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Review

Radiation-induced brain cavernomas in elderly: review of the literature and a rare case report

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Summary. Radiation-induced brain cavernomas have been mainly reported in children who underwent radiotherapy for medulloblastoma, leukemia, or low-grade glioma. Otherwise, the "de novo" appearance of a cavernoma in an elderly long-survivor patient after resection and radiotherapy of a glioblastoma is a rare event. We report the case of a 62-year-old female patient who underwent surgical resection of a right temporal glioblastoma, followed by radiation therapy of the operative field and surrounding brain and concomitant adjuvant temozolomide. Four years after the operation, a follow-up Magnetic Resonance revealed a good tumor control and a small round lesion at the superior surface of the right cerebellar hemisphere, close to the margins of the previous irradiation field. The radiological items were consistent with a cavernous angioma. Because of the small size of the malformation and the absence of related symptoms, no treatment was performed. The patient died for tumor progression 86 months after the initial operation, with unchanged cerebellar cavernoma. The occurrence of a cavernous angioma in an elderly patient after radiotherapy for brain glioblastoma is an exceptional event; the distribution of radiotherapy-induced cavernous malformations reported in current literature is presented and the mechanism of their formation is discussed. (www.actabiomedica.it)

Key words: glioblastoma, cavernous angioma, radiotherapy

Abbreviations:
CAs - Cavernous angiomas; CNS - Central Nervous System; HGG - High Grade Glioma; MRI - Magnetic Resonance Imaging; LGG - Low Grade Glioma; RICM - Radiotherapy-Induced Cavernous Malformations.

Introduction

Cavernous angiomas (CAs) are well-circumscribed vascular lesions composed of dilated thin walled venous channels without intervening normal brain tissue (1). Although benignant, CAs can be responsible for disabling neurological symptoms depending on their localization within the Central Nervous System (CNS). These lesions can be either acquired or congenital; multiple CAs (10% to 20%) are typically familiar or secondary to radiation therapy.

Acquired CAs may occasionally occur after radiotherapy, generally in addition to other more common complications such as white matter leukoencephalopathy, atrophy and dystrophic mineralization. The "de novo" presentation of CAs after radiation therapy is a relatively rare event, which may occur even after several years after the treatment, irrespective of the radiation dose and type of malignancy. Most of the reported cases (2, 3) mainly concern children (mean

age 12 years) who underwent radiotherapy for medulloblastoma, leukemia or low-grade glioma (LGA); induced CAs after radiotherapy for high grade gliomas (HGG) are less common across older age groups.

We describe the unusual case of a cerebellar CA observed after radiation therapy for temporal glioblastoma in an elderly patient, reviewing current literature on the topic.

Case Report

A 62-year-old female patient was admitted to hospital because of a 2-month history of temporal lobe epilepsy. After a first-level neurological examination, further diagnostic investigations were required to exclude secondary epilepsy causes. Magnetic Resonance Imaging (MRI) showed the presence of a large right intracerebral temporal mass with intense and inhomogeneous contrast enhancement and perilesional oedema, suggestive for a HGG (Figure 1a). A gross total tumor resection was performed through a right temporal craniotomy. Histology was consistent with glioblastoma (WHO IV). Subsequent radiation therapy of the operative field and surrounding brain (60Gy for 30 days, 2Gy per daily fraction) and concomitant adjuvant therapy with multiple temozolomide administrations (during radiotherapy: 75 mg/m² per day, 7 days per week; post-radiotherapy: 150-200 mg/m² for 5 days during each 28-day cycle) were performed.

After 26 months the patient came to our attention because of tumor recurrence (Figure 1b). Thus, she underwent re-intervention remaining symptom-free for the following 2 years. Following examinations (4) did not show significant tumor recurrence, with a good disease control.

