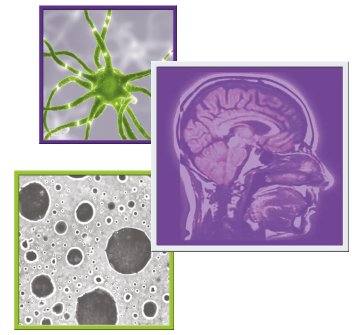
Case Report

CNS Oncology



Large mirror brain metastases from primary undifferentiated sarcoma of the breast: case report and review of the literature

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Practice points

- Primary undifferentiated sarcoma of the breast with brain metastases are extremely rare with only one case reported in the literature.
- We report the clinical case of two brain metastases from primary undifferentiated sarcoma of the breast submitted to surgical excision.
- We report the effect of our approach on the patient prognosis (overall survival of 24 months vs 3 weeks in the previous reported case).
- We make a review of the clinical, therapeutic and prognostic considerations of these aggressive tumors.
- The effect of different types of treatment on the patient's outcome is unknown, with this case we favor an aggressive approach if the patient has a favorable health status.
- We strongly believe that with this publication can increase the knowledge about these rare, challenging and serious tumors.

Primary breast sarcomas are rare high-grade tumors with a reported incidence of <1% of breast malignancies. Its dissemination to the CNS is exceptional and only one is found in the literature. The authors described the case of a 22-year-old female with history of a breast undifferentiated sarcoma that present with two large bilateral retrolenticular brain metastases. Both lesions were excised in the same procedure and she underwent adjuvant therapy. She died 24 months after surgery. Despite being aggressive lesions, aggressive treatment of primary breast sarcomas including brain metastases excision, should be considered in order to improve overall survival.

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Keywords: brain metastasis • primary breast sarcoma • surgery

Primary breast sarcomas are rare tumors with a reported incidence of less than 1% among primary breast malignancies [1]. These tumors most commonly metastasize to the lung, bone and liver [2,3]. Although breast cancer is the second most frequent cause of brain metastases [4,5], it is exceptional for primary breast sarcomas to originate brain metastasis with only one case reported [6].

Surgical excision of breast sarcoma is the standard treatment approach in patients without distant metastasis [7]. These tumors have a poor prognosis frequently influenced by the tumor diameter, tumor burden, metastasis profile and histological grade [8]. Nevertheless, due to the scarcity of cases with brain metastases, there is no data about the best treatment or its influence on the patient prognosis.

Therefore, we report the case of a patient with two large bilateral retrolenticular brain metastases from a breast undifferentiated spindle cell sarcoma (USCS), supported by a literature review and therapeutic considerations in order to improve our knowledge about this neoplastic entity.

