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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/m^2 day 1) and 5-Fluorouracil (5-FU, continuous infusion 1,000 mg/m^2 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-pulsanting 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 25×16 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

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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/m^2 day 1) and 5-FU (continuous infusion 600 mg/m^2 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, occured 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.

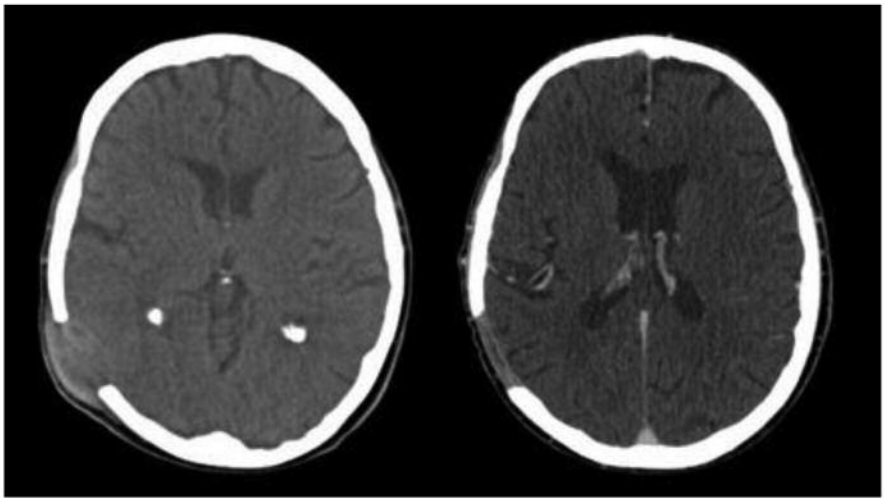

Figure 1. *Computed tomography images of the right parietal bone metastasis before (left) and after (right) local radiation therapy.*

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.

Table I. *Case reports and case series for calvarial metastases*.

Author	Study		Patient	Primary tumor	Bone involved (n lesions)	Symptoms (n cases)	Treatment	Overall survival
	Type	Year						
Constans *et al*. (3)	Retrospective	1981	14	Breast (3 pz) Thyroid (3 pz) Liver (3 pz) Kidney (2 pz) Colon (1 pz) Testicle (1 pz) Unknow (1 pz)	Parietal (6) Frontal (3) Occipital (3) Temporal (1) Central (1)	Asymptomatic (3) Headache (3) Neurologic deficit (3) Seizures (2) Increased intracranial pressure (2)	S + adj RT (40-55 Gy)	3-36 months
Nagamine *et al*. (4)	Retrospective	1985	11	Thyroid	Occipital (5) Parieto-occipital (3) Parietal (1) Frontal (1) Fronto-parietal (1)	Swelling (11) Headache (1) Hemiparesis (1) Disturbance of consciousness (1)	S + adj RT (4 pz) S + adj CHT (1 pz) S + adj RT + CHT (1 pz) RT (1 pz) S (4 pz)	4.5 years (mean)
Anegawa *et al*. (5)	Case report	1989	1	Ovarian	Parito-occipital	Acute epidural hematoma	S	
Kuratsu *et al*. (6)	Case report	1990	2	Liver	Occipital (1) Frontal (1)	Painless mass (2)	S	6 months 1 month
Sunita *et al*. (7)	Case report	1991	1	Kidney	Frontal	Asymptomatic	-	-
Molina *et al*. (8)	Case report	1991	1	Kidney	Occipital	Asymptomatic	-	14 months
Nakao *et al*. (9)	Case report	1992	1	Liver	Frontal	Palpable mass	S	15 months
Nakagawa *et al*. (10)	Case report	1992	1	Liver	Occipital	Acute epidural hematoma	S	1 month
Cheah *et al*. (11)	Case report	1992	1	Kidney	-	-	-	-
Yoshida *et al*. (12)	Case report	1993	1	Liver	Frontal	Painfull mass	S	8 month
Wahner-Roedler *et al*. (13)	Case report	1997	1	Kidney	Occipital	Asymptomatic	-	15 months
Wecht *et al*. (14)	Case series	1997	7	Kidney (3 pz) Melanoma (1 pz) Lung (1 pz) Other (2 pz)	-	-	S (6 pz) neo-adj RT + CHT + S (1 pz)	20.6 months (mean)
Koutnouyan *et al*. (15)	Case report	1998	1	Kidney	Frontal	Asymptomatic	S	9 months
Nitta *et al*. (16)	Case report	1999	1	Kidney	Occipital	Painfull mass	-	-
Hayashi *et al*. (17)	Case report	2000	1	Liver	Parietal	Acute epidural hematoma	S	2 months
McIver *et al*. (18)	Case report	2001	1	Liver	Parietal	Acute epidural hematoma	S	-
Yamamoto *et al*. (19)	Case report	2001	1	Kidney	Frontal	Asymptomatic	-	-
Michael *et al*. (20)	Retrospective	2001	27*	Kidney (13 pz) Sarcoma (6 pz) Prostate (4 pz) Melanoma (3 pz) Other (1 pz)	Fronto-parietal (5) Frontal (3) Occipital (2) Parietal (2) Parieto-occipital (1)	Painless mass (11) Painful mass (8) Neurologic deficit (5) Headache/blurred vision (4)	neo-adj CHT + S (12 pz) neo-adj RT + S (2 pz) neo-adj RT + CHT + S (3 pz) S (8 pz) Other (2 pz)	16.5 months (median)