Almost 4 years after the initial diagnosis, a follow-up MRI confirmed the absence of recurrent disease; nevertheless a new round small lesion of the right cerebellar convexity was observed close to the margins of

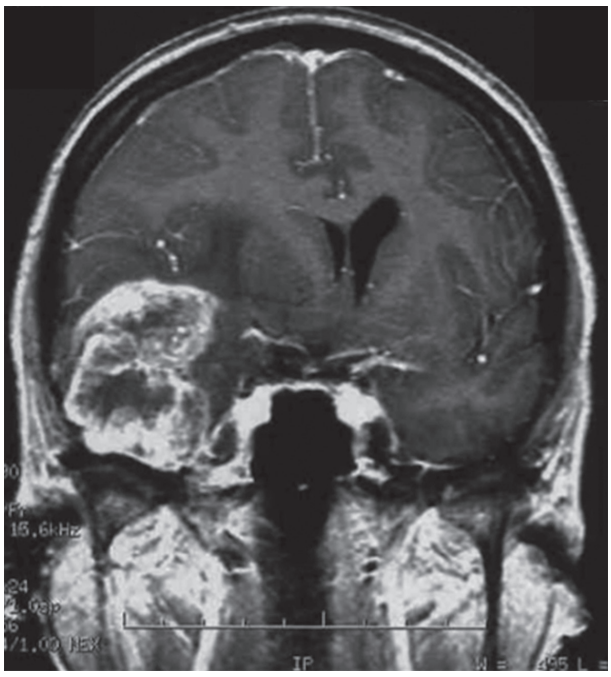

Figure 1a. Coronal contrast-enhanced T1 weighted image showing a large intra-axial right temporal lesion with intense and inhomogeneous contrast enhancement due to the presence of necrotic areas, strongly suggestive for a high-grade glioma. The lesion is surrounded by a large amount of perifocal oedema, with subsequent compressive effect on the right lateral ventricle and contralateral shift of the midline structures

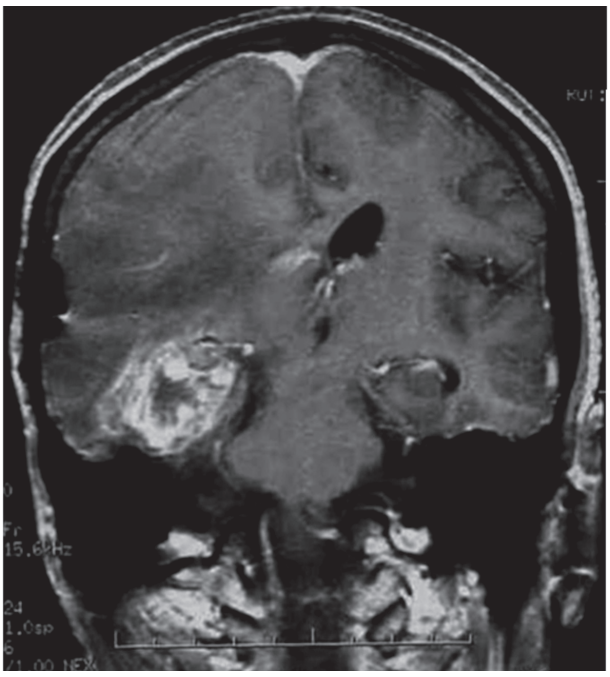

Figure 1b. Coronal contrast-enhanced T1 weighted image showing the presence of an area of intense enhancement in the right temporal region, peripherally to the surgical cavity, consistent with tumor recurrence

the previous irradiation field, showing central hyperintensity with a rim of signal loss due to hemosiderin (Figure 2b); this asymptomatic lesion was not visible in the previous MRI control (Figure 2a). Radiological findings were strongly suggestive for CA, due to the typical berry appearance on unenhanced sequences.

Because of the small size of the malformation and the absence of related symptoms, no treatment was performed. After 1 year, a further follow-up MRI showed no tumor recurrence, as well as the unchanged right cerebellar CA. The patient died for tumor progression after a 7-year disease-free survival.

