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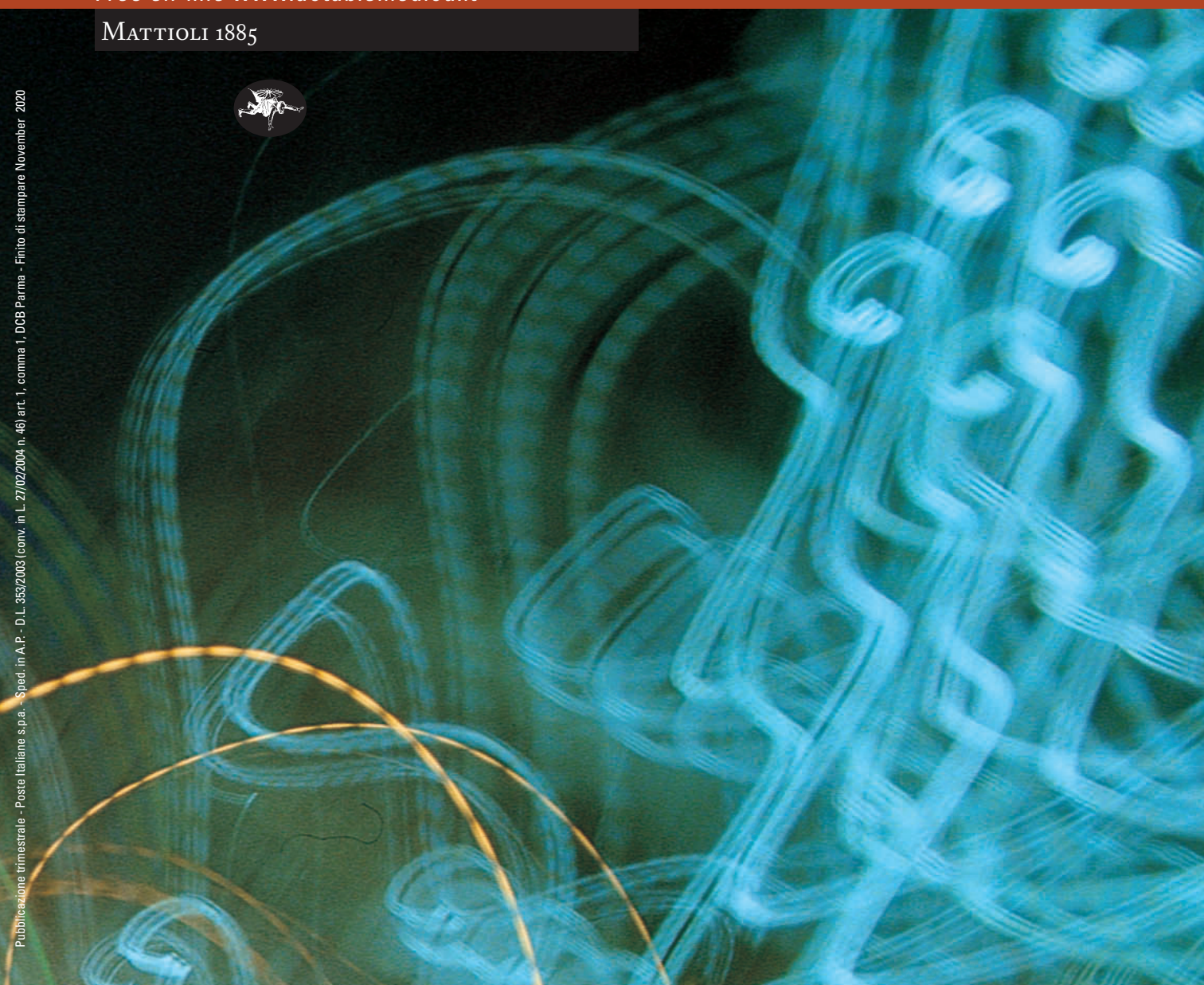

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Index

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Review

Image-guided percutaneous mechanical disc decompression for herniated discs: a technical note

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Summary. Interventional radiology plays a key role in the treatment of symptomatic herniations of intervertebral discs. Through image-guided techniques, it is possible to use minimally invasive procedures with a percutaneous approach that are usually proposed before classic surgery. Thanks to imaging guidance, it is possible to significantly increase accuracy and decrease complication rates. The pivotal principle of these mini-invasive techniques is to remove a small amount of volume of the nucleus of the intervertebral disc which results in a significant reduction in intradiscal pressure; allowing for a consequent reduction in compression of the nervous structures that generate spinal pain. However, it must be considered that this type of treatment is only addressed to contained disc herniations previously diagnosed with a suitable neuroimaging examination. There are different types of treatment using a variety of chemical, thermal or mechanical processes that result in partial removal of the nucleus pulposus. The purpose of this technical note is to illustrate mechanical disc decompression treatment via a percutaneous approach using the DISKOM device (DISKOM percutaneous discectomy probe, Biopsybell, Mirandola, Italy). Indications, complications and various methods of use are described in relation to the different levels of the spine to be treated. (www.actabiomedica.it).

Keywords: Disc herniation; percutaneous discectomy; fluoroscopy; spine; interventional radiology; pain management

Introduction

Spinal pain is one of the most frequently reported diseases in the industrialized world and is related to disability, work absence, and extensive costs in the health system (1). Minimally invasive intradiscal procedures are considered an alternative treatment and are usually proposed before classic surgical approaches.

The need to reduce complications, to improve long-term outcomes, and to minimize sub-optimal results that occasionally accompany disc surgery in herniated discs, have encouraged the development of other techniques in order to prevent open surgery through the spinal canal.

Using these methods, the reported complication rate is lower because the native disc structure is preserved and the surrounding tissues are less damaged (2,3). The main goal of image-guided procedures is to avoid the major disadvantages of surgical treatment such as tissue trauma, and higher incidence of complications, and repeated surgeries (4).

An intervertebral disc, because of its highly specialized role and relatively susceptible nature, is one of the major sources of low back pain syndrome (5-7).

Aging, stress and traumas cause a disc degeneration phenomenon and a loss of volume of the nucleus pulposus, due to a decrease in proteoglycans and water concentration (8,9).

Hydrostatic pressure between the disc and vertebral endplates, plays a very important role in the regulation of nutrient supply to the disc and in removal of waste from cells of the nucleus pulposus which is an avascular structure. With aging, disease or injury, the disc degeneration progresses causing a drop in the hydrostatic pressure mechanism of regulation (10,11).

Treatment of discogenic pain is based on the theory that a small reduction in disc volume involving removal of part of the nucleus via surgical or minimally invasive methods, can result in a large change in intradiscal pressure.

By using image-guided techniques, it is possible to significantly increase accuracy and decrease complication rates (12).

The reason that these techniques work is postulated to be a reduction in intradiscal pressure in the nucleus, resulting in a prolapsed disc retraction, thus allowing nerve decompression and potentially, resolution of radicular pain. These mechanisms are based on the study of Hijikata in 1975 concerning the role of intradiscal pressure, which stated, "Reduction of intradiscal pressure reduced the irritation of the nerve root and the pain receptors in the annulus and peridiscal area" (13). According to several studies, the success rate of these techniques varies between 75 and 80% (4, 14,15).

Image-guided therapeutic procedures for intervertebral disc herniation are different interventional radiology techniques performed on intervertebral discs with a percutaneous approach, aimed at obtaining a partial ablation of the disc itself which uses a trocar to puncture the outer annulus of the disc. Through the trocar, a variety of thermal, chemical or mechanical ablative devices can be placed inside the nucleus pulposus resulting in its partial removal. The removal of internal nuclear material decompresses the disc with the least damage of surrounding tissues.

Our aim is to describe in particular a percutaneous discectomy technique using the mechanical decompression device DISKOM (DISKOM percutaneous discectomy probe, Biopsybell, Mirandola, Italy), to provide guidance regarding the patient selection process, technical consideration and possible complications associated with the procedure.

Before the Procedure

Before the procedure, it is necessary to know the entire medical history of the patient and carefully investigate clinical and instrumental data. The verification of normal blood coagulation is generally recommended 1 or 2 days before procedure in order to avoid, though rare, uncontrolled bleeding problems.

Benefits and potential risks must always be discussed between the interventional radiologist and the patient or referral doctor. The procedure is carefully outlined by the radiologist to the patient with an informative letter containing all the information and indications to follow after the procedure and informed consent is obtained.

Preoperative imaging generally begins with simple spinal column films that are almost always simple to perform and are inexpensive. These allow us to obtain initial information regarding bone elements, possible misalignment of the vertebrae and allow us to exclude further potential causes of pain such as joint facet arthrosis, spinal canal stenosis and fractures. Subsequently, neuroimaging studies suggestive of disc herniation to which the clinical symptoms correspond, are required. The reference diagnostic imaging method is a MRI with T1- and T2-weighting sequences. The MRI should be systematically performed before each intervertebral disc decompression procedure and only in case of MRI contraindication, a CT scan should be used (3,16,17).

Ideal candidates for the treatment include patients with symptoms resulting from single level disc herniation associated with evidence of nerve root compression. In these patients the first treatment to suggest is a medical therapy to be continued for about 4 to 6 weeks, such as analgesics, corticosteroids, muscle relaxants, bed rest and physiotherapy. The ineffectiveness of medical treatment, such as prolonged use of corticosteroids, may suggest a minimally invasive approach to the disc (16,17).

The main indications for percutaneous mechanical disc decompression include: spinal pain of discogenic origin due to contained intervertebral disc herniation, previously confirmed with dedicated imaging (preferably with a MRI); nonsignificant improvement after conservative medical therapy or neurological involvement attributable to a single nerve root compression with characteristic dermatomal pain distribution (12,16-20).

On the other hand, it is also important to emphasize the possible contraindications to the procedure. The main contraindications are concomitant spine diseases such as infections, tumors, sequestered disc fragment, stenosis of spinal canal or neural foramen, segmental instability as spondylolisthesis and pregnancy (because of fetal radiation exposure) (21-23). However, some physicians do not consider spondylolisthesis an absolute contraindication as long as there is an appropriate neurosurgical counseling (20). Other relative contraindications are represented by hemorrhagic diathesis or anticoagulant therapy (these conditions can be corrected before the procedure), severe degenerative disc disease with conspicuous reduction of disc height decrease, previous treatments at the same level and primary or metastatic malignancy (14,17,22-24).

Technique

Percutaneous disc decompression technique should be performed by an experienced and adequately trained interventional radiologist. The procedure is generally performed under fluoroscopy or CT guidance using a probe approach to treat intervertebral discs of the thoracic and lumbar spine, while supine decubitus is used for cervical spine treatment.

Before starting the procedure, it is strictly essential to carefully sterilize the area of interest. The skin is carefully disinfected using an iodine solution for proper and extensive cleaning of areas that may come into contact with surgical instruments, and all surgical instruments must be included in a sterile set. Some authors suggest the administration of a pre-procedural antibiotic therapy before treatment but this is optional while others prefer intra-discal antibiotic treatment (25). Before positioning the trocar, local anesthesia is performed by inoculating the anesthetic only into the skin and subcutaneous soft tissues. During the anesthesia procedure it is very important to avoid anesthetizing the nerve root.

Proper trocar positioning varies according to the anatomical region in need of treatment. The DISKOM® device provides different types of needles to be used in different areas; the needle used for the thoracic and lumbar tract has a diameter of 1.55mm (17G) and a length of 160mm. The needle used for the cervical tract has a diameter of 1.15mm (19G) and a length of 80mm.

For lumbar levels, the disc puncture is performed using a posterolateral approach, usually under fluoroscopic guidance. To increase access to the area of the posterior disc space, pillows are placed below the abdomen to keep the lumbar spine in a semi flexed position. The C-arm fluoroscopy is tilted in different ways in order to obtain the "scotty dog view": first it is rotated in the craniocaudal direction along the plane of the disc and then in an oblique way, so that the projection of the articular process is centered in the midpoint of the vertebral body. Then, disc puncture is performed along the x-ray axis, just laterally to the articular process. The needle must slide along the articular process in order to avoid stinging the nerve root in its extraforaminal course. Once the disc has been stitched, both antero-posterior and lateral fluoroscopic projections are needed in order to confirm correct needle positioning (Figure 1).

For thoracic levels, a posterolateral approach under fluoroscopic guidance is preferred. The C-arm is rotated in the cranio-caudal direction on the disc plane and then tilted 35 degrees laterally. In this projection, the base of the rib and the pedicle are projected as two rings. At this point the puncture is performed along the axis of the X-ray beam through the two rings in correspondence with the disc of interest.

For cervical levels, disc puncture is performed with an anterolateral approach. To maximize the width of the anterior portion of the intervertebral space, the neck is kept in a hyperextended position by placing pillows under the upper portion of the thoracic spine. The carotid artery and the jugular vein must be moved laterally by pressing two fingers against the spine. The disc of interest is then pierced by inserting the needle

between the two fingers. On its way, the needle passes between the esophagus medially and the main cervical vessels laterally (Figure 2).

Once the trocar has been inserted and its correct positioning has been assessed, the inner stylet is removed to perform a discography. Discography is performed via a spinal needle to evaluate the configuration of the disc and the integrity of the annulus fibrosus by injecting a contrast medium. This step also allows us a further assessment of the discogenic origin of the pain, as the administration of contrast medium also determines a painful stimulus that must be promptly evaluated during the execution of the discography (Figure 1). This pain stimulation procedure is performed in selected cases, generally in the lumbar tract.

At this point it is possible to proceed with the decompression of the disc by inserting the helical stylet of the discectomy probe (DISKOM®) forward inside the introducer cannula, then the cannula connector can be connected to the collection chamber of the probe. Under fluoroscopic visualization, it is confirmed that the helical section of the stylet protrudes from the distal tip of the cannula by at least one full thread turn, otherwise the cannula connector should be tightened on the discectomy probe.

Once the device has been enabled using the ON button, alternate movements should be made, in particular, it is suggested to alternate continuous anteroposterior movements with circular movements. After about three minutes, the amount of estimated removed disc material approximately varies from 1 to 3 ml and once the time of about 3 minutes has passed, it is recommended to switch off and extract the device, needle and probe cannula included (Figure 3).

Postprocedure Care

In the absence of post-operative complications, patients are observed for a period of about 3 hours during which they must remain on bed rest and are discharged on the same day of the procedure. If necessary, non-steroidal anti-inflammatory drugs and myorelaxant drugs may be prescribed to the patient but it is an option to be assessed in relation to the patient's condition. No lifting of weights, bending, or stooping is permitted for 2 weeks following the percutaneous disc decompression. Patients can return to sedentary or light work after two weeks and are provided with home exercise instructions by a qualified physical therapist.

