spine, lung, liver	Hypercalcemia	XRT, nephrectomy
9	Diagnosed by FNA	Bone, lungs	Hypercalcemia	XRT

^a Still alive^b Cancer presented with mets^c Initial diagnosis and work up at another institution, further records not available**Table 3** Transitional cell carcinoma (TCC) of the bladder with metastasis to the brain

Case #	Site of mets	Presentation	Pathology	Age at TCC	Survival (years)
1	Brain (diffuse)	Headache	NA	58	2
2	Cerebellum	Gate disturbance, jerky movements, headache	High grade-poorly differentiated	73	1
3	Sphenoid, cavernous sinus	Ptosis, headache	Papillary TCC, grade II	62	1
4	Cerebellum	Headache	High grade TCC	55	7

Case #	Tobacco	Other sites	Co-morbidities	Treatment
1	30PY	Spinal cord	High triglyceride	XRT, spinal fusion, transurethral resection
2	60PY	Liver, lung	Prostate cancer	Sub-occipital craniotomy, transurethral resection
3	50PY	Liver	DVT	XRT
4	None	None	DVT	Transurethral resection, chemotherapy, sub-occipital craniotomy

Results

We describe 37 cases of metastatic CAP, RCC, and TCC to the head and neck, consisting of 24 cases of CAP, 9 cases of RCC, and 4 cases of TCC.

Carcinoma of the prostate

Among 24 patients with CAP 16 patients (67%) had a cranial metastasis. The location of the metastases consisted of brain, cerebellum, dura, skull, scalp or a combination of

these. Seven patients (29%) had a brain metastasis. Five cases (21%) had a bony skull metastasis. Three patients (13%) had a metastasis to the meninges and in two cases (11%) there was a pure dural metastasis. One of the cases with a temporal lobe metastasis also had a tumor on the scalp (not in Table). In three out of eight patients (37%) with brain metastasis, the tumor was found in the temporal lobe. One patient (13%) had a pure frontal lobe metastasis. Interestingly, both patients with frontal lobe metastases also had orbit and dural involvement. In both cases of dural involvement, the involvement was confined to the frontal dura matter. The base of the skull was a favorite site of involvement in patients with metastasis to the skull. There were two cases with spread to the clivus and base of the skull and one case of sphenoid bone involvement.

Seven patients (29%) had a tumor in their supraclavicular lymph nodes (Virchow's lymph node). Three cases (13%) had involvement of the orbit and presented with eye pain, proptosis, or loss of vision, while in one case the tumor cells had spread to the optic nerve. One case (4%) had involvement of the parotid gland.

The mean Gleason score was 7.5 (range 5–9). However, after reviewing the patient histories in the CPRS system and studying their files in the medical records, eight cases did not have a complete Gleason's grade. Those patients were diagnosed before January 1995 with the primary diagnosis made in another institution.

The average age of onset for the prostate cancer was 62.8 (range 52–85) years and the average years of survival after the diagnosis of CAP was 6.1 years (range 1–15). Two of the 24 patients (8%) are alive. The mean survival after the diagnosis of the head and neck metastases was less than 4.5 years. Bone involvement was almost a universal finding among the cases. Only two cases (11%) had only soft tissue involvement in the head and neck.

The average PSA at the time of diagnosis was 54.2, which was followed by a drop of the values after the initial treatment. This was followed by a rise before the presentation of the metastases and the average PSA at that time was 958; however, three patients had missing data. All of the cases except for one case were refractory to hormonal therapy. Craniotomy was performed in two patients with a solitary temporal lobe tumor.

Two patients had no history of CAP at the time of biopsy of the head and neck metastasis, and 12 patients (50%) had other widespread metastatic disease at the time of presentation of the metastases. Histologically, most of the tumors had epithelioid cells with prominent nucleoli and cribriform, solid, or infiltrating single cell growth patterns. PSA and PSAP immunohistochemical stains were positive in all cases except case 14 which had a positive PSA staining and negative PSAP staining. Two of 12 patients with known follow-up are alive after radiation or hormonal therapy.

Renal cell carcinoma

Among nine patients with RCC with metastases to the head and neck, six patients (67%) had metastases to the brain. There was one metastasis each to the parotid gland, the eye, and the tongue (11%). One patient among the group had metastases to both the brain and mandible. No metastases to the supraclavicular lymph node were reported. All but one of the patients with brain metastases had frontal lobe involvement; the remaining metastasis was to the cerebellum. One patient had concomitant involvement of the occipital and frontal lobes and cerebellum. The mean age of diagnosis was 50.2 (range 24–67). In five (56%) patients RCC presented with the head involvement. Two patients developed metastases after 1 year of RCC diagnosis and one patient developed eye metastasis 11 years after the initial diagnosis of the RCC. Two-thirds of the patients were tobacco users with the mean age at the presentation of their cancer of 58 versus 34.6 years in patients without history of tobacco use. Six patients had hypercalcemia at some point during the course of their disease. Three patients with single brain metastasis went through craniotomy and resection of the tumor. The mean survival was 8.6 years after the craniotomy versus 6.2 years in three patients who were not treated with craniotomy.