Discussion

CA is one of the possible complications of high dose radiation therapy, with a large number of cases reported in scientific literature at present (2, 3, 5). Almost all reported cases were described in paediatric population, whereas only a minority of case concerned adult patients. The most common primitive neoplasms associated with radiation-induced CAs include medulloblastoma and malignant hematopoietic neoplasms (2-5) as well as low grade gliomas (LGG) (3), whereas only anedoctal observations of CA in HGG are reported. The distribution of radiotherapy-induced cavernous malformations (RICMs) reported in current literature is represented in Figure 3. The radiation dose was very variable, ranging from 18 to 90 Gy; most patients (57%) received a high radiation dose of 40 up to 60 Gy. The time interval between the irradiation and the diagnosis of CAs was very variable (1 to 52 years), with most cases (65%) occurring within 10 years after irradiation. A correlation has been found between a radiation dose >30Gy and a shorter

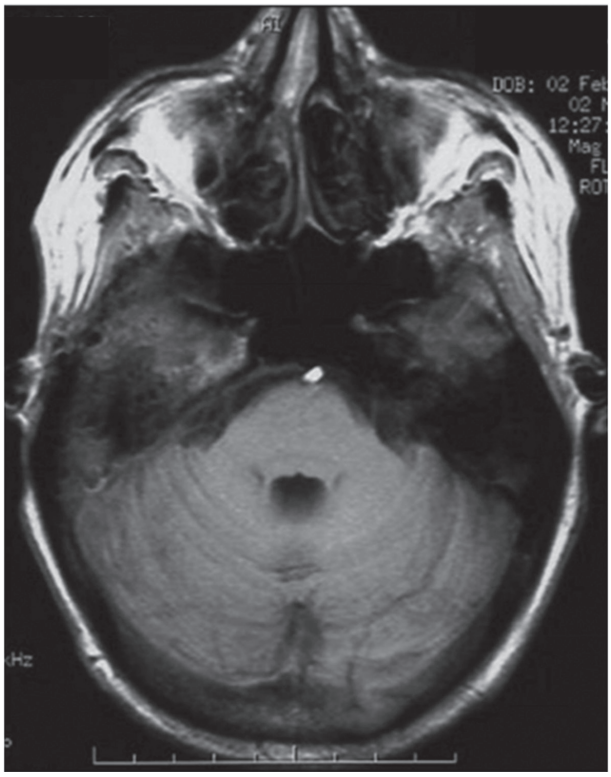

Figure 2a. Axial T1 weighted image showing regular morphology and signal of the posterior fossa structures, with no evidence of focal lesions of the cerebellar hemispheres

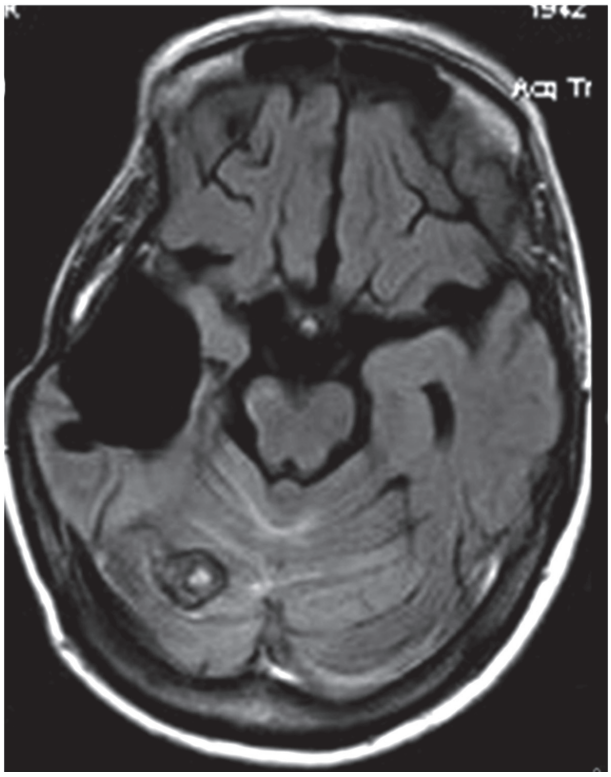

Figure 2b. Axial FLAIR image revealing surgical cavity in the right temporal region with no sign of tumor recurrence; presence of a round small lesion (transverse diameter: 1 cm) in the upper convexity of the right cerebellar hemisphere showing central hyperintensity with a rim of signal loss due to the presence of hemosiderin, consistent with CA