Complications

The main intraoperative complications that may occur are related to the instrumentation used (e.g., trocar or catheter breakage, nerve root injury) and include bleeding, infections and other general complications. According to the CIRSE classification system, complications are classified into "major" and "minor" (26). The most frequent complication is represented by discitis which, in a certain percentage of cases, can also evolve into epidural abscesses (27,17). Further complications related to the procedure, found less frequently, include allergic reactions to the materials used during the procedure, puncture of dural sac with accompanying headaches, hemorrhages, neurological damage, and pneumothorax in the case of treatment carried out on the thoracic spine and vasovagal reactions in the case of decompression carried out on the cervical tract (28,29,30). In addition, failure of maneuvers, caused by equipment breakage, represents one procedural contingency to be considered (30). Treatment setting, post-operative care and patient follow-up are all actions included in the responsibility of the operator who performed the treatment.

Conclusion

Mechanical disc decompression is a minimally invasive spine intervention that should be considered as an alternative to surgery in properly selected patients. This method can be applied in all segments of the spinal column and involves a lower risk of complications and hospitalization compared to invasive surgical techniques (3,15,18,30,31). It is also useful to underline some peculiar advantages of this technique. In particular, several advantages derive from the fact that a small-sized probe is used; this allows to make a skin incision of only a few millimeters with the consequent

reduction in the risk of causing surgical site infections. It also drastically reduces the risk of causing lesions to the ligamentous system and does not cause any bone modification or reshaping, avoiding any damage to the posterior vertebral arch and adjacent muscle structures. Therefore, after this treatment, the recovery time after the procedure is significantly shorter than the classical surgical approach. Moreover, in order to obtain higher success rates and lower complication rates, correct patient selection and the maintenance of strict sterility during the procedure and adequate patient follow up must always be followed.

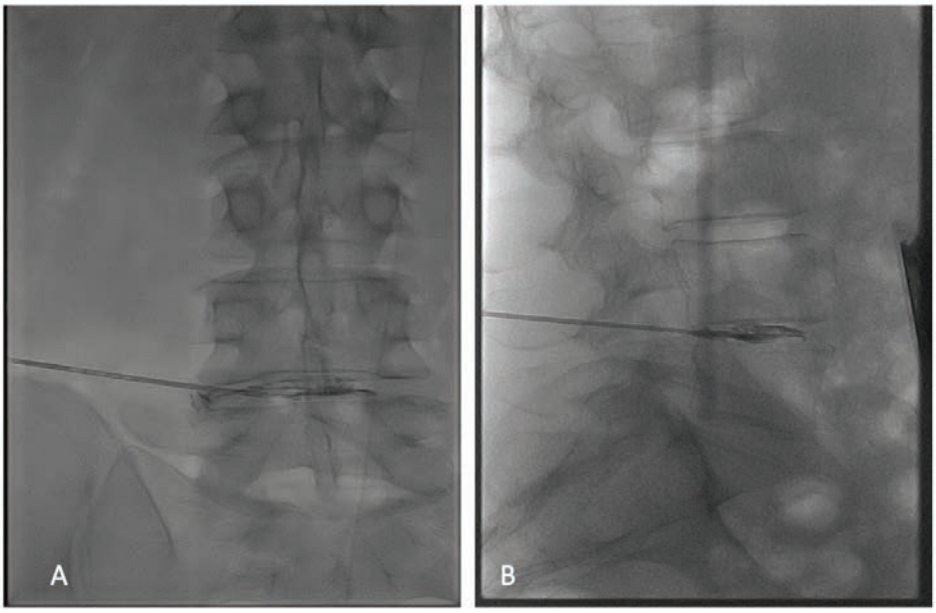

Figure 1. Discography after needle positioning during a L4-L5 discectomy procedure; antero-posterior view A; latero-lateral view B.

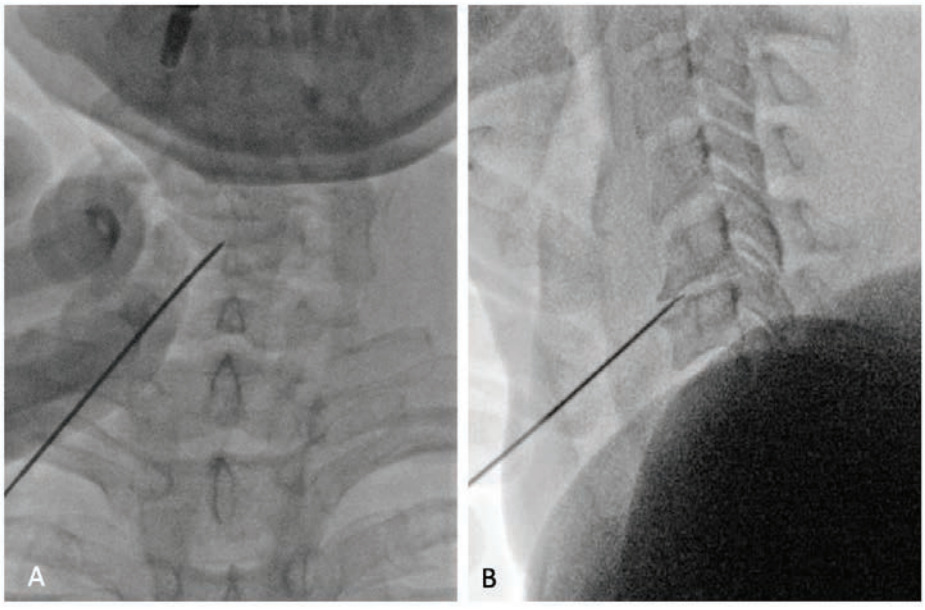

Figure 2. Cervical discectomy procedure on the C5-C6 disc; antero-posterior view A; latero-lateral view B.

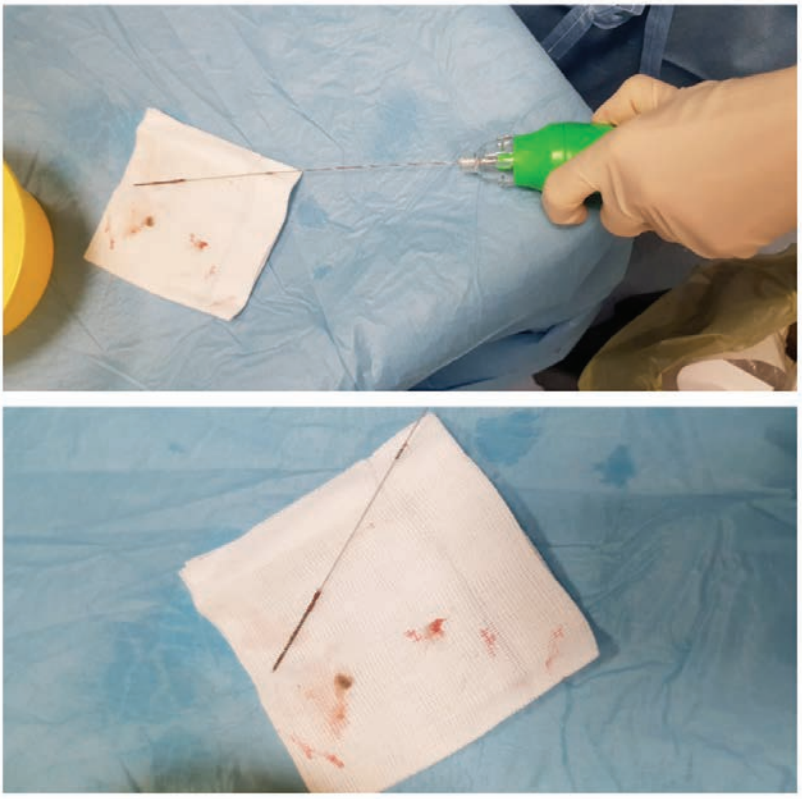

Figure 3. Disc material removed and collected along the probe stylet of DISKOM® probe.

Consent for Publication: Consent for publication was obtained for every individual person's data included in the study.

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Contribution Authors: Each author has contributed to conception and design, analysis and interpretation of the data, drafting of the article, critical revision and final approval.

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Review

Use of perfusional CBCT imaging for intraprocedural evaluation of endovascular treatment in patients with diabetic foot: a concept paper

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Summary. Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide; its global burden has increased rapidly over the past decade, enough to be considered a public health emergency in many countries. Diabetic foot disease and, particularly diabetic foot ulceration, is the major complication of DM: through a skin damage of the foot, with a loss of epithelial tissue, it can deepen to muscles and bones and lead to the amputation of the lower limbs. Peripheral arterial disease (PAD) in patients with diabetes, manifests like a diffuse macroangiopathic multi-segmental involvement of the lower limb vessels, also connected to a damage of collateral circulation; it may also display characteristic microaneurysms and tortuosity in distal arteries. As validation method, Bold-MRI is used. The diabetic foot should be handled with a multidisciplinary team approach, as its management requires systemic and localized treatments, pain control, monitoring of cardiovascular risk factors and other comorbidities. CBCT is an emerging medical imaging technique with the original feature of divergent radiation, forming a cone, in contrast with the spiral slicing of conventional CT, and has become increasingly important in treatment planning and diagnosis: from small anatomical areas, such as implantology, to the world of interventional radiology, with a wide range of applications: as guidance for biopsies or ablation treatments. The aim of this project is to evaluate the usefulness of perfusion CBCT imaging, obtained during endovascular revascularization, for intraprocedural evaluation of endovascular treatment in patients with diabetic foot. (www.actabiomedica.it).

Keywords: MRI bold, CBCT, radiology, interventional radiology, diabetic foot, perfusion imaging, cone beam

Introduction

Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide; its global burden has increased rapidly over the past decade (1), enough to be considered a public health emergency in many countries. Diabetic foot disease (DFD) and, particularly diabetic foot ulceration (DFU), is the major complication of DM: through a skin damage of the foot, with a loss of epithelial tissue, it can deepen to muscles and bones and lead to the amputation of the lower limbs.

Generally, DFD is characterized by a classical triad of neuropathy, ischemia, and infection (2) Neuropathy is manifested in the motor, autonomic, and sensory components of the nervous system (3). The most common type of diabetic peripheral neuropathy is distal symmetric polyneuropathy which accounts for approximately 75% of all diabetic neuropathies (4,5); atypical forms include mononeuropathies, (poly)radiculopathies, and treatment-induced neuropathies (6).

Changes in nerve sensitivity can lead to both increased and decreased foot sensation: the feet can become super sensitive with even light touch, creating significant pain, or, on the contrary, completely numb. This can be dangerous as a simple cut or ingrown nail can go unnoticed; even more, the foot muscles can weaken and alter the ability to walk, negatively affecting the maintenance of balance.

From the circulatory point of view, although atherosclerosis of diabetics is pathologically like that of non-diabetics, in the case of patients with DM it is more generalized, occurs prematurely and progresses at an accelerated rate. It carries macrovascular obstructions (macroangiopathic chances) especially in the coronary, cerebrovascular and peripheral arterial districts.

In particular, peripheral arterial disease (PAD) in patients with diabetes, manifests like a diffuse macroangiopathic multi-segmental involvement of the lower limb vessels, also connected to a damage of collateral circulation; it may also display characteristic microaneurysms and tortuosity in distal arteries (7).

More specifically, DM lower limb atherosclerosis tend to occur more distally (7-9); it is found at all levels of the arterial limb tree, but atheroma seems to have an apparent predilection for arteries below the knee, distally to the tibial-peroneal trunk, particularly the peroneal and posterior tibial arteries, whereas arteries proximal to the knee joint are often spared or moderately diseased and aortoiliac disease is usually less severe.

The role of PAD in the pathogenesis of DFU is to aggravate the foot infection, delay the healing of the ulcer and thus prepare for the onset of gangrene, since the reduced arterial contribution is not able to cope with the increased metabolic demand of the infected foot (10,11).

Moreover, critical limb threatening ischemia (CLTI) due to PAD, can lead to microcirculatory deficiencies with altered capillary flow and tissue oxygenation. Microcirculation, in fact, includes the terminal arterioles and capillaries beyond the arteries, which are involved in transporting oxygen and blood nutrients to the tissues. Microangiopathy, inducing thickening of capillary basal membrane, alters nutrient exchange and causes tissue hypoxia and microcirculatory ischemia; the latter represents an important point of contact between vascular and neuropathic problems related to diabetes, because among the affected micro-vessels we find vasa nervorum.

However, PAD may remain undiagnosed until the patient presents severe tissue loss, since many diabetic patients lack the classic initial symptoms of PAD such as claudication or pain at rest (12,13).

Despite DFUs result from the simultaneous actions of multiple contributing causes such as vasculopathy, neuropathy, structural deformity, and decreased immunity, the leading underlying causes are noted to be peripheral neuropathy and ischemia from PAD.

Thus, considering that about 35% of all patients with DFU have a concomitant PAD (14), early diagnosis and treatment are mandatory.

Diagnosis

The location and morphology of the PAD must be characterized prior to carrying out any revascularization to determine adequate inflow and appropriate outflow, required to keep the revascularized segment functioning and thus, the most appropriate intervention planning.

A variety of methods yielding both anatomic and physiologic information are available to assess the arterial circulation. The evaluation of a precise localization of the disease, of its extension and of its grading allow a correct therapeutic approach.

The most appropriate diagnostic approaches for the detection of macrovessels disease are represented by three techniques: duplex ultrasound (DUS), computed tomography angiography (CTA), and magnetic resonance angiography (MRA).

The location and morphology of the PAD must be characterized before any revascularization procedure is performed; the evaluation of the precise location of the disease, its extent and classification, the proper identification of adequate inflow and outflow, necessary to maintain the functioning of the revascularization segment allow the most appropriate planning of the intervention

Several methods are available to assess arterial circulation, providing both anatomical and physiological information; among them, the most commonly used diagnostic techniques for the detection of macrovascular alterations are duplex ultrasound (DUS), computed tomographic angiography (CTA) and magnetic resonance angiography (MRA).

DUS is a non-invasive, repeatable, and radiation and contrast media-free technique; it lets see vessel course and size, the wall plaques characterization, and the patency/occlusion of blood vessels.

On the other hand, DUS is operator-dependent; it has a time-costing for the sub-knee district since the average time for the study of the lower limbs is 40-60 min; it has a difficult assessment of the aorto-iliac arteries in some cases due to patient habitus (obese patients) or bowel gas; the evaluation of the leg arteries can be limited due to vessel position or extensive calcification; and its images are not useful for therapeutic planning (no panoramic images).

Multi-slice CTA is having a fast scan of wide volume, a high spatial resolution, a high quality reconstructions and it has different post-processing techniques, such as MPR, MIP, CPR, VR (15). All this, however, in the face of radiation and injection of contrast media.

MRA is a radiation-free technique and it doesn't need contrast media injection. On the other hand, MRA has a long acquisition time, a directional dependence, a predetermined sensitivity, it is dependent on flow speed and it requires to be perfected for evaluation of patients with arrhythmias (in case of Fresh Blood Imaging of the peripheral vasculature).