Future Medicine

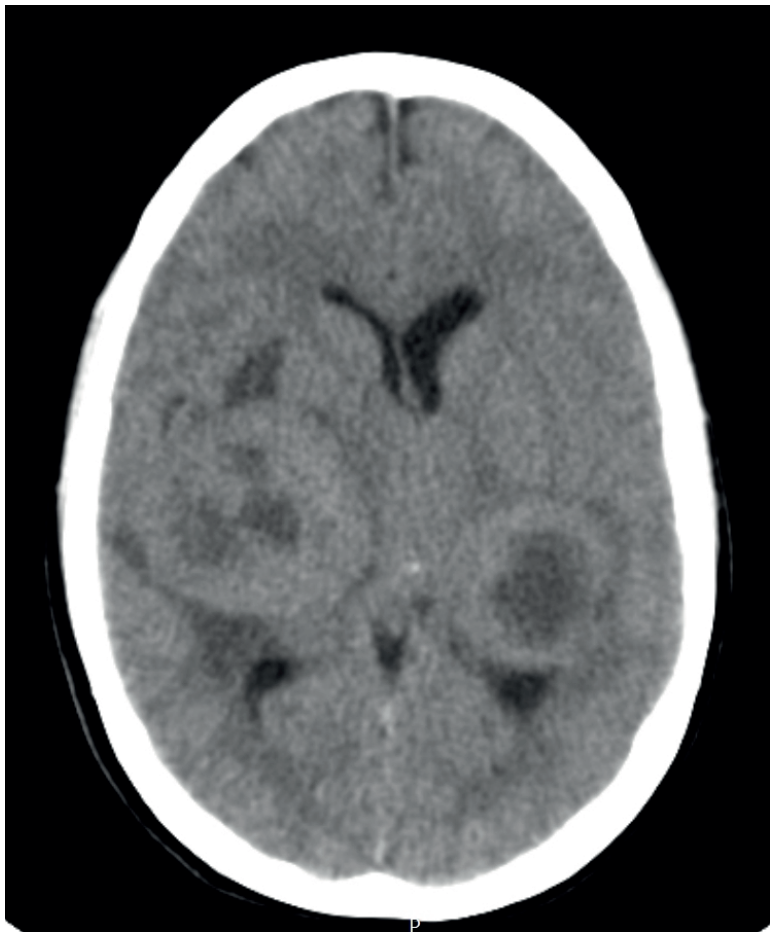

Figure 1. CT scan showing two mirror intra-axial perilenticular lesions in both hemispheres.

Case report

A 22-year-old female presented to the emergency department with severe headache associated with nausea, vomiting, prostration and gait imbalance in the 2 weeks before admission. She had history of a left breast USCS, submitted to mastectomy and adjuvant radiotherapy (total dose of 66 Gy) 2 years before. About 1 year after the primary diagnosis, she had undergone an excision of a single metastasis in the left humerus.

At admission, the neurological examination revealed a left hemiparesis, predominantly in the upper limb and gait ataxia. The CT scan showed two large retrolenticular intra-axial brain lesions in both hemispheres with perilesional edema (Figure 1). A brain MRI was performed showing a right lenticular lesion measuring 49 × 47 × 44 mm and a left retrolenticular lesion measuring 38 × 37 × 36 mm, both with a necrotic core, restriction to diffusion, heterogenous contrast enhancement and surrounded by perilesional edema (Figure 2). A staging CT chest-abdomen-pelvis revealed small pathologic nodules on the left internal mammary region, pericardial and pancreatic region. After multidisciplinary meeting discussion, the patient was considered for resection of both brain lesions through two craniotomies in the same surgical session.

The right lesion was approached first via a temporo-parietal craniotomy with the patient positioned in dorsal decubitus with the head turned 45° to the left. Then, she was positioned in right $\frac{3}{4}$ lateral decubitus with the head turned 30° to the right. Through a temporo-occipital craniotomy the left lesion was removed. Both lesions were completely removed with the aid of a tractography of the pyramidal and language tracts (Figure 3). There were no intraoperative complications and the patient had a total blood loss of 250 ml.

The pathological examination revealed spindle-shaped neoplastic cells. Immunohistochemistry was positive for S-100 but negative for AE1/AE3, CAM5.2, EMA, desmin, CD34 and SOX10 (Figure 4). The morphology and the immunophenotype confirmed USCS histologically similar with the breast neoplasm. These pathological findings allowed to conclude that both lesions were brain metastases from breast USCS.