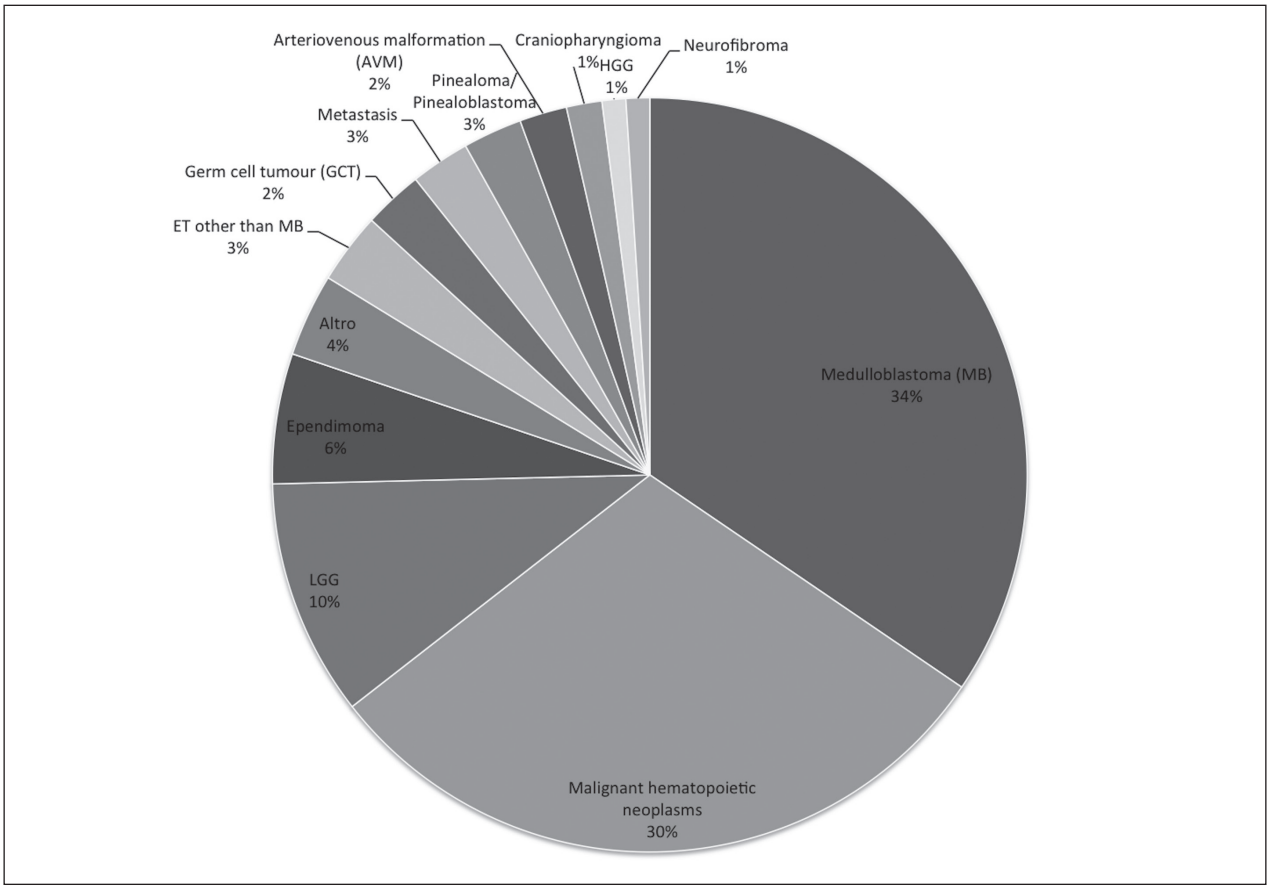

Figure 3. Distribution of CNS radiotherapy-induced cavernous malformations, according to primary tumours

latency to development of cavernomas (1). Multiple CAs were found in 36% patients, and clinical and/or radiological evidence of haemorrhage was reported in 38% of the radiation-induced cases, a significantly higher incidence compared with sporadic cavernomas (3, 6-8).