Treatments: Endovascular Revascularization

The diabetic foot should be handled with a multidisciplinary team approach, as its management requires systemic and localized treatments, pain control, monitoring of cardiovascular risk factors and other comorbidities (16).

Offloading and debridement are certainly fundamental in the healing process of DFU (17); the former is useful to redistribute force from the ulcers sites or pressure points at risk, to a wider area, through the use of methods of pressure relief, such as half shoes, wheelchairs and so on (18).

DFU could require debridement if necrotic or unhealthy tissue is present in order to eliminate the surrounding callus or the unhealthy tissue helping to reducing colonizing bacteria in the wound. In particular, in presence of infection, this must be treated aggressively. Depending on the depth of the infection, the DFU is treated with debridement, oral antibiotics, and regular dressings or it may also need hospitalization and broad-spectrum antibiotics (19).

Certainly, metabolic control, through multiple injections or continuous infusion of insulin, plays a fundamental role both in the treatment and in the prevention of diabetes complications, but considering that PAD remains the most important cause of compromised foot perfusion in diabetics (20), revascularization remains the treatment of choice for patients with DFU, and even more for patients with CTLI: a timely restoration of adequate arterial blood supply facilitates resolution of the underlying infection and therefore wound healing.

It should be pointed out that endovascular approach in infra-popliteal vascular territory is challenging, because its vessels have a small caliber, there is a slow flow of the distal bed and there is a need to preserve a run-off capacity. However, CLTI patients with severe comorbidities or with a very limited chance of successful revascularization (overwhelming infection that threatens the patient's life; rest pain that cannot be controlled; extensive necrosis that has destroyed the foot), are not candidates for revascularization: in the latter cases a primary amputation may be the most appropriate treatment.

Generally, macro-vessel endovascular revascularization is always recommended in all patients with DFU and PAD, regardless of bedside test results, when the ulcer does not heal within 4-6 weeks despite good treatment (21). More specifically, revascularization

aims at restoring arterial flow in at least one of the arteries of the foot, preferably the one afferent to the anatomical region of the ulcer (21): direct revascularization allows to restore the pulsatile blood flow through the feeding artery to the area where the ulcer is located, while indirect revascularization is given by the opening of collateral vessels from nearby "angiosomes".

About twenty years ago, in fact, Taylor and Paler introduced the count of "angiosome", as an anatomical unit (skin, subcutaneous tissue, fascia, muscle and bone) fed by a specific artery and drained by specific veins. In the ankle and foot region, six angiosomes are identified, fed respectively by the anterior tibial artery (one angiosome), the peroneal artery (two angiosomes) and the posterior tibial artery (three angiosomes) (22). Adjacent angiosomes are bounded by anastomoses of small or artery-like size, which connect them together; these vessels are important safety conduits that allow a given angiosome to indirectly provide blood flow to an adjacent one, if the artery of origin of the latter is damaged.

The endovascular revascularization based on the perfusion model of the angiosome, should be a more effective method than simply finding the best vessel, as the latter is not said to supply the area where the ulcer is located. In addition, it has recently been shown that indirect revascularization is associated with poorer results than direct one (23), because diabetics are poor in collateral circles.

Therefore, restoring flow to an artery directly supplying the affected area seems the best approach during an endovascular procedure (24).

Technical success is proven with an objective measurement of restored perfusion (21): any increase in volume flow to the foot has proven clinically beneficial when it also results in sufficient capillary perfusion with adequate oxygenation of foot tissue.

In patients with PAD and especially in diabetic macroangiopathy, pressure measurement is often unreliable due to the severity of calcified arteries (25, 26). Furthermore, perfusion of the foot does not only depend on the state of the artery inflow, but also on the state of the microcirculation.

There are currently no validated tests to predict the outcome of the treatment; functional methods such as transcutaneous partial pressure oxygen monitoring (TcPO2) (27, 28), individual tissue oxygen saturation (Sto2) (29) and so on are currently under development. However, these techniques are not so easily accessible at the time of surgery and allow to evaluate the functional level of perfusion instead of macro-circulation.

Actually, the most widely used method of validating the technical success of revascularization is digital subtraction angiography (DSA) at the time of endovascular procedure in Angio-suite. However, a technically successful revascularization on DSA is not necessarily predictive of good clinical success, and vice versa.

Other emerging techniques, especially those based on magnetic resonance imaging, make it possible to map areas of poor tissue oxygenation and perfusion throughout the foot, beyond the skin, even if not immediately available during a revascularization procedure for decision making.

Among the imaging techniques based on the use of simple old DSA data for the evaluation of foot perfusion during interventional procedures, there are two types: two-dimensional (2D) and three-dimensional (3D) techniques.

Two-dimensional CT perfusion (also known as perfusion angiography), as a representation of the time density curve of the contrast volumetric flow in the foot, has been most widely used (30, 31), but as a 2D technique, it cannot calculate the 3D volume of foot perfusion. For this reason, the emerging 3D perfusion angiography technique (called Cone-Beam CT - CBCT) has started to take hold.

CBCT is an emerging medical imaging technique with the original feature of divergent radiation, forming a cone, in contrast with the spiral slicing of conventional CT (32, 33); it performs a complete rotation around the patient and the collimated axe projected on the patient generates a complete set of 3D volumetric data; moreover it includes C-arm rotation, flat panel detector acquisition and CT reconstruction technologies.

The technique involves the use of DSA for image acquisition, followed by the transfer of image data to a workstation for volumetric reconstruction, multiple planar reconstruction and maximum intensity projection reconstruction, resulting in 3D layered images

similar to CT. It can also provide projection radiography, fluoroscopy, DSA but also volumetric CT capabilities directly in the operating room before and after procedures, without the need for patient transport, resulting in effective assessments and potentially decreasing time to retreatment (Fig. 1).

This is why, over the years, CBCT has become increasingly important in treatment planning and diagnosis: from small anatomical areas, such as implantology, to the world of interventional radiology (34, 35, 36,37, 38), with a wide range of applications: as guidance for biopsies (39) or ablation treatments (40); for perfusion evaluation of brain (41-44) and liver, such as for assessing the technical success after transarterial chemoembolization of HCC or identifying the changes in blood volume in the tumor tissue and in the adjacent liver tissue with melanoma liver metastases (45, 46). But not only, in fact it has also been used in musculoskeletal surgery, such as in total ankle replacement or for evaluation of the patello-femoral alignment after medial ligament reconstruction (47), and finally in pediatric patients for common periprocedural complications after neuro-interventions (48), for the detection of ventricular size/subarachnoid spaces changes and large volume hemorrhage.

Although for the diabetic foot CBCT has only been applied for diagnostic evaluation (49), nowadays thanks to post-processing software based on the principle of subtraction between the mask image and the contrast fill image on dual-phase CBCT with the provider-specific vascular flow detection algorithm and automatic scaling, it is possible to have CBCT-based, color-coded perfusion images (50) and to measure the skin blood volume evaluated by CBCT data, which allows further evaluation of the blood volume increase during the procedure.

In this perspective, the purpose of our project is to evaluate the usefulness of CBCT–based foot perfusion imaging, obtained during endovascular revascularization in patients with diabetic foot, for assessing foot vascularity, technical success of the procedure, and treatment response, as an alternative to perfusion angiography.

To prove its effectiveness, we'd like to propose MRI of dependent blood oxygenation (BOLD) as a validation method, to investigate foot microcirculation in patients with DFD using skeletal muscle BOLD MR, immediately after revascularization, comparing with CBCT, and during its follow-up, also preventing continued radiation exposure and, using deoxygenated

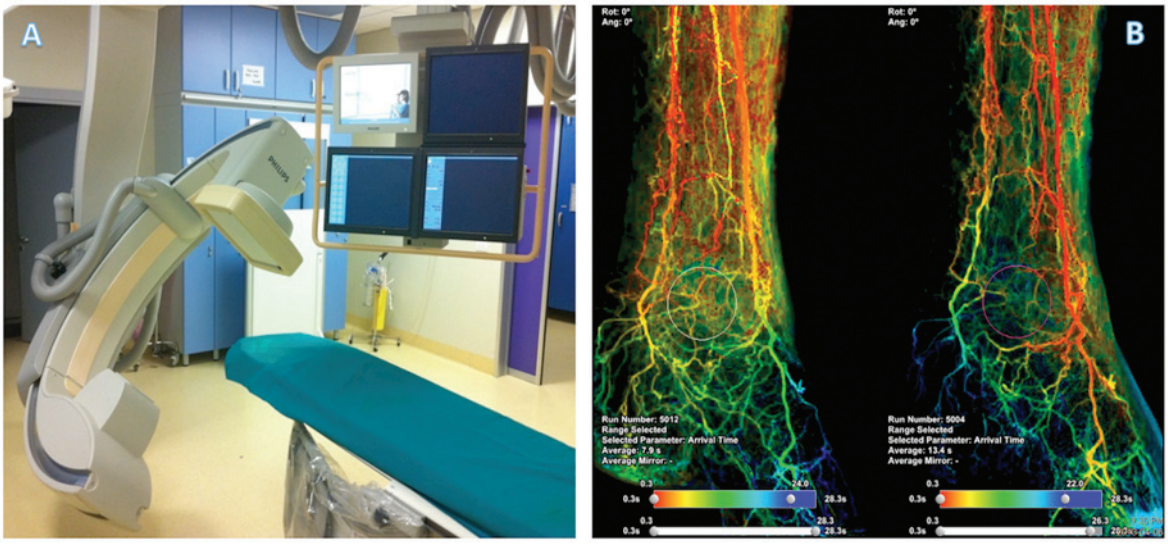

Fig. 1 - "3D Cone Beam CT perfusion angiography technique" – A. CBCT included in C-arm in angiography room; B. CBCT color-coded perfusion images.

hemoglobin as an endogenous contrast agent to perform non-invasive assessment of tissue oxygenation levels, avoiding contrast media-related reactions.

From a technical point of view, in the microvasculature, as in the large veins, hemoglobin iron changes its spin state from diamagnetic low-spin in the oxygenated state to paramagnetic high-spin in the deoxygenated state (51). This causes local magnetic field distortions in the surrounding tissue, which results in dephasing of the proton signal, consecutively leading to a signal decay with increasing intravascular deoxyhemoglobin content (52). These local field disturbances cause nearby stationary and slowly moving spins to have different resonance frequencies and phase shifts. The resultant "intravoxel dephasing" is a classic T2*-shortening effect accentuated by use of Gradient Echo (GRE) sequences with echo times close to T2*. Thus, changes in T2* in response to an ischemia-reperfusion paradigm can serve as a relative marker of tissue oxygenation (53).

It is also important to keep in mind that the oxygenation level of intravascular hemoglobin is not only dependent from oxyhemoglobin supply and deoxygenation rate of the respective tissue, but it is also sensitive to changes in perfusion, cellular pH, vessel diameter, and vessel orientation (54-59), considering the origin of BOLD-MRI signal as multifactorial. However, it has been postulated that the BOLD signal changes primarily result from changes in the concentration of deoxyhemoglobin in muscle microcirculation (60).

As already pointed out above, DM is associated with impairment of macro and microcirculation (61-63); while macroangiopathic alterations can be studied with Doppler ultrasound, MRI angiography or plethysmography (64, 65), the diagnostic evaluation of microangiopathic alterations still remains a challenge. In this scenario, since BOLD-MRI predominantly reflects oxygenation changes in peripheral microvasculature, it could be the best diagnostic tool to be used in patients with DM (66, 67) to correlate with microvascular oxygenation state (53, 68, 69).

In the past, BOLD-MRI was used to assess brain activation (52), but now it can also provide information regarding activation and oxygenation of many other tissues including the kidneys (70) and skeletal muscles (54, 60, 68), as already done by Ledermann et al. and Potthast et al. that demonstrated the value of BOLD-MRI of skeletal muscle in assessment of microvascular function in patient with PAD (71, 72). Moreover, BOLD-MRI has also been used to evaluate the efficacy of PTA of superficial femoral artery in patients with symptomatic stenosis (73), underlying its potential usefulness in evaluation of treatment approaches, as endovascular revascularization.

Conclusion

The aim of this project is to evaluate the usefulness of perfusion CBCT imaging, obtained during endovascular revascularization, for intraprocedural evaluation of endovascular treatment in patients with diabetic foot. Furthermore, we'd like to propose BOLD-MRI to validate this method, as a diagnostic tool for a non-invasive, radiation and contrast media-free follow-up helpful in evaluation of microvessels in patients with DFD undergone to endovascular revascularization.

Consent for Publication: Consent for publication was obtained for every individual person's data included in the study.

Human and Animal Rights and Informed: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Authors Contributions: Each author has contributed to conception and design, analysis and interpretation of the data, drafting of the article, critical revision and final approval.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Review

Interventional radiology management of high flow priapism: review of the literature

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Summary. *Introduction*: High-flow priapism is a persistent partial penile tumescence, related to high flow arterial blood into the corpora. It is much less common than the low-flow priapism, and history of trauma is the more common aetiology. In the treatment of high flow priapism, super-selective embolization is considered treatment of choice when conservative treatment fails as reported in the "European Association of Urology Guidelines on Priapism", but there are only few series reporting the outcome, the efficacy of different embolic materials and these studies are uncontrolled and relatively small. *Objectives*: The aim of this study is to review the literature to outline the state of the art of this interventional treatment and to analyse the outcome of the different embolic agents. *Methods:* Through Medline database (via PubMed) we searched all the English-language published articles related to priapism. Keywords were chosen according to MeSH terms. We selected case-series from 1990 to 2020 including at least five cases of high-flow priapism. The variables extracted from the selected articles were: number of patients, mean age, diagnostic imaging modality, mono or bilateral involvement of the arteries, embolization material, technical success, clinical success, complications, recurrence rate and type of reintervention, mean follow up, onset of erectile dysfunction. *Results*: We analyzed 11 papers. A total of 117 patients, mean age of 30 years, were studied during a period of 8 to 72 months. Technical success average was 99%, varying from 93 to 100%. Clinical success average was 88%, varying from 56 to 100%. After two or more treatments, resolution of priapism was obtained in all patients. No major adverse events registered. Recurrence rate of 21% (25/117) was observed, and only 4 patients underwent surgery. A total of 17 patients (15%) developed erectile dysfunction (ED). We also created a subgroup analysis focusing on specific outcome with different types of materials. Technical success was very high, 100% for all materials except for PVA particles Clinical Success was at least 70% with all kind of material. Best result was obtained with gel-foam (89%) and the worse with PVA (70%). *Conclusion*: Our data suggested comparable outcomes using different types of materials. In line with the last evidences we suggest that the choice of the embolic material should be selected basing on the expertise of the operator, the characteristic of the fistula and characteristic of the patients. (www.actabiomedica.it)

Key words: priapism, High flow priapism, endovascular treatment of priapism, penile fistula, embolization of priapism, interventional radiology, cavernous fistula

Introduction

Priapism is defined as a penile erection (partial or complete) that persists for 4h or more and is unrelated to sexual activity (1). It is a complex medical disorder described for the first time in the English medical literature in 1845 on Lancet (2). Priapism can affect all ages but its incidence is very low (0.5–0.9 cases per 100 000 person-years) (3).

