Management of Metastatic Lesions to the Craniovertebral Junction

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INTRODUCTION

Craniovertebral junction (CVJ) metastases are a rare and challenging pathology. The CVJ includes the occipital condyles and the atlanto-axial (AA) spine. The primary treatment goals for metastases to the spine are palliative in nature. Due to the rare occurrence of metastases in the CVJ region, there is very little literature, and most of the literature is limited to case series (Table 1) (1,3,4,6,10,13,17,28,33,35,40). However, principles of management of metastatic lesions to other regions of the spine can be translated to management of lesions in the CVJ. The primary goals of treating metastatic lesions to the CVJ are palliative in nature. Improvement/stabilization of neurological exam, restoration of spinal stability, pain control, and local tumor control are the goals of treatment. Furthermore, treatment is multidisciplinary including radiation, chemotherapy, and when appropriate, surgery.

ABSTRACT

The craniovertebral junction (CVJ) is a challenging region for the management of metastases. Although metastases to the CVJ are rare, the incidence is increasing as the prognoses of cancer patients continue to improve. In this review, the epidemiology and natural history are reviewed. Key features on radiographic studies are discussed so that the clinician can assess the optimal treatment paradigm for these patients. Lastly, we discuss which patients are should be considered for surgery and which patients should just have radiation without operative intervention.

KEY WORDS: Craniocervical, craniovertebral, management, metastases, occipital-cervical

Epidemiology

The spine is the third most common location of metastases after the liver and lungs (25). In fact, as much as 30-40% of cancer patients will experience metastases to their spine at some point during the course of their disease (27,38). Metastases to the craniovertebral junction (CVJ) are rare representing 0.5% of spinal metastases, and the literature is sparse in regards to the treatment of metastases to the CVJ (25). Several tumor types have been found to metastasize to the CVJ including breast (35%), non-small cell lung cancer (13%), and prostate cancer (10%) (6,10,28). Other tumor types that represent a small percentage of metastases to the CVJ include lymphoma, multiple myeloma, and renal cell carcinoma (25).

Signs and Symptoms

Patients presenting with metastases to the CVJ may have signs and symptoms manifesting form compression
Table 1: Literature pertaining to surgery for patients with CVJ metastases