Our case presents several elements of distinctiveness being unusual due to the patient age, type of radio-treated tumour and CA location in the posterior fossa. The age of our patient, both at the irradiation (62 years) and at the appearance of the cavernoma (66 years), is very atypical. Indeed, among the 100 reviewed patients, at the diagnosis only 5 were older than 40 years (9), and none was older than 50 years. Moreover, at the CAs appearance only 5 patients (10) were older than 50 years and none was older than 60 years. Interestingly, all but one of these adult patients had received radiation doses greater than 60 Gy. On the other hand, the median latency time to diagnosis was 8.2 years, similarly in younger patients reports.

The present case is only the third reported in the literature of a brain cavernoma after HGG irradiation (11-19), although it is the first report of "de novo" appearance of a cavernous malformation in a patient who had radiation therapy for glioblastoma in such an advanced age (>60 years of age). Indeed, the higher incidence observed in LGGs is probably due to the longer mean survival of these patients compared with HGGs.

The infratentorial location of CAs at the superior surface of cerebellar hemispheres is unusual as well, being this region close to the margins but not included within the irradiation field. It has been suggested that low radiation doses are more efficient to induce CAs; indeed, higher radiation dose delivered at the centre of the field of irradiation may result in extensive cellular apoptosis, thus preventing the CA formation. Con-

versely, the periphery of the field is at higher risk, as the radiation may modify the genetic stability, inducing abnormal vascular proliferation without substantial cell apoptosis (2).

The management of the radiation-induced CAs mainly depends on clinical manifestations and mean survival time associated with the primary lesion. Generally, when clinically silent, CAs may benefit from a regular MRI follow-up, especially in patients with small CAs and short life expectancy, as in the present case. Surgical treatment is indicated in cases with conspicuous haemorrhage or should be limited to younger patients with stable disease, low grade lesions and/or and long life expectancy.

Imaging plays a key role in the evaluation of different pathologic conditions, both for diagnostic and interventional purposes (20-33). In neuroradiology, the combined use of CT and MRI imaging is the approach of choice (34-43), while angiography is the primary modality used for interventional neuroradiology procedures (44, 45).

On imaging, CAs have a distinctive appearance of the nidus with little or no surrounding edema (1). CT may show ring-like calcification with a core reticulation of variable attenuation, with usually no contrast enhancement (1, 13). MRI imaging shows a reticulated core of heterogeneous signal intensity giving a typical "popcorn" appearance, with a dark peripheral rim of hemosiderin (14, 15).

A comparison between patients with RICMs and those with non-radiotherapy-induced lesions showed that there are no significant differences in size, location and imaging appearance, although RICMs are more often multiple and present some different histologic features (13, 16, 46-48).

Another difference lies in the possible clinical-radiological progression; variation in size and imaging characteristics is a more frequent feature of "de novo" cavernomas, that have significantly higher VEGF, MIB-1 and Ki-67 expression compared to congenital stable and indolent ones (17-19). Therefore, it may be suggested that the production of the angiogenic factors such as VEGF and TGF may play a crucial role in the formation of radiation-induced Cas (49-54).

The mechanism of CAs formation is not completely defined. It is controversial whether radiation therapy causes enlargement of a pre-existing small cavernoma, or induces a "de-novo" cavernous malformation due to direct radiation-induced damage in blood vessels and DNA injury in predisposed pa-tients (13).

In conclusion, the occurrence of CAs in elderly patients after glioblastoma radiotherapy is exceptional, although its prevalence may change over time. In fact, this kind of complication could become more frequent because of new treatment lines with progressively increasing survival time of patients with HGG; in this light radiation field margins should be considered particularly susceptible to this kind of vascular damage.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest: None to declare