Table I. *Continued*

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Author	Study		Patient	Primary tumor	Bone involved (n lesions)	Symptoms (n cases)	Treatment	Overall survival
	Type	Year						
Stark *et al*. (21)	Retrospective	2003	12**	Breast (4 pz) Melanoma (2 pz) Colorectal (1 pz) Prostate (1 pz) Parotid (1 pz) Sarcoma (3 pz)	-	Swelling (5) Local pain (3)	S (8 pz) S + adj RT (4 pz)	19.5 months (mean)
Arana *et al*. (22)	Retrospective	2004	21	-	Parietal (15) Frontal (13) Occipital (3)	Palpable mass (16) Neurologic deficit (3)	-	-
Gaetani *et al*. (23)	Case report	2005	2	Kidney	Frontal (1) Occipital (1)	Asymptomatic	S	9 months
Miyamoto *et al*. (24)	Case report	2007	1	Cholangio-carcinoma	Occipital	Painfull mass	S	6 months
Kanai *et al*. (25)	Case report	2008	1	Liver	Parieto-occipital	Acute epidural hematoma	S	3 weeks
Hong *et al*. (26)	Case series	2010	9	Breast (2 pz) Lung (1 pz) Kidney (1 pz) Other (5 pz)	Parietal (3) Occipital (3) Frontal (2) Temporal (1)	Asymptmatic (3) Painless mass (3) Painful mass (3)	S + adj RT	5.8 years (mean)
Chye *et al*. (27)	Case report	2011	1	Liver	Temporal	Subdural hematoma	S + Chemoembolization + adj RT	-
Mitsuya *et al*. (28)	Retrospective	2011	175***	Breast (96 pz) Lung (25 pz) Prostate (11 pz) Lymphoma (9 pz) Head and neck (1 pz) Other (34 pz)	-	Pain (5) Cosmetic problem (3) Meningeal irritation (3) Disorientation (3)	RT (63 pz) Follow-up (112 pz)	-
Fujimoto *et al*. (29)	Case report	2013	2	Cholangio-carcinoma	Parietal (2) Temporal (1)	Pailfull mass (2) Neurologic deficit (1)	SRT (1 pz) RT (30Gy) + CHT + SRT (1 pz)	12 months 4 years
Kumar *et al*. (30)	Case report	2014	1	Ovarian	Parietal	Acute epidural hematoma	S + adj RT	
Cecchi *et al*. (31)	Case report	2014	1	Endometrium	Temporo-parietal	Painless mass	S	4 months
Guo *et al*. (32)	Case report	2014	1	Liver	Parieto-occipital	Painless mass	S	18 months
Kotecha *et al*. (33)	Case series	2014	21****	Breast (5 pz) Kidney (3 pz) Sarcoma (3 pz) Liver (2 pz) Head and neck (2 pz) Other (6 pz)	-	-	GKS RT (13-24Gy)	35.9 months (median)
Chen *et al*. (34)	Case report	2015	1	Liver	-	-	S	-
Kim *et al*. (35)	Case report	2016	1	Liver	Parieto-occipital	Acute epidural hematoma	S	4 months
Ozgiray *et al*. (2)	Retrospective	2016	15	Thyroid (3 pz) Sarcoma (2 pz) Breast (1 pz) Cholangio-carcinoma (1 pz) Colon (1 pz) Other (7 pz)	Frontal (9) Parietal (6) Occipital (2) Cerebellar (1)	Swelling (10) Local pain (5) Neurologic deficit (1) Skin ulceration (1)	S	-

*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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