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th># of Patients</th>
<th>Objective</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker JF, et al. 2015</td>
<td>reviewed all surgical stabilizations</td>
<td>6 patients over 4 years</td>
<td>review results in surgical management of C2 lesions at a single institution</td>
<td>Cases were treated by posterior instrumentation from either O-C1 or C1 to the subaxial cervical spine. Median survivorship after surgery was 283 d</td>
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<td>(Baker, Shafqat et al. 2015)</td>
<td>of metastatic spine lesions at a single institution</td>
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<tr>
<td>Shin H, et al. 2006</td>
<td>Retrospective study</td>
<td>46 patients over 13 years</td>
<td>To provide recommendations based on factors associated with occipital cervical fusion (OCF)</td>
<td>Patients presenting with neck pain had a 71% chance of undergoing OCF. Patients with chordomas and metastatic tumors were most likely to require OCF. Recommend OCF if 50% or more of one condyle is removed</td>
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<td>(Shin, Barrenechea et al. 2006)</td>
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<tr>
<td>Laohacharoenombat W, et al. 1990</td>
<td>Technical note</td>
<td>3 patients</td>
<td>A method of rigid occipitocervical fixation is described which uses an occipital pin passed through the external occipital protuberance</td>
<td>The occipital pin was tested in a cadaver skull and was found to withstand a distraction force of 30-50 kgs. 3 patients with grossly unstable upper cervical spines due to metastasis were able to walk as a result of this surgery</td>
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<td>(Laohacharoenombat and Suphachatwong 1990)</td>
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<tr>
<td>Vaccaro AR, et al. 2010</td>
<td>Literature search</td>
<td>799 patients</td>
<td>Examine outcomes of various OCF surgical techniques in different disease states</td>
<td>Screw/rod techniques had the highest rate of fusion. OCF performed for tumor had the lowest fusion rate (57.14%)</td>
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<td>(Winegar, Lawrence et al. 2010)</td>
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<tr>
<td>Wozasek GE, et al. 1988</td>
<td>Case Report: Isolated C2 metastatic</td>
<td>1 patient</td>
<td>describe the unique case of cervical spinal manifestation after liver transplantation because of primary hepatic cancer</td>
<td>Pain and threatening, neurological deficit require an active action, even if curative treatment is unlikely. The remaining survival time after appearance of osseous metastasis is on the average 9-12 months and justifies an operation</td>
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<tr>
<td>(Wozasek, Wruhs et al. 1988)</td>
<td>hepatocellular carcinoma lesion</td>
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<td>Bilsky MH, et al. 2002</td>
<td>Retrospective review of a prospectively maintained spine database</td>
<td>33 patients over a 6 year period</td>
<td>To review the experience of a multidisciplinary tertiary referral oncology center in diagnosing and managing metastatic disease of the atlantoaxial spine and to establish treatment parameters.</td>
<td>Radiation therapy was used successfully to treat patients with normal alignment or minimal subluxation. Selected patients warrant immediate stabilization. Patients with persistent pain and inability to wean from a hard collar after non-operative therapy also should be considered for surgery. Posterior stabilization provides pain relief and neurologic preservation or recovery without the need for anterior decompression</td>
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<td>(Bilsky, Shannon et al. 2002)</td>
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<tr>
<td>Xu R, et al. 2010</td>
<td>Case report of metastatic non-small cell lung cancer to Occipito-atlantal joint</td>
<td>1 patient and literature review</td>
<td>To better define craniovertebral instability due to lesions occurring at the junction of the occiput and atlas</td>
<td>A drastic improvement in debilitating mechanical neck pain was noted following an O-C fusion. Spinal fusion may afford significant and rapid resolution of mechanical neck pain and should be considered in the management of patients—even those with end-stage oncologic disease.</td>
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<td>(Xu, Sciubba et al. 2010)</td>
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of the brainstem, cranial nerves, cervical spinal cord and its roots, and the CVJ-region vasculature (i.e. vertebral arteries, anterior spinal artery). Depending on the tumor pathology, the acuity of symptom presentation varies. Metastases in the CVJ can cause mechanical destabilization from cranial settling, basilar impression, and AA instability. Patients oftentimes present with neck stiffness, mechanical pain, and occipital neuralgia as their primary symptoms. As with most tumors of the subaxial spine, flexion/extension movements may elicit pain. However, patients may also develop pain with rotation of the head, which is a much more specific symptom localizing to the AA region. In fact, as much as 90% of patients with CVJ metastases may have pain associated with rotation. However, this pain may not necessarily be indicative of instability requiring surgery. Severe rotational pain at the AA region may result from stress or destruction from the AA facet articulations or from the broad insertion of muscles to C2 and the occiput. (Phillips and Levine 1989)

Compression of the C2 nerve root may result in occipital neuralgia (6).

Patients may also present with signs of spinal cord or cranial nerve compression or present with symptoms of cranial nerve dysfunction (i.e. tongue weakness), lower extremity weakness and atrophy, pyramidal tract findings, ataxia, dysmetria, gait disturbances (i.e. spastic gait), and paresthesias of the extremities (31). Significant tumor encroachment of the occipital condyles may encroach on the hypoglossal nerve as it traverses the hypoglossal canal. Myelopathy from high-grade epidural spinal cord compression can present in as much as 22% of cases. However, most of the literature quotes it as much lower and for the most part it is fairly rare given the large diameter of the spinal canal at the CVJ. When spinal cord compression occurs, it is most commonly in the context of anterior AA subluxation rather than soft-tissue epidural disease. Early presentation of neck pain in many of these patients may also bring them to medical attention before any significant compression from either epidural disease or fracture subluxation occurs. In cases where spinal cord compression does occur, weakness and hand clumsiness secondary to spasticity are the most common motor symptoms experienced by these patients (23). A syndrome consisting of neck pain, hand atrophy and weakness, and leg stiffness can be seen in some patients with CVJ metastases (7). It is unusual to see bladder incontinence but patients may experience urgency and hesitancy. Lastly, one must be cognizant that rapid deterioration and death may result from respiratory arrest and apnea caused by lesions in the CVJ (36).