References

1. Jain R, Robertson PL, Gandhi D, Gujar SK, Muraszko KM, Gebarski S. Radiation-induced cavernomas of the brain. AJNR Am J Neuroradiol 2005; 26: 1158-62.
2. Keezer MR, Del Maestro R. Radiation-induced cavernous hemangiomas: case report and literature review. Can J Neurol Sci 2009; 36: 303-10.
3. Nimjee SM, Powers CJ, Bulsara KR. Review of the literature on de novo formation of cavernous malformations of the central nervous system after radiation therapy. Neurosurg Focus 2006; 21: e4.
4. Caruso R, Colonnese C, Elefante A, Innocenzi G, Raguso M, Gagliardi FM. Use of spiral computerized tomography angiography in patients with cerebral aneurysm. Our experience. J Neurosurg Sci 2002; 46: 4-9.
5. Elefante A, Peca C, Del Basso De Caro ML, et al. Symptomatic spinal cord metastasis from cerebral oligodendroglioma. Neurol Sci 2012; 33: 609-13.
6. Larson JJ, Ball WS, Bove KE, Crone KR, Tew JM, Jr. Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children. J Neurosurg 1998; 88: 51-6.
7. Capalbo D, Elefante A, Spagnuolo MI, et al. Posterior reversible encephalopathy syndrome in a child during an accelerated phase of a severe APECED phenotype due to an uncommon mutation of AIRE. Clin Endocrinol (Oxf) 2008; 69: 511-3.
8. Chai YH, Jung TY, Lee KH, Kim SK. Progressive Multiple Cavernous Angiomas after Radiotherapy in a Pediatric Patient with Medulloblastoma: A Case Report. Pediatr Neurosurg 2015; 50: 270-4.

