Successful Treatment of Anal Canal Cancer Metastasis to the Cranial Bones: A Case Report and Literature Review

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Abstract. Single metastasis to the cranial bone represents a very uncommon occurrence that can arise from an anal canal cancer. No cases of cranial bone metastasis from anal canal carcinoma are available in the literature. Herein, we present a case of a unique metastatic lesion to the right parietal bone that occurred after curative chemoradiotherapy of primary squamous cell anal canal carcinoma. The patient received radiotherapy and systemic platinum-based chemotherapy, with optimal local control, high compliance and a well tolerable level of toxicity.

Tumors that tend to metastasize to bone structures do not neglect the dome of the skull as a target. Metastases to the cranial bones are relatively rare, accounting for less than 5% of all secondary bone locations (1). At present, they remain a challenging disease to treat and current guidelines are mainly designed to address improvement in patients’ quality of life (QoL) (2). Actually, there is lack of specific guidelines regarding the best therapeutic approach in cranial bone metastasis. Therefore, understanding the role of radiation therapy (RT), chemotherapy (CHT), surgery (S) or combinations of these modalities is of paramount importance, especially in patients with local control of primary tumor.

Herein, we describe a case of cranial bone metastasis of anal canal carcinoma, supporting the proposal that RT is a reasonable primary treatment option in the management of these patients. A comprehensive overview of metastatic tumor to the cranial bones is also provided in order to illustrate the main diagnostic, therapeutic and prognostic aspects of this entity.

All procedures performed were in accordance with the ethical standards of the institutional research committee and comparable with ethical standards. Informed consent was obtained from all individual participants included in the study.

Case Description

A 69-years old Caucasian female presented to the clinic with vaginal swelling and enlarged left-sided inguinal lymph node in June 2013. Clinical examination revealed a primary anal canal lesion. Biopsy of perianal lesion revealed a squamous cell carcinoma that was human papillomavirus (HPV)-negative. Staging computed tomography (CT) of chest, abdomen and pelvis confirmed the metastasis in inguinal lymph node and the vagina tumor invasion, without distant metastasis (cT4, cN2 M0, according to American joint committee on cancer staging 7th edition).

Due to massive loco-regional extension, before standard definitive chemoradiotherapy (CRT), two cycles of chemotherapy based on Mitomycin C (MMC, 10 mg/m² day 1) and 5-Fluorouracil (5-FU, continuous infusion 1,000 mg/m² days 1-5) were planned. Treatment was well tolerated, with high compliance and a relatively good level of toxicity. Patient received the total prescribed RT dose (59.4 Gy, 1.8 Gy per fraction) and the concurrent MMC/5-FU-based CHT during the first and last week of RT treatment. A complete clinical response, confirmed by diagnostic exam, was achieved 6 months after CRT (March 2014). But, in the meantime, the patient developed a painful mass on the right parietal bone. The lesion was fast growing, non-pulsating and covered by normal cutis. No neurological deficits were noted. A CT of the head revealed a solitary osteolytic hyperdense lesion with contrast enhancement on the right parietal bone measuring 25x16 mm without dural and brain involvement. A fine needle aspiration biopsy confirmed metastasis from squamous cell carcinoma. After a multidisciplinary discussion, local RT followed by CHT was recommended. RT was delivered with...
a 3D-conformational multiple field technique at a total dose of 45 Gy (3 Gy per fraction) to the to the skull lesion, with 6 energy photons. Patient underwent CT scan one-week prior RT. She was treated in a supine position and was immobilized in a thermoplastic shell, fixed to the couch in three places. Bolus was not used. Images were acquired with 3 mm slice thickness and were obtained from the vault to the base of the skull. Diagnostic CT images were co-registered to the planning CT. Target volume delineation was manually performed and a 5 mm margin to the gross tumor volume was added.