**Imaging**

There are multiple imaging studies that may help in the diagnosis and management of metastatic lesions to the CVJ. These studies include magnetic resonance imaging (MRI), computed tomography (CT), plain X-ray, and nuclear medicine studies such as positron emission tomography (PET).

Plain film radiography may be the first imaging modality used to assess neck pain in many patients, but it is not particularly sensitive for detecting tumor-infiltrated bone. Plain films are helpful merely in assessing spinal alignment. Dynamic flexion/extension films should be avoided in this population of patients because of the risk of iatrogenic fracture dislocation.

CT is a better imaging modality for the assessment of bone infiltration by tumor and the extent of osteolytic destruction. Reconstructed sagittal and coronal images may also be used in the assessment of spinal alignment. CT scans are also very important in surgical planning to assess and plan for potential instrumentation of the occipital keel, C1 lateral masses, and C2 pedicles or pars.

MRI is the most sensitive and specific imaging modality to assess bone and soft-tissue infiltration and destruction by tumor. The proximity and anatomic relationship between tumor and critical neurologic and vascular structures is best assessed with this modality.

Nuclear medicine modalities are helpful in assessing systemic disease burden and may detect early signs of metastasis to the CVJ. Bone scans detect increased osteoblastic activity but are nonspecific for tumor. [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) PET may be helpful in differentiating neoplastic from benign disease processes. In cases that a CVJ lesion is the only lesion detected on systemic CT and MRI, [18F]FDG PET may be helpful in determining the next step in the diagnostic workup. Percutaneous needle biopsies of lesions in the CVJ are challenging and may be very dangerous depending on the location of the tumor. Transoral biopsies are also not an option because of the fear of seeding tumor cell in oral cavity. In such a situation, [18F]FDG PET may help to differentiate a benign lesion that may be followed versus a metastatic lesion that needs to be treated more acutely. Studies have found that metastases have higher standardized uptake values (SUVs) on PET than benign lesions and thus [18F]FDG PET may play a useful role in guiding management of new CVJ lesions with uncertain lesion pathology (21).
Treatment Decision Making

Treatment of metastatic lesions to the CVJ will entail a multi-modal approach involving chemotherapy, radiation, and surgery. Chemotherapy is very specific to the tumor type and biology, and in itself can be entire discussion, thus this article will focus on radiation and surgery for metastatic lesions in the CVJ.

Radiation

Radiation may be performed as an adjuvant to surgery to irradiate any residual tumor or it can be performed alone without surgery in certain scenarios. The decision to radiate alone can be made if 1) there is mechanical stability in the CVJ and 2) there is no significant spinal canal and foraminal impingement/invasion. Several studies have supported that standard fraction external beam radiation therapy (EBRT) can be used in patients with normal spinal alignment and minimal fracture subluxations. These patients may experience an improvement in mechanical neck pain, cessation of deformity progression, and possibility of weaning from a hard cervical collar. In a retrospective review of 33 patients with metastases to the AA spine, Bilsky et al described 25 patients were initially treated non-operatively with either EBRT (n = 23) or chemotherapy (n = 2), and 8 patients underwent initial operation. In the non-operatively treated group, 23 of the 25 patients had significant pain resolution until death or last follow-up assessment. Five patients required subsequent operation either for significant fracture subluxations or after neoadjuvant chemotherapy. Of the patients with fracture subluxations, two were present before external beam radiation therapy, and one occurred later from rapid tumor progression. Posterior instrumentation was performed in all 13 patients who underwent surgery, and no patient required anterior decompression and stabilization. All the surgically treated patients experienced significant pain resolution (6). However, the effectiveness of external beam radiation therapy (EBRT) is limited by spinal cord tolerance, which can take no more than 50 Gy in 1.8-2.0 Gy fractions per 5-10cm length of spinal cord. This results in conventional external beam radiation therapy doses to be subtherapeutic for most metastatic tumors to the spine, especially solid tumors (12).