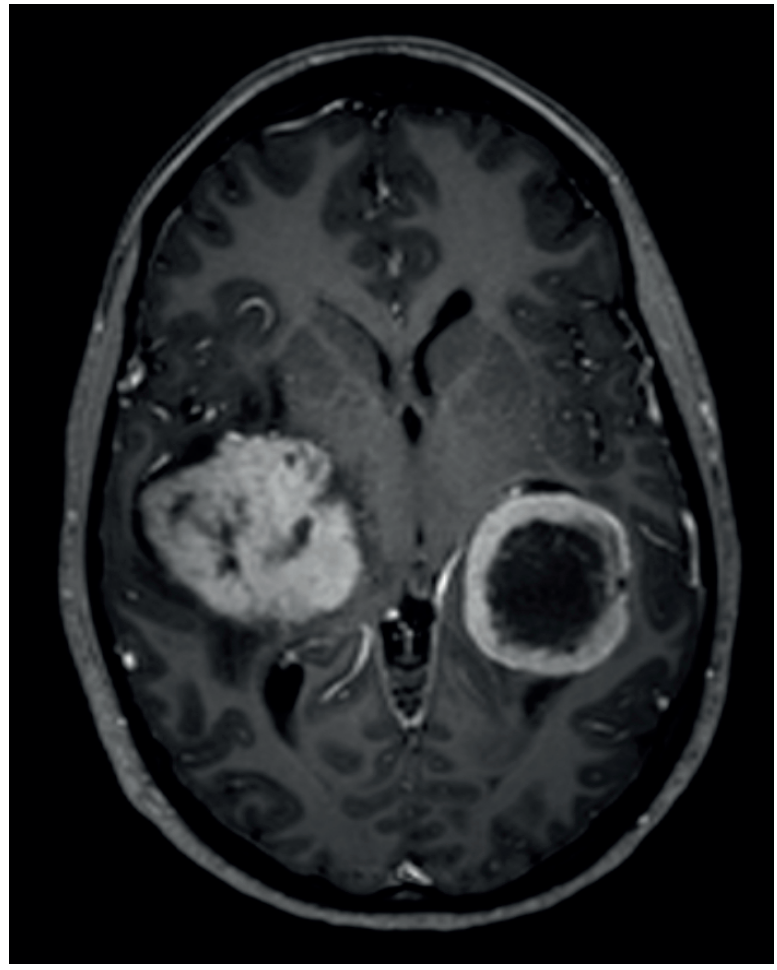

Figure 2. MRI T1 with gadolinium axial showing a right lenticular lesion measuring 49×47×44 mm and a left retrolenticular lesion measuring 38×37×36 mm with heterogenous contrast enhancement and a necrotic core.

Immediately after surgery the patient developed anomic aphasia, right homonymous hemianopia and a worsened left hemiparesis. About 1 month after surgery, the language deficit completely recovered but maintained the visual and motor deficits. She underwent physiotherapy to aid in motor recovery and was able to walk unassisted 2 months after surgery. Then, due to the aggressivity and multifocality of the brain metastases, she was submitted to whole-brain radiotherapy and 6 cycles of systemic chemotherapy with adriamycin (30 mg/m^2).

At 12-month follow-up, the patient maintained a left arm paresis (grade 4 in 5) without other neurological deficits. She repeated the brain MRI and no evidence of local recurrence was seen (Figure 5). About 20 months after surgery, a repeat staging documented liver and pancreatic metastases. These lesions progressed and caused a malignant obstructive jaundice that was submitted to palliative endoscopic biliary stenting. Overall, the systemic disease progressed with deterioration of performance status and she died 24 months after the brain surgery.

Discussion

Breast cancer is the second most common cause for brain metastases after lung cancer [4,5]. It is known that different breast cancer subtypes have a different likelihood of metastasizing to the brain [9–11]. The basal-like and HER2 positive breast cancer are among the subtypes that most commonly originate brain metastases [4].

Primary breast sarcomas are an extremely rare type of breast malignancy and only case reports and small case series are available in literature [3,12]. Similar to sarcomas originating in other topographies, metastases from breast sarcomas typically involve the lungs, liver and bone [2,3,13]. Brain is an unusual metastatic site for sarcomas in general as the frequency of brain metastasis in cases of metastatic systemic soft tissue sarcoma (STS) is 1–4% [14–17]. The most common type of sarcoma that originates brain metastases is the undifferentiated soft tissue sarcoma (USTS) [18]. Brain metastases usually occur late in disease progression, often following other lesions [18]. To the