For clinical management, priapism can be stratified into three groups: High-flow priapism (arterial or non ischaemic); Low-flow priapism (veno-occlusive or ischemic); Stuttering priapism (recurrent or intermittent) (4).

The most common is low-flow priapism (95% of all priapic episodes). It can be considered a compartment syndrome and it can be caused by many factors; is often idiopathic or associated with haematological dyscrasias (eg sickle cell disease, SCD) (4). It presents as a persistent and painful erection and is a medical emergency because a delay in the treatment can hesitate in penile erectile dysfunctions. The cavernosal blood has low pO2 levels (5). Management of these cases is the competence of urologists. First line treatment is penile blood aspiration and drug injection. When blood aspiration and intracavernous drug injection doesn't work, as a second line treatment surgery should be considered (6).

Stuttering priapism is characterized by recurrent episodes of painful priapism lasting hours. The aetiology of this pathology is similar to ischaemic priapism. Often it affects patients with SCD. Episodes of stuttering priapism usually increase in frequency and duration hesitating in full episodes of ischemic priapism.

High-flow priapism is a persistent partial penile tumescence, related to high flow arterial blood into the corpora. It is much less common than the low-flow priapism, and history of trauma is the common aetiology. The trauma results in a laceration of a penile artery leading to a high-flow fistula between the artery and the corpora (7).

The clinical presentation can be delayed (hours or days) from the trauma. Clinically is classically not painful and the penis is usually non-rigid. The cavernosal blood is arteriosus, and has high pO2 level. High flow priapism does not require emergency management (4,6). First line treatment consists in conservative measures (e.g. ice compression). Often it is not enough and super-selective embolization performed by interventional radiologists is the treatment of choice. Today surgical treatment is rarely performed given its significant risks. Is performed only in selected cases (e.g. contraindications for selective embolization, or embolization failure) (6).

In the treatment of high flow priapism, super-selective embolization is considered treatment of choice when conservative treatment fails as reported in the "European Association of Urology Guidelines on Priapism", but there are only few series reporting the outcome, the efficacy of different embolic materials and these studies are uncontrolled and relatively small (6). The aim of this study is to review the literature to outline the state of the art of this interventional treatment and to analyse the outcome of the different embolic agents.

Etiopathogenesis

Trauma is the primary cause of high-flow priapism in boys and men younger than age 55: blunt penile or perineal trauma may cause a laceration of branches of the internal pudendal artery. In older men the primary causes are malignant tumors that, in an advanced stage, can erode arteries. High-flow priapism has been described also in children with inherited diseases (e.g. SCD, Fabry's disease). Internal pudendal artery or its branches are the site of 99% of all fistulas (8).

From a hemodynamic point of view, the laceration of a cavernous artery results in direct, persistent, and irregular flow of arterial blood inside the vascular lacuna of the erectile tissue (9). The lacunar endothelium adjacent to the fistula is exposed to oxygenated blood with high velocity and turbulent flow, which creates a shear stress and stimulates the release of nitric oxide. Shear stress and high oxygen tension stimulate the synthesis and release of endothelium-derived nitric oxide, resulting in arterial and trabecular dilatation through the corpora cavernosa. The incomplete rigidity of the penis most likely depends on incomplete corporeal smooth muscle relaxation. Arterial priapism can develop early after the trauma or with a delay of several days. The delay may possibly be explained by

spasm of the injured vessel (10). As reported in literature, only two thirds of patients exhibit penile erection immediately following trauma; in the others, priapism develops over 1 to 15 hours, which suggests that hemodynamically relevant fistulas may develop from initially very small vascular defects. The bulbourethral arteries are responsible for the fistulas in about one third of patients (11).

Diagnosis of high flow priapism

To make diagnosis of priapism and classify it, it is essential to collect an accurate medical history, make a scrupulous physical examination, perform laboratory tests and complete with the most appropriate imaging.

History

High-flow priapism should be considered when the patient presents an erection not associated with pain, the erection generally is partial and the duration has not been accompanied by progressive discomfort. The patient has a history of trauma that led to the formation of an arteriovenous fistula and the appearance of priapism may be delayed for several hours or days after the initial injury (4).

Physical Exam

Examination of the genitalia, the perineum, and the abdomen is mandatory for the diagnostic evaluation of priapism. In low-flow priapism, the corpora cavernosa are rigid and very tender to palpation, but the glans penis is soft (12). In patients with high-flow priapism on exam the corpora are tumescent but not fully rigid and the penis is only partially erect (13). There may be residual bruising and some tenderness on palpation, depending on the location of the trauma and the elapsed time since the trauma.

Laboratory Testing

Laboratory evaluation should include a complete blood count, white blood cell with blood cell differential, platelet count and coagulation profile, to rule out infection and to detect hematologic abnormalities. If drugs are suspected from the psychosocial history, should be performed also urine and plasma toxicology. A corporal blood gas analysis is recommended to differentiate between low-flow and high-flow priapism: in low-flow priapism the blood is hypoxic (pO2 < 30 mm Hg, pCO2 > 60 mm Hg, pH <7.25), in high-flow priapism the blood is red in colour and oxygenated (pO2 > 90 mm Hg, pCO2 < 40 mm Hg, pH 7.40) (4).

Imaging

Colour Doppler Ultrasonography (CDUS), increasingly widespread in the setting of urologic vascular disease (14), can help in differentiation between low-flow and high-flow priapism *(fig.1)*. In low-flow priapism, cavernousal arterial flow typically demon-

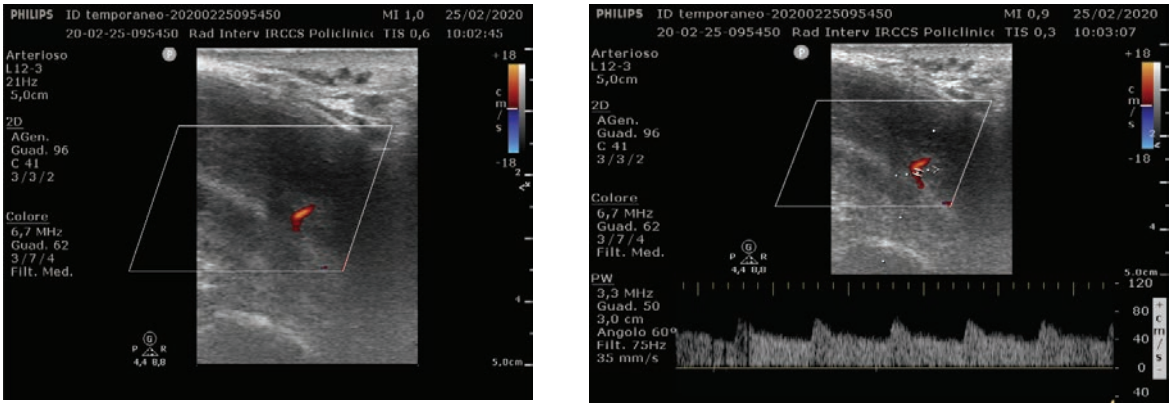

Figure 1. Detection of fistula on Colour Doppler examination: it is a hypoechoic area surrounded by echogenic tissue. Subsequently the Power Doppler shows a venous base flow with arterial peaks

strates a "high-resistance, low velocity" waveform and arterial flow is usually absent. In high-flow priapism, CDUS demonstrates a "low-resistance, high-velocity" arterial waveform (15,16). Is important to underline that the sensitivity of CDUS in localizing an arteriocavernosal fistula is nearly 100% (17).

The arteriocavernosal fistula is a hypoechoic area surrounded by echogenic tissue with mixed signal at the power doppler evaluation. CDUS is also preferred in follow-up of these patients.

The use of magnetic resonance imaging (MRI) in the diagnosis of priapism has not been already well established, and MRI has a limited role in the initial diagnosis because priapism represents an emergency situation and MRI takes too much time. There has been only few studies that reported MRI findings in cases of high-flow priapism *(fig.2-3)*. In the study of White et al, MRI showed the arteriocavernosal fistula in all patients (18). The authors of that article underlined that while CDUS demonstrates characteristic flow patterns of priapism, MRI can better characterize tissue and demonstrate the presence of arteriocavernosal fistula or thrombus (18). Additional benefits of MRI include its ability to predict nonviable smooth muscle within the corpora after episodes of priapism and detecting unusual conditions such as malignant infiltration (12).

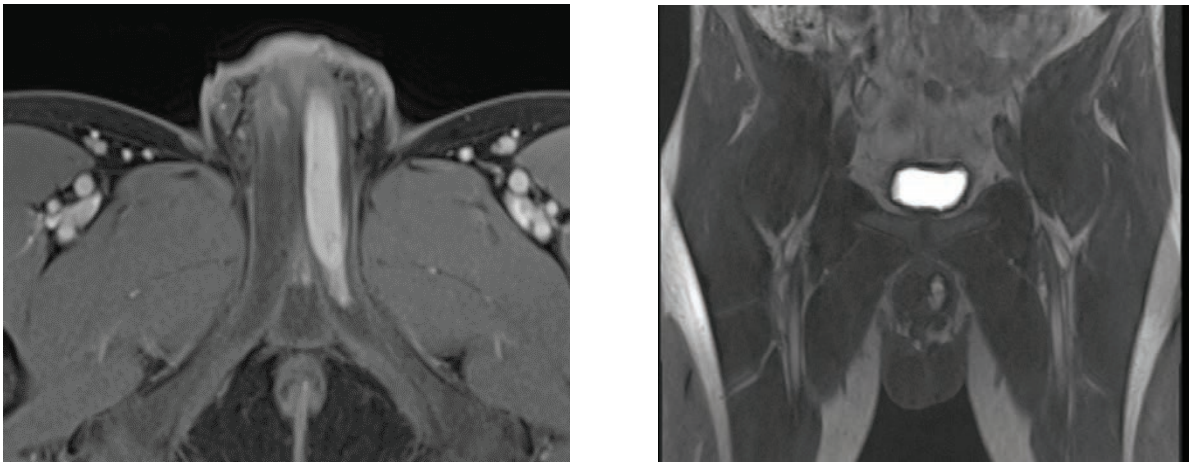

Figure 2. Contrast-enhanced T1 images on axial and coronal plane that show arterial enhancement of the left cavernous body because of the presence of arteriocavernosal fistula.

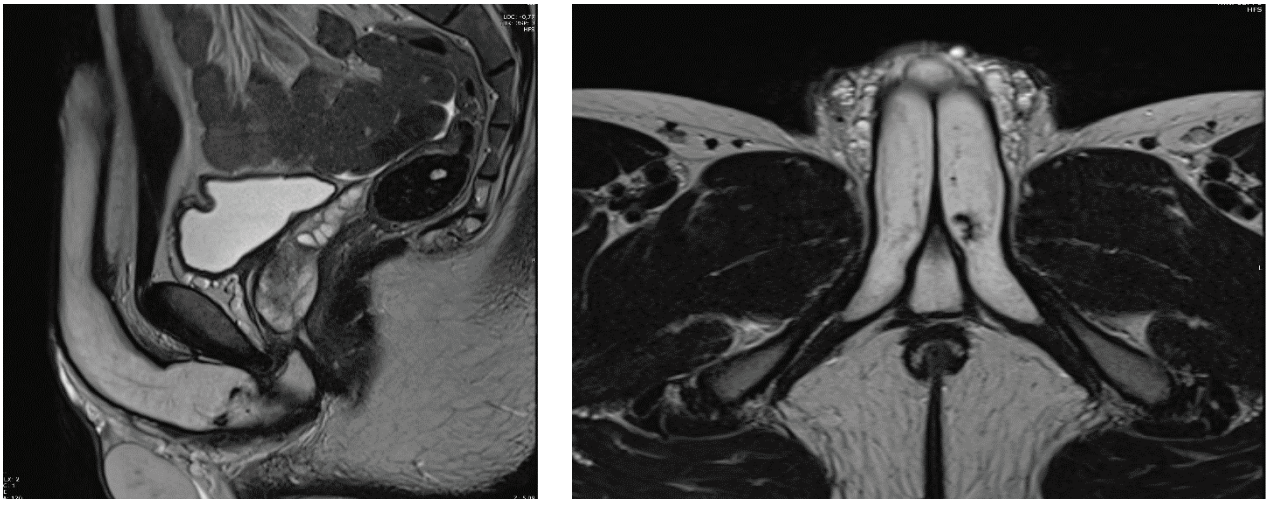

Figure 3. T2 images on sagittal and axial plane that show flow void in the left cavernous body.

When high-flow priapism is related to a pelvic trauma, contrast-enhanced CT is recommended to assess associated diseases (19) but is not useful in diagnosis of priapism (20).

Materials and Methods

We searched electronic information sources through Medline database (via PubMed) and bibliographic lists of relevant articles to identify studies reporting outcome of endovascular treatment of post traumatic priapism.

All the articles related to human medicine among English-language published literature were selected. Keywords were chosen according to Medical Subject Heading (MeSH) terms: "High flow priapism", "High flow priapism endovascular treatment", "High flow priapism and interventional radiology", "Post traumatic penile arteriovenous fistula", "Penile arteriovenous fistula", "Endovascular treatment and penile arteriovenous fistula", "Embolization and penile fistula", "penile cavernous arteries fistula", "Interventional treatment penile cavernous fistula", "interventional radiology and priapism".

Additional studies were identified through manual research of the bibliographies from primary studies, review articles, and key journals.

Articles consisting in case-series from 1990 to 2020 including at least five cases of high-flow priapism, were considered eligible for inclusion in the present review.

First, the articles were selected by the titles focusing on our area of interest. Then the abstracts were reviewed to find the best matching articles. All articles containing data reported previously were excluded. Then the second step consisted in reviewing the full text version of the selected articles. The variables extracted from the selected articles were: number of patients, mean age, diagnostic imaging modality, mono or bilateral involvement of the arteries, embolization material, technical success, clinical success, complications, recurrence rate and type of reintervention, mean follow up, onset of erectile dysfunction. When not mentioned the information was classified as not available.

Before the extraction of data from the studies, the following clear definitions of all outcomes of interest were established. Clinical success was defined as complete resolution of priapism after one or two (when fistula was bilateral) interventions. Technical success was established as the exclusion of the fistula on the final angiography. Recurrence rate was considered as priapism persistence or relapse after one or two (when fistula was bilateral) interventions. Erectile dysfunction was defined as a IIEF-5 value under 22 (when reported) or as the impossibility to have satisfactory sexual intercourse. Adverse events were considered complications related to procedure, excluding erectile dysfunction. When adverse events were not reported we considered absence of adverse events.