CHT consisted of up to 4 cycles of three-weekly cisplatin (60 mg/m² day 1) and 5-FU (continuous infusion 600 mg/m² days 1-5). Treatment was well tolerated, with no interruptions and severe toxicity. Two months later, in June 2014, follow-up CT imaging showed a complete clinical response (Figure 1). Progression-free survival was achieved until September 2015, when follow-up diagnostic exams confirmed pathological pelvic lymph nodes and vulvar recurrence. Palliative chemotherapy treatment was left to the oncologist’s discretion. At December 2017 brain metastasis was documented. Patient’s general condition progressively deteriorated and she died in February 2018.

Discussion

We describe a case of metastatic anal canal cancer to the cranial bone successfully treated with local RT and systemic CHT. After treatment, the patient remained free of relapse for 17 months. This multidisciplinary approach was safe and effective and it was mainly proposed to ensure low morbidity and mortality. Usually, in patients with primary anal canal cancer, the most likely mode of spread to distant sites is through systemic circulation, implying potential systemic tumor dissemination. Based on this rationale, the utility of local RT was explored to reduce the excess of radiation exposure to the peri-lesional brain parenchyma and systemic CHT to control micro-metastasis. The aim was to positively influence survival time, local control and improve patient’s QoL.

At present, there are no standardized algorithms to manage cranial bone metastasis. In order to determine the treatment approach, a literature search using PubMed database up to October 2018 was performed using the following combinations of research criteria: “metastasis”, “metastatic”, “anal canal carcinoma”, “cranial”, “bone”, “skull”, “calvarial”, “surgery”, “radiotherapy”, “radiosurgery”, and “magnetic resonance image”. No articles on cranial bone metastasis from primary anal canal carcinoma were available. To best of our knowledge, our patient represents the first case described in medical literature. Therefore, it was not possible to limit the search to this setting of patients and consequently we enlarged it to include cranial bone metastasis of different origin sites. The search was restricted to English-language papers. English literature lacks large series highlighting cranial bone metastasis. It consists mostly of single case reports (n=21) and a scarce number of case series (n=13) (2-35). Data from each study were tabulated and included authors, year of publication, sample size, primary tumor, cranial bone metastasis characteristics, treatment details and follow-up. A total of 34 studies representing 339 patients were identified. Details are listed in Table I. Reports have described calvarial metastasis from different types of primary cancers, most commonly from kidney (n=30), liver (n=16) and breast (n=15) cancers (It should be noted that (n) indicates the number of patients). Frontal and parietal bones were the most common sites involved (n=91) (2-7, 9, 12, 15, 17-20, 22-23, 25-27, 29-32). Clinical presentation mainly depended on the location of the metastatic lesion. Cranial bone metastases were often asymptomatic (n=13) (3, 7-8, 13, 15, 19, 23, 36), due to the absence of the innervations of the calvarium (26). Involvement of the outer table of the skull caused superficial focal pain and cosmetic problems (n=93) (2, 4, 6, 9, 12, 16, 20-22, 24, 26, 28-29, 31-32). Whereas the infiltration of the inner table was related to neurological symptoms, such as headache and nausea (n=8) (3-4, 20). The subsequent extension to eloquent cortex, as well as the impairment of cranial nerves caused neurological deficit (14). Major symptoms, including increased intracranial pressure, meningeal irritation and seizures, occurred if the dura and intradural spaces were involved (n=21) (2-4, 20, 22, 28-29). CT scan with bone window was the method of choice to detect bone erosion (22). With CT, calvarial metastasis often presented as an osteolytic lesion. To better delineate lesion boundaries, as well as soft tissue and dural invasion, magnetic resonance imaging (MRI) with non-contrasted sequences was performed in several cases (2, 37-39). Cranial bone metastasis showed hypo-intensity on non-enhanced T1-weighted images and a variable appearance on T2-weighted images, in contrast with the hyper-intensity of normal bone marrow (21, 28, 31). Nowadays, MRI should be considered a standard exam to better classify cranial bone metastasis. Recently, Mitsuya et al. have proposed a classification of skull metastasis based on MRI features (28). A total of 218 metastases were classified with regard to i) location – calvarium or cranial base, ii) distribution within the plane of the cranial bone – confined to one bone or diffuse to another bone spreading across a suture, iii) invasion – in cranial bones only, into the scalp or inward to the dura. Globally, 121 patients have been identified with calvarial bone metastases. The vast majority (n=86, 71%) were circumscribed. Of these lesions, 48 were classified as intraosseous and the remain as invasive. However, in case of suspected lesion, a needle biopsy should be performed to clarify diagnosis and assist with the decision on optimal management.