Transitional cell carcinoma

In this study, we had four patients with TCC who developed cranial metastases during the course of their disease. Two patients had metastases to the cerebellum, and in both the tumor was resected. All but one of the patients with TCC had over 30 pack year history of tobacco use. One patient with metastasis to the cerebellum lived for 7 years following craniotomy. One patient had metastases to the bony and vascular structures of the skull without brain parenchyma involvement. None of the patients in this group had involvement of the neck or facial structures.

Discussion

Surgery and radiation therapy, recently augmented by induction chemotherapy, can be effective in the treatment of head and neck carcinomas. These results demonstrate a fair prognosis with possible prolonged survival with metastatic CAP to the head and neck after appropriate diagnosis and subsequent hormone and radiation therapy. Given this survival advantage with treatment, it is critical to consider the diagnosis of metastatic CAP when evaluating a metastatic malignant epithelioid tumor in the head and neck of an elderly man. In this study, temporal lobe was a favorite site for metastasis among patients with intracranial spread of the

tumor. This finding along with the fact that 50% of the cases had a single tumor allows for the possibility of potentially improving the patients' prognosis with craniotomy and resection of the tumor. Correct diagnosis is crucial, as these patients may achieve remission and prolonged survival with irradiation and hormonal therapy.

Our results show a clear tendency of RCC to metastasize to the frontal lobe. The second favorite location for this cancer to metastasize was to the cerebellum. It was shown that patients with solitary RCC metastasis to the brain greatly benefit from aggressive intervention and tumor resection. This finding further emphasizes the importance of early detection and management of these metastases in this patient population with special attention to any newly developed headache, and motor or sensory deficit in this group. Including a thorough neurologic examination in each follow-up visit for patients with RCC might have a positive influence on their life expectancy. The finding of lower age of onset in RCC patients without a history of tobacco use might be explained by a genetic propensity for developing cancer in this group. All the patients in the RCC group who had age of onset of over 50 years also had a history of tobacco use. This finding was striking in that it could pose tobacco use as a major risk factor for RCC patients to develop head and neck metastases. This finding was also true in patients with TCC in whom 75% with brain metastases had a strong history of tobacco use.

In general, the presence of metastases in the patient population with genitourinary cancers heralds a poor prognosis making the discovery of these cancers in the head and neck an oncologically important finding. The negative impact of head and neck metastases was especially shown to be true in prostate cancer patients whereas under certain circumstances patients with metastatic RCC to the head and neck might be good candidates for further intervention and have better outcomes.

Partial or total nephrectomy is the therapeutic approach usually used in metastatic disease to improve the quality of life or symptomatic relief [22]. Treatment of RCC metastasis in the head and neck is directed mainly towards palliation. Excision is usually performed to control pain and to manage any potential complications from a space occupying mass in the head and neck region, including the brain. Radiotherapy can improve symptomatic relief or quality of life for perhaps a few months. Little data exist regarding the use of systemic therapy in the setting of RCC metastasis to the head and neck. Still, most of the patients die within 1 year after detection of head and neck metastasis; therefore, therapeutic decisions should maximize comfort and minimize morbidity considering the poor long-term prognosis at this stage of the disease.

Lymph node metastasis has long been known to be a poor prognostic factor in kidney cancer and is an important

prognostic factor even in the presence of distant hematogenous metastasis. Lymph node involvement has a poor prognosis with a 5-year survival rate of 5–30%, which happens to be similar to systemic metastases. In spite of studies suggesting benefit from extended lymph node dissection, there appears to be inconclusive data from controlled, randomized studies to support any surgical advantage [23]. Whether a patient will benefit lymph node dissection involving an early or isolated involvement of lymph nodes has yet to be investigated in controlled, randomized clinical studies.

Chemotherapy combined with interferon has shown to provide palliative benefit in some patients with RCC. One prospective trial compared and showed that in properly selected patients with metastatic disease, immunologic therapy following radical nephrectomy may improve time to progression. Nephrectomy combined with systemic cytokine gave a greater survival advantage over the group treated with only immunotherapy [24]. Nevertheless, immunologic agents are limited and often prematurely stopped due to their systemic side effects and toxicity.

Newer agents targeting the VEGF pathway such as bevacizumab and sorafenib have shown to improve progression-free survival in metastatic RCC [25, 26]. Early phase trials with bevacizumab and sorafenib may provide hope for cytokine-refractory patients with metastatic RCC.

Genitourinary tumors have been shown to metastasize to the head and neck region in rare instances. Therefore, the work-up of a new head or neck lesion in light of a history of genitourinary tumors should include metastases as part of the differential diagnosis. If a diagnosis of genitourinary metastases is established, additional therapeutic options, including immunotherapy, surgery, and chemotherapy should be discussed with the patient despite the poor prognosis.

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