Results

We analyzed endovascular treatment of high flow priapism in 11 papers (8-11,21-27), published during the last 30 years (1990-2020) which met our inclusion criteria. Table 1 summarizes all the data collected by the studies focusing on interventional treatment of high flow priapism.

A total of 117 patients, mean age of 30 years, were studied during a period of 8 to 72 months, with a median follow-up of 30 months. The only imaging modality used was CDUS, which is the mainstay of diagnosis. Technical success average was 99%, varying from 93 to 100%. Clinical success average was 88%, varying from 56 to 100%, but after two or more treatments, resolution of priapism was obtained in all patients. No major adverse events registered, only 4 patients developed minor complications related to the access site, brushing or pain.

A recurrence rate of 21% (25/117) was observed, in most cases after a second treatment detumescence was obtained, and only 4 patients underwent surgery. A total of 17 patients (15%) developed erectile dysfunction (ED), most of them were already mild impotent or developed ED after surgery. Only in 8 patients, ED may be related to transarterial embolization. In any case, sildenafil administration has been sufficient to have satisfactory intercourse.

Table 1. Collection of data from our selected case series

Study	Patients	Mean Age	Imaging	Artery involved Mono/bilateral	Embolization Matherial	Tech succ	Clin succ	Adverse Events	*Recurrence rate (prev intervention)	Type of reintervention **	Mean FUP (months)	Erectile disfuction
Ciampalini Et al. 2002	9	36	CDUS	NA	Absorbable syntetic Clot	100%	66%	No	3(33%)	2(clot) 1(surgical ligature)	41	20%
Gorich Et al. 2002	6	16	CDUS	2 Monolateral 4 Bilateral	3 Gelatin Sponge 3 Microcoils	100%	83%	No	1(17%) (microcoil)	1 (microcoil)	11.8	0
Bertolotto Et al. 2003	9	29	CDUS	8monlateral 1bilateral	PVA beads (300-500)	100%	56%	No	4(44%)	3 (PVA) 1 (PVA than surgery)	NA	1(11%)
Savoca Et al.2004	15	32	CDUS	13monolateral 2 bilateral	PVA beads (350-500)	93%	73%	4 (27%) bruising and pain in site of needle	4(27%)	3 (PVA) 1 (2 PVA than surgery)	55	1(7%)
Bartsh Et al. 2004	6	NA	CDUS	3monolat 3bilateral	Gelatin Sponge Microcoil	100%	83%	NA	1(17%) (microcoil)	1(vasospasm)	48	0
Sullivan Et al. 2006	5	31	CDUS	5 monolateral	2 Gelfoam 1 autol clot 1 Microcoils 1 Microcoil+ Gelfoam	100%	60%	NA	2(40%) (1blood clot, 1microcoil)	2(gelfoam+ microcoil)	12	1(20%)

(*Continued*)

Table 1. Collection of data from our selected case series (*Continued*)

Kim Et al. 2007	27	39	CDUS	16monolateral 11 bilateral	12 Gelfoam 12 autol clot 1 Microcoils 1 NBCA 1 PVA beads(500-700)	100%	89%	No	3 (11%) 2 autol clot 1sponge	2 (1 autologous clot, 1 gelfoam) 1 (1 emb, than surgery)	13	7(26%)
Liu Et al. 2008	8	33	CDUS	7 monolateral 1 bilateral	2 gelfoam 6 Microcoils	100%	75%	NA	2 (25%) (gelfoam)	2 (microcoils)	18	2(25%)
Cantas-demir Et. al 2010	7	10	CDUS	7 monolater	7 autol clot	100%	85%	No	2 (29%) (aut clot)	2 (aut clot)	72	0
Pei Et al.2018	16	24	CDUS	15monolateral 1bilateral	10 Microcoil 4 Gelfoam 2 Micro-coil+gelfoam	100%	94%	No	1 (6%) (Microcoil)	1(microcoil+ spongel)	8	2(13%)
De Magis-tris Et al.2019	9	33	CDUS	5 monolateral 6 bilateral	6 Microcoils 2PVA 1Gelfoam	100%	78%	No	2 (22%) (Micro-coil monolaterl)	2 MicroCoil	24	1(11%)
Total/ Mean	117	30	CDUS	81monolateral 29 bilateral	See Tab2	99%	80%	No	25(21%)	25 (4 surgery)	30	17(15%)

*Recurrence rate and type of embolization performed **Type of reintervention and type of used material

Table 2. Subgroup analysis of different embolization materials. AE= Adverse events. RR= Recurrence Rate

Materials	Patients	Tech success	Clinical success	AE	RR	Material for Reintervention	Erectile Disfunction
PVA (300/350-500 o 500-700)	27	26(96%)	19(70%)	No	8(29%)	8	2 (7%)
Microcoils	27	27(100%)	21(78%)	No	6(22%)	5	5(19%)
Gel-foam	23	23(100%)	20(87%)	No	3(13%)	1	4(17%)
Autologous Clot	29	29(100%)	21(72%)	No	8(28%)	5	5(17%)

We created a subgroup analysis (Table 2) focusing on specific outcome with different types of materials, excluding the only case treated with NCBA. As expected from previous studies, technical success was very high, 100% for all materials except for PVA particles which were not able to embolize sufficiently in one case.

Clinical Success was at least 70% with all kind of material. Best result was obtained with gel-foam (89%) and the worse with PVA (70%). It is important to underline that detumescence was obtained in 100% of patient after repeating embolization or surgery.

No adverse events related to the material has been reported.

Low recurrence rate was obtained in patients treated with gel-foam followed by those treated with microcoils, respectively 13% and 22%.

Patients treated with PVA particles and autologous blood clot had a recurrence of 28% and 29% respectively.

ED was less than 20% in all cases and, if we exclude patients who was mild impotent before treatments, only 10 patients on 117 developed ED.

Discussion

Non-ischemic priapism is not a medical emergency and does not require urgent medical intervention, thus conservative management, such as watchful waiting, must be considered an alternative option (17,28). In fact it has been reported that non-ischemic priapism often resolves spontaneously (17) and most patients affected by this kind of priapism are able to have normal erections and satisfactory sexual intercourse.

The rationale of the conservative approach is to obtain detumescence at an early stage with ice or compressive perineal dressing that may be expected to cause vasospasm and thrombosis of the ruptured artery in days to weeks.

However, excessive arterial inflow with high oxygen levels and chronic erection, caused by activation of guanylate cyclase enzyme, may be dangerous to the cavernosal smooth muscle and connective tissue matrix, leading to irreversible corporal fibrosis and consequently to erectile dysfunction (9).

For these reasons it is essential to perform embolization in trauma-related cases as soon as possible avoiding too long watchful waiting periods, because of the increased risk of secondary vascular alterations.

Interventional radiology has a key role in the management of high flow priapism, as reported in many guidelines as the "European Association of Urology Guidelines on Priapism".

Superselective TAE represents a minimally invasive and efficacious approach. In literature it is reported that near 100% of patients had a satisfactory detumescence with recurrence rate of 6.3% (25).

We reported a comparable technical and clinical success but higher recurrence rate: 25% vs 6.5%. It is important to underline that, contrary to previous studies who differentiated recurrence from persistence considering recurrence only as a relapse in our study, recurrence rate is referred to persistence and/or relapse of detumescence after one embolization, so we included all potentially includable patients.

Superselective arterial embolization may be performed with a number of agents including microcoils, polyvinylalcohol (PVA), N-butylcyanoacrylate (NBCA), gel-foam and autologous blood clot (20).

Temporary embolic agents are preferred by many interventional radiologists because there is lower risk

of postprocedural impotence (1). NBCA is rarely used and we have found very few case series in the literature.

For Cantasdemir et al (25) autologous blood clot is a good occlusive agent because of its numerous advantages. It carries low risk of foreign body reaction and antigenicity, does not require additional costs for use, and more importantly, it is a temporary occlusive agent that allows recanalization of the cavernosal artery and subsequently restores the normal erectile mechanism (29).

Moreover it can be successfully used in the embolization of fistula especially for treating priapism in children (22).

Gel-foam (also called Spongel or gelatin sponge) is a temporary occlusive agent with a duration of action of 5/6 weeks after being injected. Detumescence can be achieved with gel-foam without permanent vascular occlusion (30). O'sullivan et al believe that this increases the probability of preserving the patients erectile function (22).

In the experience of Kim et al, using autologous blood clot or gelatin sponge there was no significant change in the quality of patients erection during the follow-up period and also there was no difference affecting the requirement for repeat embolization (23). The disadvantages of Gel-foam is that might lead to recanalization and priapism recurrence. It is also considered difficult to control and its positioning could result in occlusion of unexpected vessels (24).

When the preliminary angiographic study shows multiple small caliper fistulas, it is preferred to use PVA microparticles (300–500μm) because of the ability to penetrate the microvascular network (27,31). Particulate embolic injection should be performed with gradual pressure to avoid the proximal reflux and the unintentional peripheral embolization that can lead, especially with PVA, to infection and mostly ischemia (27). Ethylene-vinyl alcohol copolymer is not used in high flow priapism, even though has been demonstrated to be safe and effective in arterial embolization (32).

Microcoils are permanent occlusive agents. According with the study of Liu et al., microcoils were more effective and permanent, with accurate positioning in the desired vessel. They suggested that microcoil is a more reliable agent, even for recurrent cases and longstanding priapism. Theoretically, microcoils increase the risk of permanent vascular occlusion and subsequent erectile dysfunction (24) but no major ischaemic events have been demonstrated in literature (20).

Nevertheless, several studies have shown microcoils to have a preservative effect on erectile function, even with bilateral embolization.

Superselective cavernous artery embolization with microcoils has a satisfactory detumescence effect and might help to preserve erectile function, especially for younger patients with a unilateral arterial fistula. Therefore, Liu et al. suggest that embolization with microcoils should not be indicated for older patients (24). In our study, microcoils has not the lowest recurrent rate. Nevertheless the most of patients treated with microcoils who developed recurrence were patients with multiple fistulas and after repeat embolization fistulas has been closed either spontaneously (vasospasm) or using again microcoil and/or microcoil+spongel. Moreover, patients treated with spongel who developed recurrence, received a second embolization with microcoil solving priapism. This evidences strengthen the idea of exceptional ability of microcoils to close fistulas in high flow priapism and the importance of positioning the coil correctly which depends on operator experience in the use of this specific material *(fig.4)*.

As expected microcoil was the material which caused more cases of ED (19%) also excluding patients with previous ED, confirming the risk of ED with the use of this type of permanent embolization material.

Conclusion

Our data suggested comparable outcomes using different types of materials.

It is clear that the type of embolo-therapy was not the major factor affecting the recurrence of priapism and this concept was underlined in more recent papers, particularly by Kim et al. (23), a multicenter study comparing treatment results among embolic agents in 27 patients, which represents the largest series reported in literature.

In line with the last evidences we suggest that the choice of the embolic material should be selected bas-

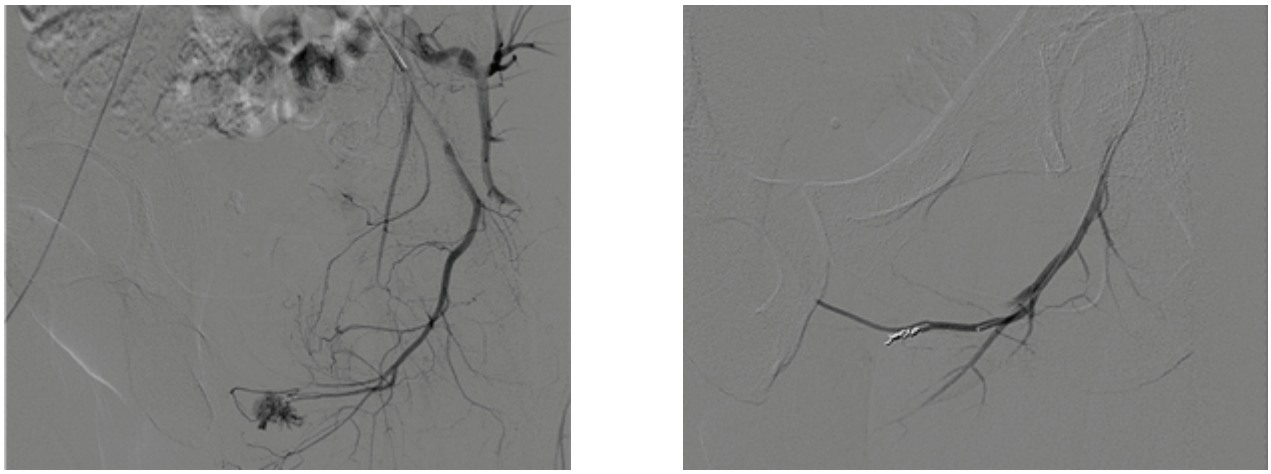

Figure 4. Angiography pre and post embolization with microcoils.

ing on the expertise of the operator, the characteristic of the fistula and characteristic of the patients.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Written informed consent to the CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Percutaneous lung microwave ablation versus lung resection in high-risk patients. A monocentric experience

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Summary. *Background and aim of work:* Lung microwave ablation (MWA) is considered an alternative treatment in high-risk patients, not suitable for surgery. The aim of our study is to compare MWA and pulmonary lobectomy in high-risk, lung cancer patients. *Methods:* This was a single-center, propensity score-weighted cohort study. All adult patients who underwent CT guided MWA for stage I NSCLC between June 2009-October 2014 were included in the study and were compared with a cohort of patients submitted to lung lobectomy in the same period of time. Outcomes were overall survival (OS) and disease-free survival (DFS). *Results:* 32 patients underwent MWA, and 35 high-risk patients submitted to lung lobectomy in the same period were selected. Median follow-up time was 51.1 months (95% CI: 43.8-62.3). Overall survival was 43.8 (95% CI: 26.1-55) and 55.8 months (95% CI: 49.9-76.8) in the MWA group and Lobectomy group, respectively. Negative prognostic factors were MWA procedure (HR:2.25, 95% CI: 1.20-4.21, p= 0.0109) and nodule diameter (HR: 1.04, 95% CI: 1.01-1.07; p= 0.007) for OS, while MWA procedure (HR: 5.2; 95% CI: 2.1-12.8: p < 0.001), ECOG 3 (HR: 5.0; 95% CI: 1.6-15.6; p = 0.006) and nodule diameter (HR: 1.1; 95% CI: 1.0-1.1; p = 0.003) for DFS. *Conclusions:* Our study demonstrated a high percentage of local relapse in the MWA group but a comparable overall survival. Although lung lobectomy remains the gold standard treatment for stage I NSCLC, we can consider the MWA procedure as valid alternative local treatment in high-risk patients for stage I NSCLC. (www.actabiomedica.it)

Key words: Microwave ablation (MWA), lung lobectomy, lung cancer

Background and Aim of Work

Lung cancer continues to be one of the most common types of cancer in the world and the leading cause of cancer-related death.