With the advent of image-guided intensity-modulated therapy, clinicians are now able to deliver high-dose radiation (i.e., stereotactic radiosurgery [SRS]) to tumors, with a significantly larger biological effective dose while sparing the spinal cord or toxic radiation doses. Even radiation-resistant tumors are found to respond. Several series studying spinal SRS using single fraction doses of 14-24 Gy have reported local control rates of more than 90% at 16-36 months of follow-up compared with only 20% control rates with conventional EBRT (11,22,41). Thus, SRS may be highly effective in the local control of CVJ metastases (Figure 1). In a study of 25 patient with CVJ metastases, Azad et al found that in the absence of unstable pathological fracture and spinal cord compression, metastatic tumors of the CVJ can be safely and effectively treated with SRS with radiographic tumor stability in 80% of patients, pain alleviation in nearly two-thirds, and no serious complications from SRS (4). Furthermore, as will be discussed below, SRS is a powerful adjunct in the setting of separation surgery (26).

Surgery

Surgery is indicated in patients who present with spinal instability from fracture subluxation, neurologic deterioration from spinal compression, or inability to provide any further radiation to the region because of exceeded maximal doses. Patients presenting with mechanical neck pain with radiographic signs of spinal instability including significant fracture subluxation (greater than 5mm subluxation or 3.5mm subluxation along with greater than 10 degrees angulation) (9). In such patients, instrumented stabilization is necessary and may improve mechanical neck pain (33). Surgery may be contemplated even when there is normal spinal alignment if the patient has lytic lesions to a spine and unable to tolerate a hard cervical collar. However, most patients with normal alignment will not require surgery. Other indications for surgery in the treatment of metastases to the CVJ include, exceeded maximal radiation to an existing CVJ metastasis that continues to enlarge, high-grade epidural spinal cord compression, and planned resection after neoadjuvant therapy for certain tumors such as osteogenic sarcoma.

Several studies have demonstrated that posterior fixation provides sufficiently durable fixation for patients with CVJ lesions (Figure 2) (6,10,15,18,33). Fusion across each level has significant consequences on range of motion and thus it must be considered carefully which levels require fixation from instability. For example, need to instrument up to the occiput is dependent on spinal alignment and the need to reduce the fracture subluxation. Laminectomy and occipital cervical fixation are necessary when the fracture subluxation cannot be reduced. If there is normal spinal alignment
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Figure 1: This is a 68 year-old woman with a history of metastatic renal cell carcinoma who presented with a 2 week history of worsening neck pain. A,B) pre- and post-gadolinium MRI showed an enhancing lytic lesion in the C2 body and odontoid process. C) There was minimal canal stenosis. Shortly after initial imaging, she sustained a mechanical fall with sudden worsening of pain. She remained neurologically intact. CT of the neck revealed a new pathologic fracture of C2. She was urgently taken for surgical stabilization and vertebroplasty. G) C1-3 instrumented fusion was performed. Vertebroplasty was performed at C2. H) Post-operatively, she underwent fractionated stereotactic radiosurgery using Cyberknife. She received a dose of 27 Gy delivered in 3 fractions to the margin of the target volume (PTV) and her spinal cord was constrained to < 18Gy. CT myelogram was used to delineate the spinal cord due to artifact from surgical hardware.
or the fracture subluxation can be reduced in extension, instrumentation of the posterior elements can provide adequate fixation without requiring instrumentation up to the occiput. Such constructs include Sonntag, Gallie, Brook-Jenkins, or C1-2 screw (i.e. transarticular screws, C1 lateral mass, C2 pars or pedicle screws) techniques. In cases that the lamina is preserved, sublaminar wires or interlaminar hooks may also be used.

Extension of fixation to the occiput is necessary when patients present with spinal instability from fracture subluxation. These patients often have significant osteolytic and ligamentous destruction of multiple spinal elements including the occipital condyles, C1-2 lateral masses, or C2 body/odontoid. Inability to reduce a significant AA subluxation is another indication to extend instrumentation to the occiput. Several studies have suggested that the majority of fractures cannot be reduced in extension and thus require occipital cervical fixation (10,25). Occipital cervical fixation techniques have great evolved over the years. Early techniques of occipitocervical fusion includes Luque rectangles with sublaminar and occipital wires augmented with bone grafts (29). With the development of lateral mass and pedicle screws, several new occipital fixation techniques such as the use of occipital plates were developed. With occipital plating systems, it is important to place them along the midline occipital keel, where the bone thickness is greatest, in order to maximize the pullout strength of the screws. The occipital plate should be placed below the superior nuchal line and external occipital protuberance to avoid injury to the transverse sinus and torcula.