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At present, a universally accepted treatment approach cannot be determined. These studies have presented different treatment approaches, including single modality (n=138) (2, 4, 6, 9, 12, 14-15, 20-21, 23-24, 28-29, 31-34), multidisciplinary options (n=54) (3-4, 14, 20-21, 26-27), and palliative care/follow-up (n=120) (5, 10, 17-18, 25, 28-30, 35). Of note, there are no treatment data in 27 cases. The collected studies do not show an absolute benefit of one treatment over the others as they are not case control studies and, therefore, are underpowered. We combined their results to add power to any tentative conclusion proposed by individual studies. However, no statistical value can be given to this analysis, thus the best treatment in cranial bone metastasis patients is still uncertain. Surgery alone with curative or palliative intent was proposed in 58 patients (2, 4-6, 9-10, 12, 14-15, 17-18, 20-21, 23-25, 31-32, 34-35) and en-bloc resection was the preferred technique (14, 20-21). Systemic CHT, mainly using a platinum-based regimen, was especially provided to fit patients (36). In total, 126 (37.2%) (3, 4, 14, 20-21, 26-30, 33) patients underwent local RT, as exclusive (in 86 patients), adjuvant (in 34 patients) or neoadjuvant (in 6 patients) modality. Actually, adequate information on radiation technique, field size and margins, doses, fractionation schedules and beam energy were poorly documented and the little technical details available were heterogeneous. The treatment of choice was 3D conformal RT with conventional fractionation (2 Gy per fraction) up to 55 Gy (3, 29). Clinical experience with other RT techniques, such as stereotactic RT, was only limited to a retrospective analysis of 14 calvarial bone lesions (33). A 201-source 60Cobalt gamma knife radiosurgery system was used. To artificially extend the surface to target distance, a 5 mm bolus was applied over the treatment site in 7 cases. The median prescription margin dose was 15 Gy (range=13-24 Gy). The approach was feasible, safe and effective, also in those patients who had received prior RT.

In conclusion, cranial bone metastasis represents an extremely rare clinical scenario in patients with primary diagnosis of anal canal carcinoma. Maybe, its incidence is likely underreported due to no specific clinical presentation. Progress in oncological treatment, as well as modern imaging techniques routinely used in follow-up programs could slightly increase its diagnosis rates in the near future. MRI should be performed to better describe lesion characteristics. RT seems to be useful and could provide significant local control and positively influence patient’s QoL. Surely, a multidisciplinary team should offer to patients the most appropriate treatment option, mainly according to primary tumor control, estimated survival, performance status and comorbidities.

**Conclusion**

Treatment for cranial bone metastatic anal cancer is anecdotal. Local RT and systemic CHT represent a safe and effective multimodal treatment option, with optimal local control and no severe toxicity.

**Conflicts of Interest**

All Authors declare no conflicts of interest regarding this study.