Early stage (stage I) non-small-cell lung cancer (NSCLC) includes 16% of all lung cancer cases, with 5-year survival rates of 70-90% for small, localized tumours (1).

The treatment of choice for standard-risk operable patients with stage I disease is lobectomy. In selected cases, sub-lobar resection, comprehending both segmentectomy and atypical wedge resections, could be alternative treatments for high-risk operable patients (2).

Different therapeutic alternatives have been introduced for patients who have excessive risk of surgical morbidity and mortality, such as stereotactic radiotherapy and MWA (3).

The use of percutaneous thermal ablation has increased for the treatment of early stage lung cancer, and can be performed by radiofrequency ablation or MWA. The best candidates for percutaneous MWA are patients with stage I NSCLC who present contraindications to surgery or stereotactic radiotherapy due to cardiac and/or respiratory co-morbidities or insufficient vital lung reserve (4). The main advantage of this technique is to destroy a small pathological lung tissue by locally heating, causing minimal damage to the surrounding tissue.

The use of MWA was introduced for the treatment of hepatic tumors. Subsequently, starting in the early 2000s, this technique was widely used for the treatment of primary and secondary lung malignancies (5).

The aim of our study is to compare computed tomography guided percutaneous MWA and pulmonary lobectomy as therapy of NSCLC in high risk patients, in terms of overall survival and relapse of disease.

Methods

This was a single-center, propensity score-weighted cohort study of prospectively collected data. The study was conducted at Thoracic Surgery Department of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, an University, considered a third-level Hospital of Milan. All adult patients underwent CT guided MWA for stage I non-small cell lung cancer between June 2009-October 2014 were included and were compared with a cohort of patients submitted to lung lobectomy in the same period of time. Data were downloaded from our Institutional electronic database. All patients were affected by cytological or histological proven Stage I NSCLC. The baseline demographics of patients (age, sex, ECOG performance status) (6), characteristics of tumours (size, location, histological type, 18F-FDG uptake) and treatment details (MWA or surgery) were collected from our database. Histological subtypes were classified as adenocarcinoma and squamous cell carcinoma. Patients submitted to computed tomography guided percutaneous MWA were compared with a cohort of high-risk patients submitted to lung lobectomy. Inclusion criteria used to select patients submitted to surgery were: age >70 year-old, presence of at least one of the following major co-morbidities: COPD Gold 2 or 3 (7); Severe Type II diabetes mellitus, coronary artery disease, severe vascular artery disease. The outcomes of interest in this study included overall survival and relapse (local or distant) of disease. The manuscript was written following STROBE Statement criteria (8).

Microwave ablation technique

The procedure was usually performed under Thorax CT-scan guide. Patients were positioned under CT scan in prone, supine or lateral decubitus position, depending on the side of the target lesion. Local anesthesia and deep sedation was performed, with the assistance of an anesthesiologist. Needle placement was always performed under multi-slice thorax CT guidance. It can show the exact position of the needle as well as the occurrence of pneumothorax or bleeding. This is an extremely important phase of the whole procedure, which depends on the success of the treatment. We used the Emprint™ Ablation System (Medtronic, Minneapolis, MN, USA) for the MWA procedure. Post-procedure monitoring was made by CT scan in the immediate and Chest X-Ray after 1 hour or before (depending on clinical conditions) in order to diagnose eventual lung hemorrhage or pneumothorax. Short term follow up was performed by PET/CT 3 months after MWA procedure. Long term follow up was performed by Thorax CT-scan and PET scan every 6 months. We used RECIST criteria (9) to diagnose local or distant relapse.

Lung lobectomy technique

A pulmonary lobectomy is the removal of a pulmonary lobe, after individual dissection of vein, arteries and bronchus: it is, by definition, an anatomical operation, in which the lobe-specific lymphatic drainage is removed. It is conducted under general anesthesia with a double lumen endotracheal tube, in order to obtain single lung ventilation; recently, some non-intubated thoracic surgery (NITS) procedures have been reported. The surgical approach can be by thoracotomy or by video-assisted thoracoscopic surgery (VATS):

various VATS techniques have been described, which vary in the number of ports and the position of the utility incision (10). Regardless of the type of VATS approach, the most relevant difference from the open surgery is the rib spreading, that is avoided in the VATS technique.

In case of primary lung cancer malignancies, the removal of mediastinal lymph nodes is mandatory, for ensuring a correct N staging. A systematic ipsilateral mediastinal lymphadenectomy is recommended, rather than lymph node sampling, for a more accurate and complete N staging (11).

VATS lobectomy is now considered as a valid alternative to conventional thoracotomy for early-stage primary lung cancer: postoperative pain is significantly reduced, compared to open surgery. Moreover, clinical evidence indicates that VATS lobectomy for early-stage NSCLC is associated with fewer postoperative complications and less negative biological impact than open lobectomy (14). In our Institution, since 2011 we started to treat lung cancer patients with VATS approach. Currently, about 90% of cancer operations are performed with this well defined technique, even the most complex cases. Improvements in camera systems, instruments and stapler technology have facilitated this development.

Statistical analysis

Quantitative parameters were described by median and 95% confidence interval (CI), while qualitative parameters were reported by frequency and percentage. The Kaplan-Meier test was used to describe overall survival and disease-free survival (DFS); the latter was defined as the time between the date of treatment and the date of local or distant recurrence. Overall survival parameter considered death regardless of the cause. We used Cox model to analyze the associations with overall survival and DFS, with multivariate analysis to identify the independent prognostic factors. To compare the adjusted survival for patients treated by MWA or pulmonary lobectomy we used an inverse probability of treatment weighting approach based on propensity scoring with regression adjustment for the following covariates: age, gender, ECOG score, histological finding and diameter of the nodule.

Results

In the period of study (June 2009-October 2014), 32 patients were submitted to microwave ablation (MWA group) for Stage I lung cancer. 35 high-risk patients submitted to lung lobectomy in the same period of time have been extracted from our Institutional Database, according to inclusion criteria. The location of the target lesion in MWA group was: left upper lobe (LUL) in 12 patients (37.5%), right lower lobe in 8 patients (25%), right upper lobe (RUL) in 7 patients (21.9%), left lower lobe (LLL) in 4 patients (12.5%) and right middle lobe (RML) in 1 patient (3.1%). Lobectomies performed were as follows: 13 (37.1%) RUL, 4 RLL (11.4%), 2 RML (5.7), 13 LUL (37.1) and 3 LLL (8.6%). Main demographics and clinical data are presented in Table 1. In the current observational study, patients treated with MWA were significantly older and showed worse ECOG performance status than patients who received pulmonary

Table 1. Demographics and clinical data

	MWA group (n=32)	Lobectomy group (n=35)	P value
Male, n (%)	23 (48.9)	24 (51.1)	0.769
Age, years, median, (95% CI)	77 (76.0-79.0)	74 (70.2-75.0)	0.001
Adenocarcinoma	27 (51.9)	25 (48.1)	0.207
Squamous cell carcinoma	5 (33.3)	10 (66.7)	
Tumor size, mm, mean (95% CI)	22.5 (17.0-26.0)	24 (20.0-29.0)	0.399
ECOG score	2 (from 1 to 2)	0 (from 0 to 1)	< 0.001

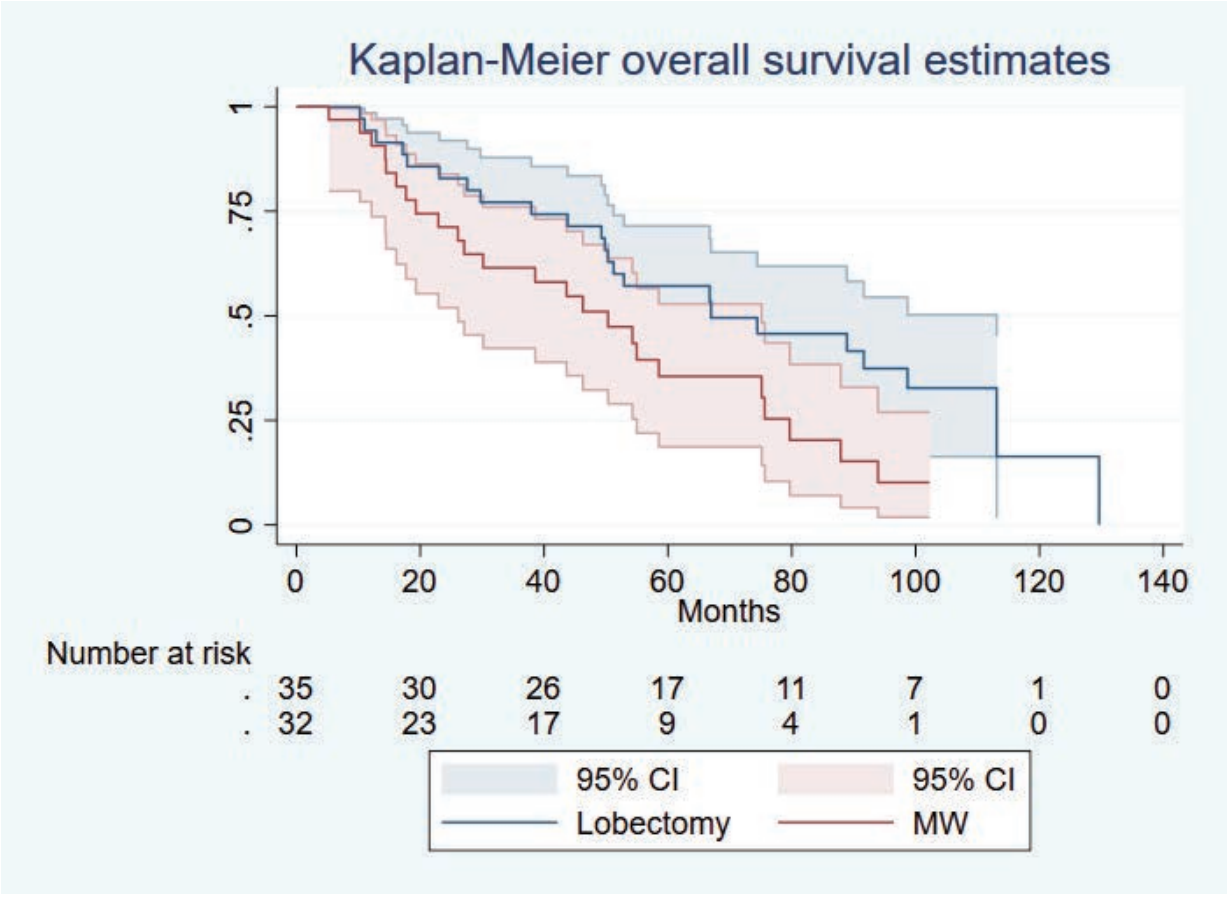

Figure 1

lobectomy. The median follow-up time was 51.1 months (95% CI from 43.8 to 62.3). The MWA group had a median survival of 43.8 months (95% CI from 26.1 to 55.0) while the Lobectomy group had 55.8 months (95% CI from 49.9 to 76.8). The unadjusted overall survival time at three years was 62.5% and 77.1% for the MWA group and Lobectomy group, respectively. Figure 1 shows the Kaplan-Meier curves of unadjusted overall survival as function of treatments (log-rang test, p = 0.041). Negative prognostic factors of overall survival by multivariate Cox proportional hazard regression models with stepwise method were MWA procedure (HR: 2.25, 95% CI from 1.20 to 4.21, p= 0.0109) and nodule diameter (HR: 1.04, 95% CI from 1.01 to 1.07; p= 0.007); conversely, age, gender, ECOG score and histological type were not significant. Using inverse probability of treatment weighting on propensity score, the average treatment effect (ATE) for MWA was estimated at 15.9 months (95% CI from -40.9 to 9.1; p= 0.214) less than pulmonary lobectomy; the latter had estimated potential outcome mean (POM) of 56.4 months (95% CI from 33.3 to 79.5; p< 0.001).

We observed 25 local relapses; twenty-two relapses were in the MWA group and three in the Lobectomy group. Figure 2 shows the Kaplan Meier curves of disease-free survival. Table 2 reports the relapses distribution and time to relapse. Stepwise Cox proportional hazard regression models for DFS (local + distant relapse) identified MWA procedure (HR: 5.2; 95% CI from 2.1 to 12.8: p < 0.001), ECOG performance status 3 (HR: 5.0; 95% CI from 1.6 to 15.6; p = 0.006) and diameter of the nodule in millimeters (HR: 1.1; 95% CI from 1.0 to

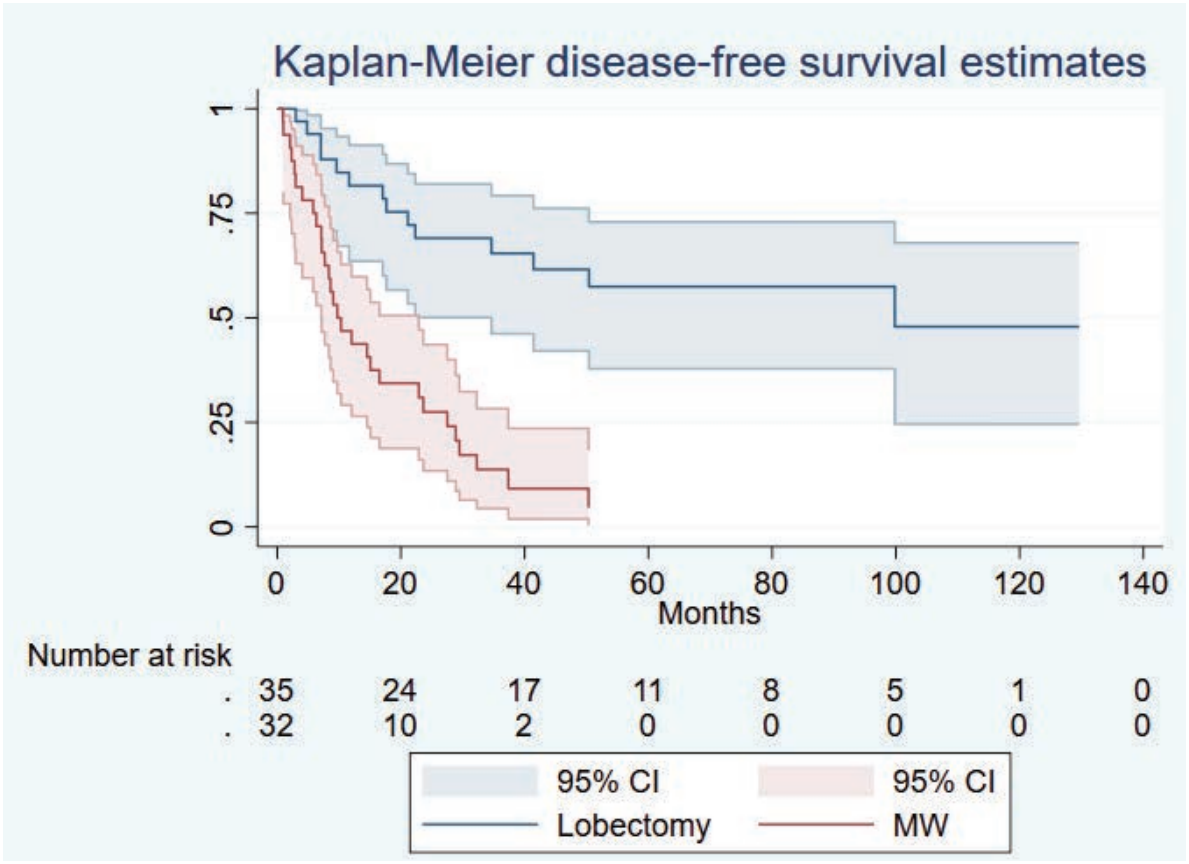

Figure 2

1.1; p = 0.003) as negative prognostic covariates. On the contrary this regression model did not include age, gender, histological type and local recurrence because considered not significant. Using inverse probability of treatment weighting on propensity score for DFS, the ATE for MWA was estimated at 32.8 months (95% CI from -46.6 to -19.3; p < 0.001) less than pulmonary lobectomy; the latter had estimated POM of 48.2 months (95% CI from 34.6 to 61.8; p< 0.001).