9. Lew SM, Morgan JN, Psaty E, Lefton DR, Allen JC, Abbott R. Cumulative incidence of radiation-induced cavernomas in long-term survivors of medulloblastoma. J Neurosurg 2006; 104: 103-7.
10. Furuse M, Miyatake SI, Kuroiwa T. Cavernous malformation after radiation therapy for astrocytoma in adult patients: report of 2 cases. Acta Neurochir (Wien) 2005; 147: 1097-101.
11. Fukushima S, Narita Y, Miyakita Y, et al. A case of more than 20 years survival with glioblastoma, and development of cavernous angioma as a delayed complication of radiotherapy. Neuropathology 2013; 33: 576-81.
12. Noel L, Christmann D, Jacques C, et al. [Intracerebral radiation-induced cavernous angiomas]. J Neuroradiol 2002; 29: 49-56.
13. Martino A, Krainik A, Pasteris C, et al. Neurological imaging of brain damages after radiotherapy and/or chimiotherapy. J Neuroradiol 2014; 41: 52-70.
14. Rigamonti D, Drayer BP, Johnson PC, Hadley MN, Zabramski J, Spetzler RF. The MRI appearance of cavernous malformations (angiomas). J Neurosurg 1987; 67: 518-24.
15. Muccio CF, Tedeschi E, Elefante A, Caranci F, Cerase A. Primary central nervous system vasculitis mimicking a brain tumor on conventional magnetic resonance imaging: the usefulness of perfusion-weighted imaging. A case report. Acta Neurol Belg 2018;
16. Cutsforth-Gregory JK, Lanzino G, Link MJ, Brown RD, Jr., Flemming KD. Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort. J Neurosurg 2015; 122: 1214-22.
17. Maiuri F, Cappabianca P, Gangemi M, et al. Clinical progression and familial occurrence of cerebral cavernous angiomas: the role of angiogenic and growth factors. Neurosurg Focus 2006; 21: e3.
18. Schettino C, Caranci F, Lus G, et al. Diffuse glioblastoma resembling acute hemorrhagic leukoencephalitis. Quant Imaging Med Surg 2017; 7: 592-97.
19. Briganti F, Tortora F, Elefante A, Volpe A, Bruno MC, Panagiotopoulos K. An unusual case of vertebral arteriovenous fistula treated with electrodetachable coil embolization. Minim Invasive Neurosurg 2004; 47: 386-8.
20. Masciocchi C, Conti L, D'Orazio F, Conchiglia A, Lanni G, Barile A, Errors in Musculoskeletal MRI, in: Romano L., Pinto A. (Eds.), Errors in Radiology, Springer Milan, Milano, 2012, pp. 209-17.
21. Ferrari F, Arrigoni F, Miccoli A, et al. Effectiveness of Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) in the uterine adenomyosis treatment: technical approach and MRI evaluation. Radiol Med 2016; 121: 153-61.
22. Arrigoni F, Barile A, Zugaro L, et al. Intra-articular benign bone lesions treated with Magnetic Resonance-guided Focused Ultrasound (MRgFUS): imaging follow-up and clinical results. Med Oncol 2017; 34:
23. Mangini M, Lagana D, Fontana F, et al. Use of Amplatzer Vascular Plug (AVP) in emergency embolisation: preliminary experience and review of literature. Emerg Radiol 2008; 15: 153-60.
24. Valeri G, Mazza FA, Maggi S, et al. Open source software in a practical approach for post processing of radiologic images. Radiol Med 2015; 120: 309-23.
25. Mocchegiani F, Vincenzi P, Coletta M, et al. Prevalence and clinical outcome of hepatic haemangioma with specific reference to the risk of rupture: A large retrospective cross-sectional study. Dig Liver Dis 2016; 48: 309-14.
26. Schicchi N, Valeri G, Moroncini G, et al. Myocardial perfusion defects in scleroderma detected by contrast-enhanced cardiovascular magnetic resonance. Radiol Med 2014; 119: 885-94.
27. Tarantini G, Favaretto E, Napodano M, et al. Design and methodologies of the postconditioning during coronary angioplasty in acute myocardial infarction (POST-AMI) trial. Cardiology 2010; 116: 110-16.
28. Salvolini L, Urbinati C, Valeri G, Ferrara C, Giovagnoni A. Contrast-enhanced MR cholangiography (MRCP) with GD-EOB-DTPA in evaluating biliary complications after surgery. Radiol Med 2012; 117: 354-68.
29. Barile A, Regis G, Masi R, et al. Musculoskeletal tumours: Preliminary experience with perfusion MRI. Radiol Med 2007; 112: 550-61.
30. Di Cesare E, Gennarelli A, Di Sibio A, et al. Image quality and radiation dose of single heartbeat 640-slice coronary CT angiography: A comparison between patients with chronic Atrial Fibrillation and subjects in normal sinus rhythm by propensity analysis. Eur J Radiol 2015; 84: 631-36.
31. Buffa V, Solazzo A, D'Auria V, et al. Dual-source dual-energy CT: dose reduction after endovascular abdominal aortic aneurysm repair. Radiol Med 2014; 119: 934-41.
32. Barile A, Bruno F, Arrigoni F, et al. Emergency and Trauma of the Ankle. Semi Musc Rad 2017; 21: 282-89.
33. Barile A, Bruno F, Mariani S, et al. What can be seen after rotator cuff repair: a brief review of diagnostic imaging findings. Musculoskelet Surg 2017; 101: 3-14.
34. Splendiani A, D'Orazio F, Patriarca L, et al. Imaging of post-operative spine in intervertebral disc pathology. Musculoskelet Surg 2017; 101: 75-84.
35. Splendiani A, Perri M, Marsecano C, et al. Effects of serial macrocyclic-based contrast materials gadoterate meglumine and gadobutrol administrations on gadolinium-related dentate nuclei signal increases in unenhanced T1-weighted brain: a retrospective study in 158 multiple sclerosis (MS) patients. Radiol Med 2018; 123: 125-34.
36. Caranci F, Briganti F, La Porta M, et al. Magnetic resonance imaging in brachial plexus injury. Musculoskelet Surg 2013; 97: S181-S90.
37. Cicala D, Briganti F, Casale L, et al. Atraumatic vertebral compression fractures: Differential diagnosis between benign osteoporotic and malignant fractures by MRI. Musculoskelet Surg 2013; 97: S169-S79.
38. Muccio CF, Di Blasi A, Esposito G, Brunese L, D'Arco F,