**Authors’ Contributions**

IB prepared the literature search and wrote the manuscript under the close supervision of FDF. FDF guaranteed the integrity of entire study, DM designed the study preliminarily and contributed to data acquisition. NB, RC1 and VT participated in the design and coordination of the case. IB, FDF, NB, RC1, RC2 DM, VT critically revised the manuscript and approved it.
| Author                  | Study                  | Year | Patient | Tumor (n lesions) | Symptom (n cases) | Treatment                          | Overall survival |
|-------------------------|------------------------|------|---------|------------------|-------------------|------------------------------------|------------------|
| Constans et al. (3)     | Retrospective          | 1981 | 14      | Breast (3)       | Parietal          | Asymptomatic                       | 3-36 months      |
|                         |                        |      |         | Thyroid (3)      | Fronto-parietal    | Headache (3)                       | S + adj RT (40-55) |
|                         |                        |      |         | Liver (3)        | Occipital         | Neurologic deficit (3)             | S + CHT (6)      |
|                         |                        |      |         | Colon (1)        | Frontal           | Seizures (2)                       | S + adj RT + CHT |
|                         |                        |      |         | Testicle (1)     | Occipital         | Increased intracranial pressure (2)| S + adj RT + CHT |
|                         |                        |      |         | Unknown (1)      | Parieto-occipital | S + adj RT + CHT (1)               | S + adj RT + CHT |
| Nagamine et al. (4)     | Retrospective          | 1985 | 11      | Thyroid (5)      | Parieto-occipital | Swelling (11)                      | 4.5 years (mean)
|                         |                        |      |         | Parietal (3)     | Frontal (1)                    | Headache (11)     | S + adj RT + CHT (1) |
|                         |                        |      |         | Occipital (5)    | Frontal (1)       | Hemiparesis (1)                   | S + adj RT + CHT |
|                         |                        |      |         | Fronto-parietal (1)| Frontal (1)     | Disturbance of consciousness (1)  | S + adj RT + CHT |
|                         |                        |      |         | Parieto-occipital| Fronto-parietal   | Acute epidural hematoma            | S + adj RT + CHT |
| Anegawa et al. (5)      | Case report            | 1989 | 1       | Ovarian          | Occipital (1)     | Painless mass (2)                 | 6 months         |
|                         |                        |      |         |                  | Fronto-parietal   | Asymptomatic                       | 1 month          |
|                         |                        |      |         |                 |                  |                                    | -                |
| Kuratsu et al. (6)      | Case report            | 1990 | 2       | Liver            | Occipital (1)     | Painless mass (2)                 | 8 months         |
|                         |                        |      |         |                 | Frontal (1)       | Asymptomatic                       | 15 months        |
|                         |                        |      |         |                 |                  |                                    | -                |
| Sunita et al. (7)       | Case report            | 1991 | 1       | Kidney           | Occipital (1)     | Asymptomatic                       | 14 months        |
| Molina et al. (8)       | Case report            | 1991 | 1       | Kidney           | Occipital (1)     | Asymptomatic                       | 15 months        |
| Nakao et al. (9)        | Case report            | 1992 | 1       | Liver            | Occipital (1)     | Palpable mass                      | S                |
| Nakagawa et al. (10)    | Case report            | 1992 | 1       | Liver            | Occipital (1)     | Acute epidural hematoma            | 1 month          |
|                         |                        |      |         |                 |                  |                                    | -                |
| Cheah et al. (11)       | Case report            | 1992 | 1       | Kidney           | -                 | -                                  | -                |
|                         |                        |      |         |                 |                  |                                    | -                |
| Yoshida et al. (12)     | Case report            | 1993 | 1       | Liver            | Frontal           | Painfull mass                      | 15 months        |
| Wahner-Roedler et al. (13)| Case report         | 1997 | 1       | Kidney           | Occipital (1)     | Asymptomatic                       | 15 months        |
| Wacht et al. (14)       | Case series            | 1997 | 7       | Kidney (3)       | -                 | -                                  | 20.6 months      |
|                         |                        |      |         | melanoma (1)     |                  |                                     | (mean)           |
|                         |                        |      |         | Lung (1)         |                  | S (6)                              |                   |
|                         |                        |      |         | Other (2)        |                  | neo-adj RT + CHT + S (1)           |                   |
| Koutnouyan et al. (15)  | Case report            | 1998 | 1       | Kidney           | Frontal           | Asymptomatic                       | 9 months         |