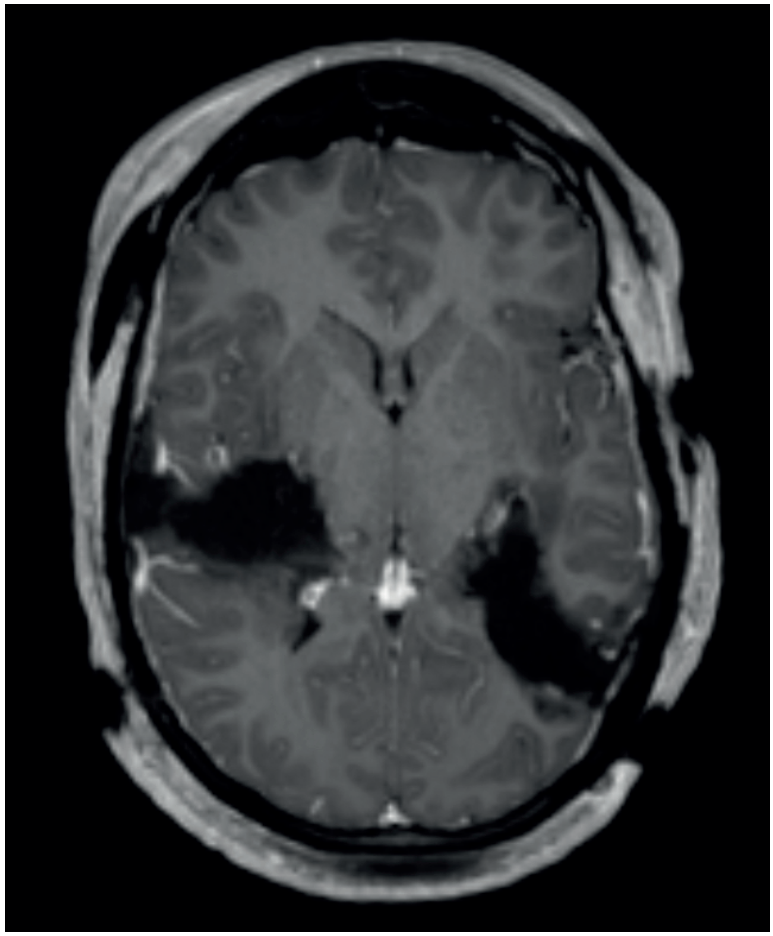

Figure 3. Postoperative MRI with gadolinium showing total excision of both perilenticular lesions.

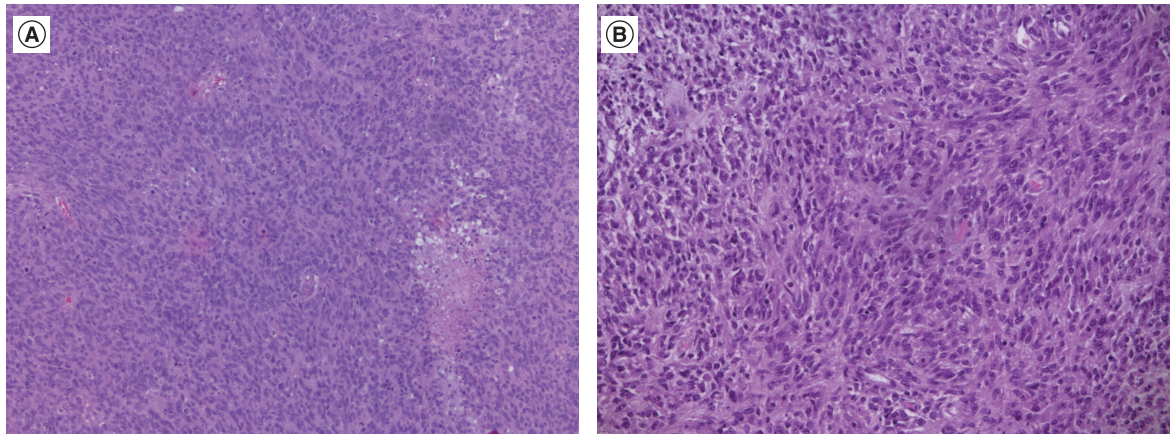

Figure 4. Pathological image of the brain metastasis from breast undifferentiated soft tissue sarcoma with H&E staining. (A) 10× amplification showing the tumor hypercellularity with a sarcomatous aspect, **(B)** 20× amplification showing spindle-shaped neoplastic cells.

best of our knowledge, there is only one case of brain metastization from a primary breast sarcoma reported in the literature [6].

USTSs are aggressive tumors that account for about 20% of all STS and a quarter of these are radiation associated tumors [19,20]. This is a group of tumors incorporated into the WHO classification of soft tissue tumors [19,21]. This new category of tumors was included in the 2013 classification revision [19,22]. There are five subtypes of USTS