As mentioned earlier, the spinal canal diameter is the CVJ is relatively large and thus spinal cord compression rarely occurs in the absence of anterior fracture subluxation of the body or dens of C2. If subluxation cannot be reduced with extension or instrumentation alone, then laminectomy of C1 and C2 may be needed to decompress the spinal cord. Although multiple different anterior (i.e. transoral-transpharyngeal, transoral tranlabiombidibular transpharyngeal, anterolateral retropharyngeal transcervical, mandibular swing transcervical approach) and lateral transervical approaches have been described for primary tumors of the CVJ, (2,8,13,19,24,32,34). these approaches are rarely indicated in the treatment of metastases to the CVJ. One potential application of an anterior approach for CVJ metastases would be in the case of significant anterior epidural metastatic disease compressing on the spinal cord however significant mortality rates as high as 32% have been reported (16). These approaches can be associated with pharyngeal dysfunction, tumor seeding in the oral cavity, malocclusion. Temporary tracheostomies and gastrostomies may be required for these patients. Numerous anterior reconstruction strategies are available including bone grafts with a kickout plate and a Harms cage with flanges secured to adjacent vertebrae with screws, (25) but these anterior reconstructions are nevertheless still associated with a high failure rate (1,30). Given the substantial morbidity associated with an-

Figure 2: This is a 78 year-old man with known urothelial cancer who initially presented with 2 months of severe neck pain, lancinating pain down the left arm, and legs giving out every time he looked up. Magnetic resonance images (MRI’s) of the atlanto-occipital junction. A) An axial image demonstrating an extensive C2 lesion encompassing the odontoid and much of the paraspinal tissues. The lesion is beginning to encroach on the spinal canal, but there are no signal changes yet in the spinal cord. There was also neural foraminal stenosis at C2/3, 3/4, 4/5, and 5/6. B) On sagittal it is evident that the tumor is completely encompassing the ventral elements of C1-2. The patient had known urothelial carcinoma. C) Because of instability at C1-2 and significant complaints of neck pain, the patient was instrumented from occiput to C4 (avoiding instrumentation at C1-2) and decompressed from C1-3. The patient did very well after surgery with significant improvement in his mechanical neck pain.
terior approaches to CVJ tumors, it is best to avoid these approaches if possible. Fortunately, most CVJ metastases can be adequately decompressed and the spinal alignment corrected with instrumentation all through a posterior approach. If anterior epidural disease does need to be decompressed, a posterolateral approach may be utilized. With the posterolateral approach, the C1/2 joint is partially resected. However, care must be taken not to injure the vertebral artery. At C2, the vertebral artery is lateral to the spinal cord but care must be taken as tumor may displace the vertebral artery away from its normal location of the foramen transversarium. Decompression of anterior epidural disease at C1 is more complicated because the vertebral artery courses inferomedially to avoid the vertebral artery. An adequate amount of tumor needs to be removed to relieve compression on the spinal cord and provide for a safe corridor to deliver SRS. Furthermore, lateral paraspinal tumor adjacent to the vertebral arteries may be treated with conventional EBRT or SRS.

CONCLUSION

Although CVJ metastases are relatively rare, their incidence is likely to continue to increase as the life expectancy of cancer patients continues to improve. Thus, it is important to be comfortable with the management of lesions to this challenging and dangerous region of the spine to avoid catastrophic consequences such as quadriplegia and respiratory arrest. Clinicians must be able to detect early signs of CVJ involvement, such as neck pain with a rotational component, so that radiographic workup can be started early in the disease course before significant spinal instability results. In the absence of spinal instability and neurological deficits, most metastases to the CVJ can be managed with EBRT or SRS. The patients should be kept in a hard cervical collar until demonstration of spinal stability. The primary indications for surgery are spinal instability from fracture subluxation, neurologic deterioration, or inability to provide any further radiation to the region because of exceeded maximal dose. When surgery is required, decompression and fixation can be accomplished through a posterior approach, and an anterior approach is rarely necessary. Baring these principles in mind will help in more safely managing this metastases in the CVJ.

REFERENCES


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