| Nitta et al. (16)       | Case report            | 1999 | 1       | Kidney           | Occipital (1)     | Painfull mass                      | -                |
| Hayashi et al. (17)     | Case report            | 2000 | 1       | Liver            | Parietal (1)      | Acute epidural hematoma            | 2 months         |
| McIver et al. (18)      | Case report            | 2001 | 1       | Liver            | Parietal (1)      | Acute epidural hematoma            | -                |
| Yamamoto et al. (19)    | Case report            | 2001 | 1       | Kidney           | Frontal           | Asymptomatic                       | -                |
| Michael et al. (20)     | Retrospective          | 2001 | 27      | Kidney (13)      | Parieto-occipital (1) | Painless mass (11) | neo-adj CHT + S (12) |
|                         |                        |      |         | Sarcoma (6)      | Fronto-parietal (5)| Painful mass (8)                  | 16.5 months      |
|                         |                        |      |         | Prostate (4)     | Frontal (3)       | Neurologic deficit (5)            | neo-adj RT + CHT |
|                         |                        |      |         | Melanoma (3)     | Occipital (2)     | Seizures (5)                      | neo-adj RT + S (3) |
|                         |                        |      |         | Other (1)        | Parieto-occipital (1)| Headache/blurred vision (4) | S (8)             |
|                         |                        |      |         |                 |                  |                                    | Other (2)        |
| Author          | Type            | Year | Patient | Primary tumor | Bone involved (n lesions) | Symptoms (n cases)                  | Treatment                          | Overall survival       |
|-----------------|-----------------|------|---------|---------------|---------------------------|-------------------------------------|------------------------------------|------------------------|
| Stark et al.    | Retrospective   | 2003 | 12**    | Breast (4 pz) | -                         | Swelling (5) Local pain (3)         | S (8 pz) S + adj RT (4 pz)         | 19.5 months (mean)     |
| et al. (21)     |                 |      |         | Melanoma (2 pz) | Parietal (15) Frontal (13) | Palpable mass (16) Neurologic deficit (3) | -                                   | -                     |
|                 |                 |      |         | Colorectal (1 pz) | Occipital (3) Frontal (1) | -                                   | -                                   | -                     |
|                 |                 |      |         | Prostate (1 pz) | Occipital (1)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Parotid (1 pz) | Occipital                  | -                                   | -                                   | -                     |
|                 |                 |      |         | Sarcoma (3 pz) | Temporal                   | -                                   | -                                   | -                     |
| Arana et al.    | Retrospective   | 2004 | 21      | Kidney        | -                         | Parietal (3) Temporal              | S                                  | 9 months               |
| et al. (22)     |                 |      |         | -             | Parietal (15)              | -                                   | -                                   | -                     |
| Gaetani et al.  | Case report     | 2005 | 2       | Kidney        | -                         | Occipital (3) Asymptomatic          | S                                  | 6 months               |
| et al. (23)     |                 |      |         | -             | Occipital (1)              | -                                   | -                                   | -                     |
| Miyamoto et al. | Case report     | 2007 | 1       | Cholangiocarcinoma | -             | Occipital Painfull mass               | S                                  | 6 months               |
| et al. (24)     |                 |      |         | -             | Occipital                  | -                                   | -                                   | -                     |
| Kanai et al.    | Case report     | 2008 | 1       | Liver         | Parieto-occipital          | Acute epidural hematoma             | S                                  | 3 weeks                |
| et al. (25)     |                 |      |         | -             | -                         | -                                   | -                                   | -                     |
| Hong et al.     | Case series     | 2010 | 9       | Breast (2 pz) | -                         | Parietal (3) Asymptomatic (3)       | S + adj RT (4 pz)                   | 5.8 years (mean)       |
| et al. (26)     |                 |      |         | Lung (1 pz)   | Occipital (3)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Kidney (1 pz) | Occipital (1)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Other (5 pz)  | Occipital                  | -                                   | -                                   | -                     |
|                 |                 |      |         | -             | Temporal                   | -                                   | -                                   | -                     |
| Chye et al.     | Case report     | 2011 | 1       | Liver         | -                         | Subdural hematoma S + Chemoembolization + adj RT | -                                   | -                     |