Caranci F. Perfusion and spectroscopy magnetic resonance imaging in a case of lymphocytic vasculitis mimicking brain tumor. Pol J Radiol 2013; 78: 66-69.
39. Caranci F, Napoli M, Cirillo M, Briganti G, Brunese L, Briganti F. Basilar artery hypoplasia. Neuroradiol J 2012; 25: 739-43.
40. Battipaglia G, Avilia S, Morelli E, Caranci F, Perna F, Camera A. Posterior reversible encephalopathy syndrome (PRES) during induction chemotherapy for acute myeloblastic leukemia (AML). Ann Hematol 2012; 91: 1327-28.
41. Cirillo M, Caranci F, Tortora F, et al. Structural neuroimaging in dementia. J Alzheimers Dis 2012; 29: 16-19.
42. Cappabianca S, Scuotto A, Iaselli F, et al. Computed tomography and magnetic resonance angiography in the evaluation of aberrant origin of the external carotid artery branches. Surg Radiol Anat 2012; 34: 393-99.
43. Cappabianca S, Colella G, Russo A, et al. Maxillofacial fibrous dysplasia: Personal experience with gadoliniumenhanced magnetic resonance imaging. Radiol Med 2008; 113: 1198-210.
44. Briganti F, Leone G, Marseglia M, Cicala D, Caranci F, Maiuri F. P64 Flow Modulation Device in the treatment of intracranial aneurysms: Initial experience and technical aspects. J Neurointerv Surg 2016; 8: 173-80.
45. Dialetto G, Reginelli A, Cerrato M, et al. Endovascular stent-graft treatment of thoracic aortic syndromes: A 7-year experience. Eur J Radiol 2007; 64: 65-72.
46. Tedeschi E, Caranci F, Giordano F, Angelini V, Cocozza S, Brunetti A. Gadolinium retention in the body: what we know and what we can do. Radiol Med 2017; 122: 589-600.
47. Cocozza S, Russo C, Pontillo G, et al. Is advanced neuroimaging for neuroradiologists? A systematic review of the scientific literature of the last decade. Neuroradiology 2016; 58: 1233-39.
48. Cha YJ, Nahm JH, Ko JE, et al. Pathological Evaluation of Radiation-Induced Vascular Lesions of the Brain: Distinct from De Novo Cavernous Hemangioma. Yonsei Med J 2015; 56: 1714-20.
49. De Filippo M, Onniboni M, Rusca M, et al. (2008). Advantages of multidetector row CT with multiplanar reformation in guiding percutaneous lung biopsies. RAD. MED, vol. 113, p. 945-953, ISSN: 0033-8362, doi: 10.1007/s11547-008-0325-y
49. Bertolini L, Vaglio A, Bignardi L, et al (2011). Subclinical interstitial lung abnormalities in stable renal allograft recipients in the era of modern immunosuppression. Transplantation Proceedings, vol. 43, p. 2617-2623, ISSN: 0041-1345, doi: 10.1016/j.transproceed.2011.06.033.
50. Palma BD, Guasco D, Pedrazzoni M, et al. Osteolytic lesions, cytogenetic features and bone marrow levels of cytokines and chemokines in multiple myeloma patients: Role of chemokine (C-C motif) ligand20. Leukemia. 2016 Feb;30(2):409-16. doi: 10.1038/leu.2015.259. Epub 2015 Sep 30.
51. Bozzetti C, Nizzoli R, Tiseo M, et al. ALK and ROS1 rearrangements tested by fluorescence in situ hybridization in cytological smears from advanced non-small cell lung cancer patients. Diagnostic Cytopathology, vol. 43, p. 941-946, ISSN: 8755-1039, doi: 10.1002/dc.23318.
52. De Filippo M, Gira F, Corradi D, Sverzellati N, Zompatori M, Rossi C. (2011). Benefits of 3D technique in guiding percutaneous retroperitoneal biopsies. RAD. MED, vol. 116(3), p. 407-416, ISSN: 0033-8362, doi: 10.1007/s11547-010-0604-2
53. Quarrell OW, Handley O, O'Donovan K, et al. Discrepancies in reporting the CAG repeat lengths for Huntington's disease. Eur J Hum Genet 2012; 20: 20-26.
54. Perri M, Grattacaso G, Di Tunno V, et al. MRI DWI/ADC signal predicts shrinkage of lumbar disc herniation after O2-O3 discolysis. Neuroradiology Journal 2015; 28(2): 198-204.

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