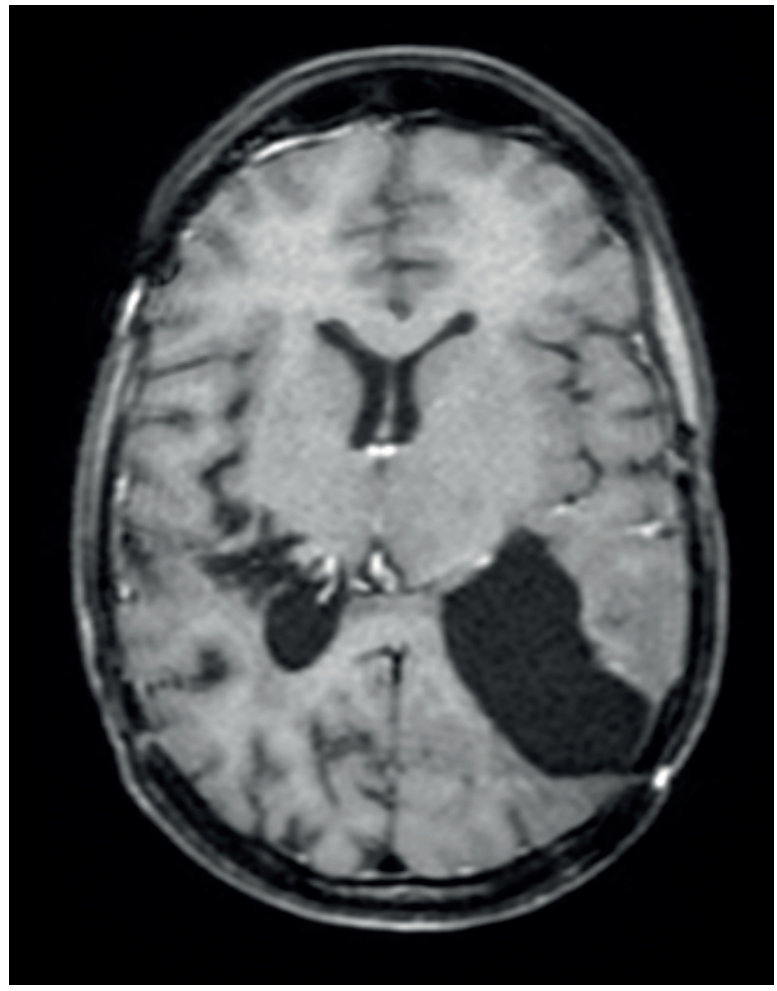

Figure 5. Postoperative MRI with gadolinium 12 months after surgery with no evidence of local recurrence.

Table 1. Undifferentiated breast sarcomas with brain metastasis described in the literature.

Case report (year)	Gender	Age	Clinical presentation	Tumor location	Treatment	Histology	Follow-up	Ref.
Chakrabarti (2013)	Female	60	Headache, generalized tonic clonic seizure	Left cerebellar hemisphere	Stereotactic biopsy	UPS	3 weeks, DOD	[6]
Present case	Female	22	Headache, left hemiparesis with gait imbalance	Bilateral mirror perilenticular	Both surgical excision + whole-brain RT + CT	USCS	24 months, DOD	

CT: Chemotherapy; DOD: Dead of disease; RT: Radiotherapy; UPS: Undifferentiated pleomorphic sarcoma; USCS: Undifferentiated spindle cell sarcoma.

which are the USCS, undifferentiated pleomorphic sarcoma, undifferentiated round cell sarcoma, undifferentiated epithelioid sarcoma and the undifferentiated sarcoma not otherwise specified [7,21]. These subtypes are distinguished only by variable morphological traits [22,23]. because they show no definable line of differentiation using currently available immunochemistry technology [21,24].

After careful literature review, only one previous report concerning primary breast sarcoma with brain metastasis were made (Table 1). We excluded the cases of malignant phyllodes tumors with brain metastasis, despite having similar biological behavior, as they are considered different types of tumors [25,26]. These cases are significant different. Our patient was younger (22 vs 60 years old) and with better performance status than the previously reported. Both patients present with severe headache – probably related with raised intracranial pressure. This patient presented with focal neurological deficit – hemiparesis and gait imbalance – in a context of previous known USCS whereas the patient reported in literature presented with seizures in a context of brain metastatic disease in the absence of known primary. Regarding the location and number of lesions, this patient had two perilenticular bilateral mirror metastases with approximately 50 and 40 mm each, while the previous reported patient had a single

posterior fossa lesion with approximately 30 mm. Concerning the therapeutic approach, we performed complete excision of both mirror lesions followed by whole-brain radiotherapy, as opposed to the other where a stereotactic biopsy was made. Also, this patient was submitted to systemic chemotherapy and had a longer survival – 24 months – when compared with patient previously reported in the literature overall survival (OS) of 3 weeks after the diagnosis.