| et al. (27)     |                 |      |         | -             | -                         | -                                   | -                                   | -                     |
| Mitsuya et al.  | Retrospective   | 2011 | 175***  | Breast (96 pz)| -                         | Pain (5) Meningeal irritation (3)   | RT (63 pz) Follow-up (112 pz)     | -                     |
| et al. (28)     |                 |      |         | Lung (25 pz)  | Occipital (3)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Prostate (11 pz) | Occipital (3)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Lymphoma (9 pz) | Occipital (3)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Head and neck (1 pz) | Occipital (3)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Other (34 pz) | Occipital                  | -                                   | -                                   | -                     |
|                 |                 |      |         | -             | Temporal                   | -                                   | -                                   | -                     |
| Fujimoto et al. | Case report     | 2013 | 2       | Cholangiocarcinoma | -             | -                                   | SRT (1 pz) RT (30Gy) + CHT S + adj RT | 12 months (mean)       |
| et al. (29)     |                 |      |         | -             | Parietal (2) Temporal (1)  | -                                   | -                                   | -                     |
| Kumar et al.    | Case report     | 2014 | 1       | Ovarian       | Parietal                   | Acute epidural hematoma             | S                                  | 4 years                |
| et al. (30)     |                 |      |         | -             | -                         | Neurologic deficit (1)            | RT + SRT (1 pz) S + adj RT         | -                     |
| Cecchi et al.   | Case report     | 2014 | 1       | Endometrium   | Temporo-parietal           | Painless mass                       | S                                  | 4 months               |
| et al. (31)     |                 |      |         | -             | Parieto-occipital          | -                                   | -                                   | -                     |
| Guo et al.      | Case report     | 2014 | 1       | Liver         | Parieto-occipital          | Painless mass                       | S                                  | 18 months              |
| et al. (32)     |                 |      |         | -             | -                         | -                                   | -                                   | -                     |
| Kotecha et al.  | Case series     | 2014 | 21****  | Breast (5 pz) | -                         | -                                   | GKS RT (13-24Gy)                   | 35.9 months (median)   |
| et al. (33)     |                 |      |         | Kidney (3 pz) | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | Sarcoma (3 pz) | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | Liver (2 pz)  | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | Head and neck (2 pz) | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | Other (6 pz)  | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | -             | -                         | -                                   | -                                   | -                     |
| Chen et al.     | Case report     | 2015 | 1       | Liver         | Parieto-occipital          | Acute epidural hematoma             | S                                  | -                     |
| et al. (34)     |                 |      |         | -             | -                         | -                                   | -                                   | -                     |
| Kim et al.      | Case report     | 2016 | 1       | Liver         | Parieto-occipital          | Acute epidural hematoma             | S                                  | 4 months               |
| et al. (35)     |                 |      |         | -             | -                         | -                                   | -                                   | -                     |
| Ozgiray et al.  | Retrospective   | 2016 | 15      | Thyroid (3 pz)| Frontal (9)                | -                                   | S                                  | -                     |
| et al. (2)      |                 |      |         | Sarcoma (2 pz)| Parietal (6)               | -                                   | -                                   | -                     |
|                 |                 |      |         | Breast (1 pz) | Occipital (2)              | -                                   | -                                   | -                     |
|                 |                 |      |         | Cholangiocarcinoma (1 pz) | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | Colon (1 pz)  | -                         | -                                   | -                                   | -                     |
|                 |                 |      |         | Other (7 pz)  | -                         | -                                   | -                                   | -                     |

*The bones involved were specified only for dural sinus calvarial metastases; **Include 5 patients with skull-base metastases; ***Include 43 patients with associated skull-base metastases; ****Include 12 patients with skull-base metastases. N: Number; S: surgery; adj: adjuvant; RT: radiotherapy; Gy: Gray; CHT: chemotherapy; neo-adj: neo-adjuvant; GKS: gamma knife surgery.
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