Table 2. Outcome variables

Outcome variable	MW group (n=32)	Lobectomy group (n=35)	P value
Overall survival, months, median (95% CI)	43.8 (26.1-55.0)	55.8 (49.9-76.8)	
3-year survival rate	62.5%	71.1%	
Local relapse, n (%)	22 (68.7%)	3 (8.6%)	<0.001
Time to local relapse, months, median (95% CI)	9 (6-16)	50.4	0.185
Distant relapse, n (%)	18 (56.2)	13 (37.1)	0.119
Time to distant relapse (95% CI), months	17.3 (7.3-28.1)	17.1 (7.1-28.1)	0.904
Recurrence (Distant + Local relapses), n (%)	28 (90.6)	14 (40.0)	<0.001
Time to recurrence, months, median (95% CI)	10.0 (7.2-17.7)	37.9 (21.4-55.3)	<0.001

Conclusions

Microwave ablation as a treatment for lung cancer has been shown to be safe in high risk patients (5). This technique has not yet been widely adopted and in stereotaxic radiation therapy continues to be used as the first choice treatment for inoperable patients in many centers.

Many studies published consider heterogeneous patients with different stages of NSCLC. Analyzing the long-term outcomes of patients treated with thermal ablation for stage I NSCLC would help physicians choose the best treatment for high risk patients. Our report compares patients submitted to computed tomography guided percutaneous MWA with a cohort of patients submitted to lung lobectomy in the same period of time, downloaded from our Institutional database. Overall survival was comparable in both groups. Zachary and colleagues reported a review of long-term results, which included 108 patients, all-cause survival at 1, 2, and 3 years was 83%, 59%, and 43%, respectively (13). Narsule et al. had performed 21 radiofrequency ablation and 4 MWA for a total of 25 ablations. Stage I disease was present in 21 patients. Mean follow-up was 42 months, median survival was 39 months, and overall survival at three years was 52% (14). Palussiere et al. examined eighty-two patients that were treated with RFA electrodes and five with MWA. Overall survival (OS) and disease-free survival (DFS) were 58,1% and 27,9%, respectively (15).

In our study, local progression occurred in twenty-two relapses in the MWA group and three in the Lobectomy group. Narsule et al. observed that local progression occurred in 10 patients (47,6%) and the median time to that was 35 months (14). Dupuy et al. published the results of the American College of Surgeons Oncology Group Z4033 (Alliance) Trial which showed similar local control rates after radiofrequency ablation of stage IA NSCLC of 68.9% at 1 year and 59.8% at 2 years (16). Palussiere et al. observed a 21,1% rate of local progression at 3 years post-ablation. In univariate analysis, increasing tumor size (P = 0.003) was the only predictive factor related to risk of local tumor progression (15). This data was confirmed by our study, which demonstrate a high percentage of local relapse in the MWA group but a comparable overall survival. Although lung lobectomy remains the gold standard treatment for stage I NSCLC, looking at our results we can consider the MWA procedure as a valid alternative local treatment in high-risk patients not suitable for surgery for stage I NSCLC. Furthermore, lung MWA treatment can be repeated overtime, in case of local relapse, in addition to conventional radiotherapy.

We highlighted the extremely similar "time to distant relapse" between MWA group and Lobectomy group in our study. On the other hand, looking at the percentage of local relapse, it is worth noticing that in the MWA group there is a sub-optimal local cancer control. Notwithstanding the weighted overall survival was not different in two groups.

Even though the lobectomy group cohort was selected according to severity criteria and major comorbidities, it resulted statistically younger and with lower ECOG score, compared to MWA group; this is to consider as an unavoidable selection bias, due to the non-randomized nature of the study. A randomized trial between MWA and surgery it is, in fact, extremely difficult and unethical.

Strengths and limitations of the study

To the authors' knowledge, this is the first report of propensity score weighted comparison between lung MWA and surgery for lung cancer with therapeutic purpose. The study has some limitations: firstly it is a retrospective study and is lacking the power of a prospective, randomized study. This is justified by the impossibility to propose an alternative local treatment in patients that are suitable for surgery, which remains the gold standard for treatment of stage I lung cancer. Another limitation is the monocentric nature of the study, that is a limit for its clinical applicability. Furthermore, the relatively small sample size does not allow to make firm conclusions.

To conclude, although lung lobectomy remains the gold standard treatment for stage I NSCLC, looking at our results we can consider the MWA procedure as a valid alternative local treatment in high-risk patients not suitable for surgery for stage I NSCLC.

Furthermore, lung MWA treatment can be repeated overtime, in case of local relapse, in addition to conventional radiotherapy.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Software-assisted US/MRI fusion-targeted biopsy for prostate cancer

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Abstract. *Background*: Prostate cancer is the first cancer diagnosis in men. European Association of Urology (EAU) Guidelines for Prostate Cancer underline the importance of screening, performed through PSA testing on all men with more than 50 years of age and before on men with risk factors. The diagnosis is still histopathologic, and it is done on the basis of the findings on biopsy samples. *Materials and Methods***:** Fusion biopsy is a relatively new technique that allows the operator to perform the biopsies in office instead of the MRI gantry, without losing the detection capability of MRI. The T2-wighted images obtained during a previous mpMRI are merged with the real-time ones of the TRUS. *Results***:** Fusion biopsy in comparison with the systematic standard biopsy has a better detection rate of clinically significant cancers and of any cancers. *Conclusion***:** EAU 2020 guidelines still do offer a list of indications of when the biopsy should be performed, but it still appeared to be overperformed. The aim of our study is to underline how, in accordance with the recent literature result, fusion biopsy has showed a better detection rate of any cancer and clinically significant disease with a reduced numbers of samplings, and no substantial difference between the multiple software. (www.actabiomedica.it)

Key words: Prostate biopsy, Prostate cancer, Fusion Biopsy, TRUS

Background

Prostate cancer is the first cancer diagnosis in men representing the 20% of all cancer diagnosis in men in the 2019 in the United States of America, and is the second death cause for cancer in men representing the 20% of all the deaths for cancer in the United States of America in 2019 (1).

Thanks to the improvement in the diagnosis and to the screening campaigns, is it possible now to ensure a prompt diagnosis to ensure the most adequate and timely treatment for the patient.

Clinical suspect of prostate cancer normally comes from a positive family anamnesis for prostatic cancer, suspicious findings during a digital rectal exploration (DRE) and from an increment of the value of prostate specific antigen (PSA). The recent introduction of the multiparametric (mpMRI) permits a non-invasive evaluation of prostatic lesions.

The diagnosis is still histopathologic, and it is done on the basis of the findings on biopsy samples, specimen from transurethral resection of prostate (TURP) and on prostates obtained after radical prostatectomy.

Prostate biopsy has changed over time and can be targeted and non-targeted and can be performed with an Ultra Sound (US) guidance, a Magnetic Resonance Imaging (MRI) guidance (MRI-Guided In-Bore Biopsy) or through a fusion of the previous techniques that can be cognitive or provided by a software.

As recommended in the EAU 2020 guidelines prostate lesions samples should be evaluated through a score system, the International Society of Urological Pathology (ISUP) 2014 system, in order to estimate the cancer aggressiveness (2,3).

Materials and Methods

Screening

In accordance with the latest version of the EAU Guidelines for Prostate Cancer PSA testing should be used to screen all men with more than 50 years of age, men with more than 45 years of age and a positive family history of prostate cancer or an African descent and men with more than 40 years of age if carrying BRCA2 mutations. PSA testing should be done after a detailed counselling of the beneficial effects and potential risks (4).

The EAU guidelines 2020 underlines also the absence of a PSA threshold so it recommends, in order to minimize the number of prostate biopsies, that are still overperformed, to calculate the risk and to perform imaging investigations in those patients with a PSA level between 2-10 mg/ml and a negative DRE (2,5,6).

It also specifies that mpMRI should not be used as a screening tool, instead the usage of the mpMRI imaging is strongly recommended prebiopsy in the naïve patients and in patients with a prior negative prostate biopsy. MpMRI should be performed and interpreted in accordance with PI-RADS guidelines (7,8).

Prostate biopsy

The biopsy could be targeted and non-targeted, the targeted ones require a previous imaging to identify the location of the lesion.

The traditional approach of prostate biopsies is the systematic non-targeted TRUS. The technique consists in collecting bilateral systematic samplings from apex to base of the prostatic gland, the cores collected varies according to the volume of the prostate, going from 8 cores in 30 ml prostates to 10-12 in larger glands. The great limitation of this technique is represented by the lack of sampling of the central zone and by the risk of non-recognition of a prostatic neoplasia, because the samplings normally are collected form the peripheral zone of the gland (4,9,10).

US guided biopsies can be performed with both a trans rectal (TR) and a trans perineal (TP) approach. Recent studies have demonstrated a substantial equality between the two techniques, except for the sepsis risk that appears to be reduced in the TP approach meanwhile the pain is minor in the TR approach (2).

One of the advantages of the US guided biopsies is to be performed in office. TRUS still lacks on the evaluation of apical and anterior lesions, the limitation of the US technique is the worse definition in the localization of the lesion.

Due to the better detection of MRI in localizing the lesions, MRI can be used as guidance in the prostate biopsy, of course, the limitation of the technique is represented by the costs and by the necessity of performing the biopsy in outside the office ambient, in the RMI gantry (11,12).

Another way of performing the biopsy is represented by the cognitive biopsy, in this approach the operator in accordance with the findings of the mpMRI locates the lesion and performs a targeted biopsy, the great limitation of this technique is clearly the operator-dependency.

In this context fusion biopsy is a relatively new method, that allows to synthetize the capability of mpMRI in detecting the lesion with the real-time approach of US techniques.

Fusion biopsy is a technique that allows the operator to perform the biopsies in office instead of the MRI gantry, without losing the detection capability of MRI. This might represent an important tool in high-flow centers with short availability of time and no dedicated MRI for biopsy procedures. The T2-wighted images obtained during a previous mpMRI are merged with the real-time ones of the TRUS.

The biopsy is performed with US guidance and the approach can be both Trans-Rectal and Trans-Perineal, in accordance with the capability of synthesis

of the used system (13). The US approach permits to have a real time visualization and once the lesion is located via US the software merges the US images with the mpMRI ones (8,11).

Fusion technique

In order to correctly assess the characteristics of prostate lesions, mpMRI should be performed through multiple sequences, including anatomic sequences, like a multiplane T2 and at least two functional sequences, normally a diffusion weighted imaging (DWI) and a dynamic contrast enhancement (DCE) (14).

There is many different software to perform the fusion biopsy, they vary in the tracking mechanism, in the biopsy route and in the imaging fusion technique.

Although they present differences, all the available platforms follow the same steps. The first step consists in performing a mpMRI and locating the target lesion. Once the suspicious lesions are assessed, the target lesion and the prostate undergo a process of segmentation on mpMRI and the data are uploaded in the US system.

The image registration is performed, the method might require a delimitation of the prostate boundaries or the identification of landmarks, in order to overcame the deformation of the prostate on the US. Subsequently the prostate undergo a US segmentation thought the acquisition via a sweep of the US probe of bidimensional (2D) images and the three-dimensional (3D) US volume is obtained.

Once the prostate evaluation via US is done, the data acquired by US and mpMRI are fused together.

The fusion process has the aim of aligned images obtained by US and mpMRI. This procedure differs between the several fusion systems and require the identification of the boundaries and the region of interest (ROI) on both the US and the mpMRI images and the eventual transformation of the latter images. The transformation process can be rigid or elastic.

In the rigid registration the images cannot be deformed, they can be translated and rotated. This system allows a preservation of the anatomy of the prostate and lesion's location.

In the elastic registration the images can be translated and rotated and in addition the operator can alter the image scale deform it, in order to match perfectly the US images and the mpMRI ones. This second form of registration might alter the anatomy of the gland.

To optimize the location of the targeted lesion the majority of software are now equipped with both registrations to allow the operator to obtain a more accurate fusion of the US and mpMRI images and location of the targeted lesion.

The presentation of the fused images varies according to the system used, images can be showed side-by-side or superimposed.

Before performing the biopsy, the ROI should be localized on the real-time US images, the software through a process of mapping, tracking and navigation allows the operator to optimize the visualization of the ROI. Mapping consist in assess and register the likely location of the biopsy cores on the mpMRI images, while navigation is the acquisition of real-time images to improve the targeting of the lesion. Tracking eventually represents the ability of visualizing the US probe and the needle in a 3D volume during the procedure. This process optimizes the spatial definition of the ROI, ensuring a better targeted biopsy. Tracking differs between the various software, it can be generated by an electromagnetic field, as in the Electromagnetic Tracking, by angle sensor as in the Smart Robotic Arms Tracking or by the US acquisition as in the Image-Base Software Tracking (11,15,16).

Fusion Software

Artemis (Eigen, Grass Valley, CA) is a platform that uses a mechanical tracking system. The workflow follows the steps previously reported, a pre-biopsy mpMRI, targeting of the prostatic lesion, segmentation of the gland, registration of the images, mapping, navigation and tracking of the lesion. The peculiarity of Artemis is represented by the tracking system that is performed thought angle sensing encoded joints located on a mechanical robotic arm positioned on the operating table, which held the US probe. The probe can be rotated with only 2 degrees of freedom. The fixed robotic arm corrects the human error and arise the accuracy in targeting the lesion. The fusion process is semiautomatic and merges the mpMRI data with the US ones, creating a 3D model. The platform allows

to collect cores with an interval of 3 mm, to increase the accuracy of the procedure.