Since primary breast sarcoma is extremely rare, the best treatment approaches have not yet been established [7]. The National Comprehensive Cancer Network guidelines for STS state that surgery is the most effective treatment and should be combined with either chemotherapy or radiotherapy depending on the patient's performance status [27]. Surgery is considered the standard approach in patients without distant metastasis [8]. According to some authors, patients with sarcoma brain metastasis should perform aggressive therapy including surgical resection, radiosurgery or multimodality treatment, especially chemotherapy, in order to improve OS [17,28,29].

The prognosis of USTS is poor but not fully understood. Altogether, these tumors had a local recurrence rate between 19–31% and a metastatic rate of 30–35% [30]. According to case series and cohorts of USTS with brain metastases, the median OS was between 3.5 and 11.8 months [16,18,29,31]. USTS with isolated brain metastasis are uncommon [29]. A retrospective study of brain USTS treated with conservative versus a more aggressive approach show a trend toward an improved survival benefit in patients who were treated aggressively, median OS of 1.2 versus 3.7 months [29]. Another study with a large series of sarcoma brain metastases reports a survival outcome of 7.2 months (0.6 years) from first brain metastasis diagnosis [18]. The OS of this patient is much longer than the OS reported in the literature. Therefore, it is important to better understand the genomics of the USTS in order to develop targeted immunotherapy that will improve the prognosis of this high grade disease [23].

Our case supports an aggressive approach for the treatment of these rare tumors. Surgical resection of brain metastases should be considered in patients with good performance status and controlled systemic disease in order to improve OS. Even in cases with two big lesions, like this case, we favor surgical resection if the patient has a good performance status.

Conclusion

Brain metastases from primary breast sarcomas are rare. Although this is a high-grade tumor, aggressive therapy including brain metastases resection, should be considered in patients with good performance status in order to improve OS. Better understanding of the genomic profile of USTS is crucial to develop efficient personalized therapy.

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No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

As the individual participant in the study is deceased, informed consent was obtained from her father, as the next of kin.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Berg JW, Hutter RVP. Breast cancer. *Cancer* 75(S1), 257–269 (1995).
2. Lum YW, Jacobs L. Primary breast sarcoma. *Surg. Clin. North Am.* 88(3), 559–570 (2008).

3. Kumar S, Sharma J, Ralli M, Singh G, SonuKalyan, Sen R. Primary stromal sarcoma of breast: a rare entity. *Iran J. Pathol.* 11(5), 469–473 (2016).
4. Witzel I, Oliveira-Ferrer L, Pantel K, Müller V, Wikman H. Breast cancer brain metastases: biology and new clinical perspectives. *Breast Cancer Res.* 18(1), 1–9 (2016).
5. Ostrom QT, Wright CH, Barnholtz-Sloan JS. Chapter 2. In: *Brain Metastases: Epidemiology (1st Edition)*. Schiff D, van den Bent MJ (Eds). Elsevier BV, USA (2018).
6. Chakrabarti I, Ghosh N, Giri A. Cytologic diagnosis of undifferentiated high grade pleomorphic sarcoma of breast presenting with brain metastasis. *J. Neurosci. Rural Pract.* 4(2), 188–190 (2013).

•• **Reports the only previous case report of undifferentiated breast sarcoma with CNS metastasis.**

7. Yamazaki H, Shimizu S, Yoshida T *et al.* A case of undifferentiated pleomorphic sarcoma of the breast with lung and bone metastases. *Int. J. Surg. Case Rep.* 51, 143–146 (2018).

• **Explains that the standard of care of undifferentiated sarcomas is unknown due to the rarity of these tumors.**

8. Li N, Cusidó MT, Navarro B *et al.* Breast sarcoma. A case report and review of literature. *Int. J. Sur. Case Rep.* 24, 203–205 (2016).

• **Explains the known factors that influence the prognosis of breast undifferentiated sarcomas.**

9. Kennecke H, Yerushalmi R, Woods R *et al.* Metastatic behavior of breast cancer subtypes. *J. Clin. Oncol.* 28(20), 3271–3277 (2010).
10. Sihto H, Lundin J, Lundin M *et al.* Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study. *Breast Cancer Res.* 13(5), 1–11 (2011).
11. Soni A, Ren Z, Hameed O *et al.* Breast cancer subtypes predispose the site of distant metastases. *Am. J. Clin. Pathol.* 143(4), 471–478 (2015).
12. Zelek L, Llombart-Cussac A, Terrier P *et al.* Prognostic factors in primary breast sarcomas: a series of patients with long-term follow-up. *J. Clin. Oncol.* 21(13), 2583–2588 (2003).
13. Trent JC II, Benjamin RS, Valero V. Primary soft tissue sarcoma of the breast. *Curr. Treat. Options Oncol.* 2(2), 169–176 (2001).
14. Espat NJ, Bilsky M, Lewis JJ, Leung D, Brennan MF. Soft tissue sarcoma brain metastases: prevalence in a cohort of 3829 patients. *Cancer* 94(10), 2706–2711 (2002).
15. Postovsky S, Ash S, Ramu IN *et al.* Central nervous system involvement in children with sarcoma. *Oncology* 65(2), 118–124 (2003).
16. Tanaka H, Sasayama T, Nishihara M *et al.* Brain metastasis of undifferentiated sarcoma and response to temozolomide treatment. *Neurol. Med. Chir.* 50(8), 689–693 (2010).
17. Miki K, Yoshimoto K, Yamada Y *et al.* Rapid growth of metastatic brain tumor from gastric undifferentiated pleomorphic sarcoma: a case report. *Surg. Neurol. Int.* 10(74), 1–4 (2019).

•• **Report demonstrates the beneficial influence that a rapid and aggressive approach can have on a patient's outcome.**

18. al Sannaa G, Watson KL, Olar A *et al.* Sarcoma brain metastases: 28 years of experience at a single institution. *Ann. Surg. Oncol.* 23(May 2015), 962–967 (2016).

•• **Highlights what is the type of soft tissue sarcoma that more often causes brain metastases as well as its influence on the patient outcome.**

19. Jo VY, Fletcher CDM. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. *Pathology* 46(2), 95–104 (2014).
20. Reichardt P. Soft tissue sarcomas, a look into the future: different treatments for different subtypes. *Future Oncol.* 10(Suppl. 8), 19–27 (2014).
21. Vilanova JC. WHO classification of soft tissue tumors. In: *Imaging of Soft Tissue Tumors (4th Edition)*. Vanhoenacker FM, Parizel PM, Gielen JL. (Eds). Springer, USA, 187–196 (2017).
22. Fletcher CDM. The evolving classification of soft tissue tumours - an update based on the new 2013 WHO classification. *Histopathology* 64(1), 2–11 (2014).
23. Steele CD, Pillay N. The genomics of undifferentiated sarcoma of soft tissue: progress, challenges and opportunities. *Semin. Cancer Biol.* 61, 42–55 (2020).
24. Widemann BC, Italiano A. Biology and management of undifferentiated pleomorphic sarcoma, myxofibrosarcoma, and malignant peripheral nerve sheath tumors: state of the art and perspectives. *J. Clin. Oncol.* 36(2), 160–167 (2018).
25. Wang F, Jia Y, Tong Z. Comparison of the clinical and prognostic features of primary breast sarcomas and malignant phyllodes tumor. *Jpn. J. Clin. Oncol.* 45(2), 146–152 (2015).
26. Tan BY, Acs G, Apple SK *et al.* Phyllodes tumours of the breast: a consensus review. *Histopathology* 68(1), 5–21 (2016).
27. von Mehren M, Randall RL, Benjamin RS *et al.* Soft tissue sarcoma, version 2.2018: clinical practice guidelines in oncology. *J. Natl Compr. Canc. Netw.* 16(5), 536–563 (2018).
28. Kasper E, Mahadevan A. Stereotactic radiosurgery for sarcoma. *J. Neurosurg. Spine* 2(4), 1032 (2014).

29. Chua C, Raaj J, Pan S *et al.* Brain metastasis in sarcoma: does metastasectomy or aggressive multi-disciplinary treatment improve survival outcomes. *Asia-Pacific J. Clin. Oncol.* 12(1), e16–e22 (2016).

●● **This retrospective study of brain undifferentiated soft tissue sarcoma states the influence on patient outcome that a conservative or an aggressive approach can have.**

30. Goldblum JR. An approach to pleomorphic sarcomas: can we subclassify, and does it matter? *Modern Pathol.* 27(Suppl. 1), S39–S46 (2014).

31. Bindal RK, Sawaya RE, Leavens ME, Taylor SH, Guinee VF. Sarcoma metastatic to the brain: results of surgical treatment. *Neurosurgery* 35(2), 185–191 (1994).