The Artemis offers the operator the possibility of registering and tracking the biopsy's site, permitting the operator to re-perform the biopsy in the same site. The fixed arm permits to correct the errors related with the unsteadiness of the human and.

BiopSee platform (Pi Medical, Greece), as Artemis, used a mechanical tracking system, operating through mechanical fixation device with two built-in tracking encores, located over the operating table. As in the Artemis platform the TRUS in placed in the fixation device and can me moved only by rotation with 2 degrees of freedom. The peculiarity of BiopSee is to use only the TP approach.

The software design is modular with each procedure step mapped in a separate software module. The workflow of the process is the same as the one preformed in Artemis. Biopsee only allows a rigid registration system.

Virtual Navigator (Esaote, Genoa, Italy) works following the same fusion steps as all other platforms described. Its application has involved majorly other interventional procedures. The platform offers a rigid registration and the mpMRI images are overlaid on the US ones.

The **UroNav** platform (Invivo/Philips, USA): developed by the National Institutes of Health (NIH).

The process requires a pre-biopsy mpMRI. The radiologists locate the lesion and proceed to the segmentation of the prostate and the targeted lesion, those data and information are sent to the UroNaV software. The platform works through an electromagnetic tracking, so the field generator is placed to the operating table and positioned on the pelvis of the patient, who is laid on the operating table. This form of tracking gives the operator the possibility to manipulate the US probe with multiple degrees of freedom. In addition, the UroNav system offers both rigid and elastic registrations in order to allow a better alignment of the US and MRI images. The fused images are presented both side-by-side and overlaid. To reach the ROI the operator uses a freehand US probe, permitting the evaluation of multiple different approach and visualization angles. As reported in literature the UroNav system has a high level of accuracy and with a reported margin of error in registration and tracking of 2-3 mm.49 The latest versions of UroNav system offers both TR and TP approaches. The limitation of the platform is represented by the unsteadiness of free-hand approach. UroNav like Artemis has the possibility of register the site of the biopsy, in order to allow the operator to eventually re-biopsy in the same zone (Fig. 1).

Urostation (Koelis, France) is an Image-based tracking Platform. The workflow is the same as the other systems. Urostation differs from the other platforms by the absence of an external tracking hardware, due to the technology that allows to perform the tracking only on the base of the 3D TRUS image.

A panoramic 3D reference volume image of the prostate is constructed after the acquisition of three 3D TRUS images from different views. A manual segmentation of the mpMRI is performed on the 3D reference volume, the images are registered to reduce the errors related to the US probe deformation. During the procedure the operator uses both 2D real-time TRUS images and 3D TRUS images, the first ones are used as a guide to locate, once the targeted lesion is located the 3D TRUS is used to acquire positional information. Eventually the biopsy needle is positioned and a 3D TRUS image is acquired retrospectively to locate the biopsy site.

Complications

The most frequent complication following the TRUS is represented by haematospermia, other complications related with the procedure are hematuria, rectal bleeding, urinary tract infections, fever and urinary retention. A major complication is sepsis, it could represent a life-threatening condition that requires hospitalization, due to the presence of a rectal bacterial flora. Recent studies have demonstrated a substantial equality between the two techniques, except for the sepsis risk that appears to be reduced in the TP approach meanwhile the pain is minor in the TR approach. TP approach appeared to be associated with a reduced risk of injury to the Santorini plexus, related with biopsy of the anterior area of the prostate (17-20).

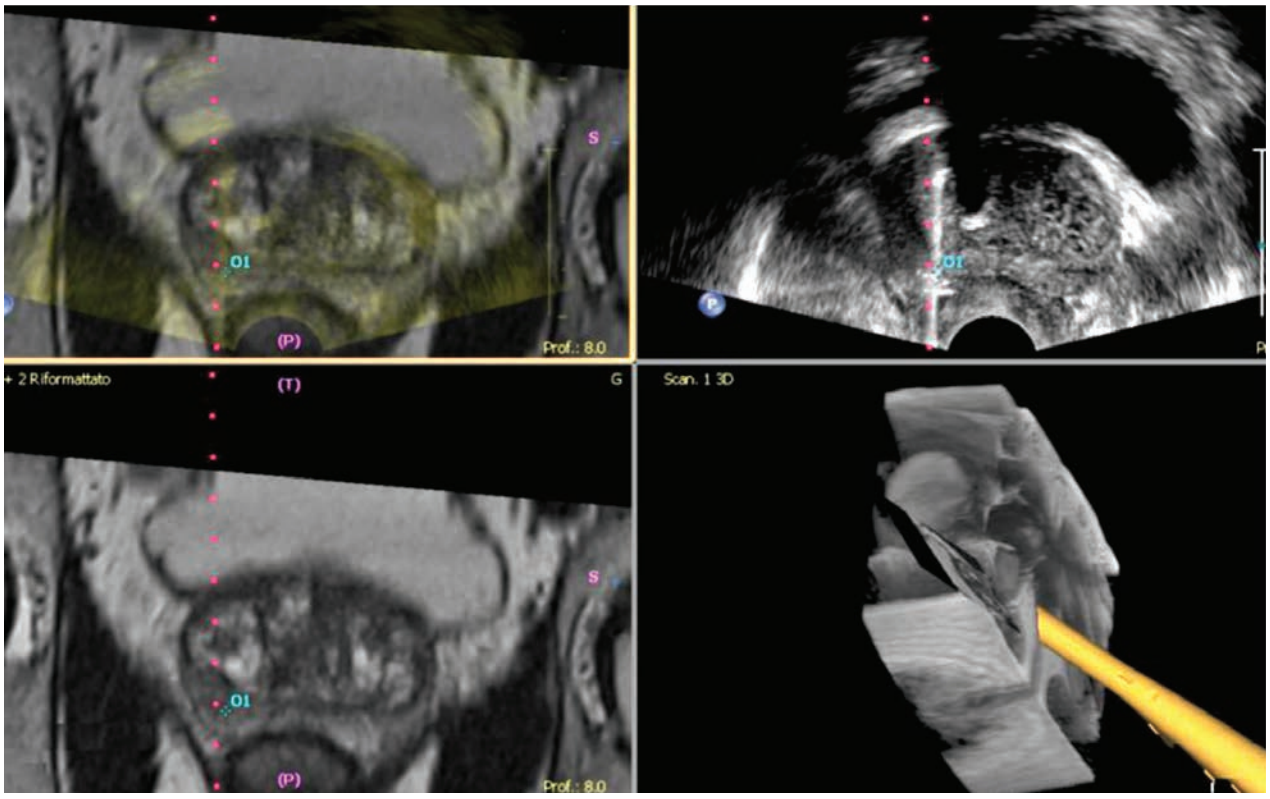

Figure 1. A 70-year-old man with a PSA value of 4.5 ng/mL. MpMRI was performed, showing a right peripheral lesion located in the intermediate zone evaluated in accordance with the PI-RADS v2.1 guidelines as PI-RADS 3. Images of the fusion biopsy performed with the UroNav platform (Invivo/Philips, USA) with a TR approach. MpMRI images overlaid on the TRUS images. [A] Real-time TRUS images showing the needle (16G) in the targeted lesion. [B] T2-weighted axial view MpMRI images showing a hypointense area in the right peripheral zone (01).[C] 3D reconstruction of the fused images showing the position of the rectal probe during the procedure. [D] Targeted biopsy demonstrated a 4+4 Gleason score cancer.

Results

As Valerio et al outlined in their review made in the 2015 fusion biopsy in comparison with the systematic standard biopsy has a better detection rate of clinically significant cancers and of any cancers. The results presented showed a median detection of clinically significant disease of 23.6% (range: 4.8–52%) for standard systematic biopsy versus the 33.3% (range: 13.2–50%) median detection rate of the fusion targeted biopsy. Thee review also underlined the substantial equality of the outcomes of the different software used in the different studies. The clinically significant disease was indicated as the presence of a Gleason pattern ≥ 4 in the biopsy samples (21). Standard systematic biopsy showed a median detection rate of in identifying the presence of any cancer 43.4% (range: 14.3–59%) while fusion biopsy had a median rate of 50.5% (range: 23.7–82.1%) (22). As Martorana et al underlined in their revision in 2010 the TP approach allows a major accuracy in sampling the anterior part of the gland, which is poorly sampled in the traditional TR approach, resulting in a greater detection rate of clinically relevant cancers located in the anterior area of the gland. No significant difference was found between the TR and the TP approaches in targeting the lesion located in the other portions of the prostate (19). The infectious complications related to the procedure appeared to be reduced in the TP as for the risk of injury to the Santorini plexus, associated with biopsy of the anterior area of the prostate. The main disadvantage of the TP approach is represented by a higher pain for the patient that might require a sedation(19,23).

As demonstrated by Wegelin et al in the review of the 2017, fusion target biopsy and in-bore MRI target biopsy have similar results in detecting both clinically significant diseases and any cancers (24).

In addition, as reported by Kayano et al in their retrospective study of the 2019 fusion target biopsy appeared to be associated with a lower rate of Gleason upgrading if compared to the standard TRUS biopsy, demonstrating the possibility of improving prostate cancer characterization at biopsy (25).

Conclusion

The EAU 2020 guidelines still do offer a list of indications of when the biopsy should be performed, but it still appeared to be overperformed (2). The literature results have showed better outcomes in detection rate of any cancer and clinically significant disease of the fusion biopsy in comparison with the standard systematic biopsy. Those results are obtained with a reduced numbers of samplings (22). Moreover, the studies have showed no substantial difference between the multiple software. Our aim is to underline the benefits of the fusion biopsy as the better detection rate of clinically significant disease compared with the standard systematic US guided biopsy associated with the possibility of performing the procedure in-office. Of course, this procedure in not free of limitations, the main one is the high cost of the fusion software. TRUS is still the more performed approach, in particular among the fusion biopsies, the TP approach is offered only by few software even though the benefits of this technique, in reducing the infectious complications and the hospitalization have been outlined in recent literature (19).

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent to the CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Efficacy, safety and usability of bronchial artery embolization using a new anti-reflux microcatheter in the management of haemoptysis

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Summary. *Purpose:* Haemoptysis (Hp) is a potentially life-threatening medical condition. We investigated the safety, efficacy and usability of bronchial artery embolization using a new anti-reflux microcatheter in patients with haemoptysis. *Materials and methods:* The study was held as a single-center retrospective study. Four patients underwent bronchial arterial embolization, using the new microcatheter. Then, we evalueted technical success, immediate clinical success, haemoptysis recurrance rate and safety in reducing reflux complications. *Conclusion* Bronchial artery embolization for hemoptysis with the new microcatheter is a safe and effective method with high technical and clinical success rates. Short and medium-term results are excellent. (www.actabiomedica.it).

Keywords: radiology, embolization, bleeding, microcatheter, intervantional radiology, bronchial arteries

Introduction

Haemoptysis (Hp) is a potentially life-threatening medical condition (1–3).

Its aetiology and epidemiology vary a lot among studies according to geographic locations, time of publication and epidemiological design (1,2,4-8). The most common causes of life-threatening Hp include bronchiectasis from infectious and non-infectious aetiologies, bronchogenic carcinoma, and various lung infections such as tuberculosis (TB), depending on geographical location (1,9-14).

In Italy, malignancies and bronchiectasis were most common causes of moderate (20–500 mL in 24 h) and severe (> 500 mL in 24 h) Hp (3); there are also other aetiologies described in the literature include mycetomas, necrotizing pneumonia, and cryptogenic Hp (1,9-14).

No consensus has been determined about Hp severity throughout the literature; however, more and more agree to divide Hp into two categories: massive and non-massive, rather than "mild, moderate and severe". There is no precise cut-off in relation to which it is decided whether to subject a patient to embolization.

It is estimated that 5–14% of patients presenting with Hp will have life-threatening Hp (1,15,16). Life-threatening Hp, also called massive Hp, has been variably defined based upon criteria such as the volume per hour of bleeding, the total volume of bleeding

per 24h, or the presence of abnormal gas exchange or hemodynamic instability (1,9,15). Hp fatality is much more frequently associated with asphyxiation rather than exsanguination.

Although over 90% of Hp are self-limiting (17), both diagnosis and treatment of massive Hp are challenging (18).

The optimal diagnostic approach to Hp has not been determined. The most frequently used modalities for studying Hp include chest radiography (CXR), bronchoscopy (FOB) and multidetector computed tomography (MDCT) angiography, useful to determine the bleeding site and they can be used alone or in combination.

In the absence of guidelines on the treatment of Hp, there are essentially four treatment options for haemoptysis with respiratory and haemodynamic supports: drug therapy, catheter intervention, such as bronchial artery embolization (BAE), bronchoscopic intervention and surgery (lung resection) (19-24).

Mild or moderate Hp can often be managed by conservative treatment of the underlying pathology.

On the other hand, there are several modalities to treat life-threatening Hp, but there are no existing guidelines on how to best manage it.

Following initial stabilization and localization of the bleeding site, bronchial artery embolization (BAE) via the transfemoral approach has become the first-line therapy for treating massive and recurrent Hp (22,25-27,28).

BAE, which controls the bleeding by angiography-guided injection of embolic substance into pathologic bronchial arteries, has largely replaced emergent surgery for the management of life-threatening Hp, due to the availability of safe and effective endovascular embolization techniques (29).

Sopko et al. described that a surgical lung resection has a 40% of mortality when executed in emergency, instead of 18% of mortality when an election procedure is performed. Therefore, there are vary indications to surgical intervention in patients with massive Hp, such as technical failure of BAE or recurrent Hp despite multiple BAE intervention. (30)

Microcatheters are commonly used during several arterial embolization procedures. SeQure® is a new microcatheter for peripheral embolization procedures, which is a reflux-control microcatheter that uses flow dynamics to create a fluid barrier designed to deliver more treatment to the target vessel and reduce the risk of non-target embolization for less potential damage to surrounding tissue. The device has side slits through which contrast media can't exit, putting up a barrier that prevents embolic agents from going where they shouldn't. It means that SeQure® microcatheter helps interventional radiologists to deliver a high quality of care during image-guided BAEs.

Non-target embolization is a complication of embolization procedures, which can also be very serious, arising upon unintentional reflux of embolic beads to adjacent vessels, above all after occlusion of the target vessel. In particular one of the worst complications of BAE is the inadvertent embolization of anterior spinal arteries, with possible severe neurological consequent (e.g. paraplegia).

The aim of our study was to evaluate the effectiveness, the safety and the short and medium-term results of BAE performed using the new SeQure® microcatheter (Guerbet, France).

Material and methods

Patients

The study was held as a single-center retrospective study. Written informed consent was taken from all patients before the procedure, and the local ethical committee approved the study.

This case series includes 4 patients who underwent BAE using SeQure® microcatheter (Guerbet, France) for Hp. From March 2019 to February 2020, a total of 4 patients (3 men and 1 woman) with a mean age of 38 years were treated.

All patients had massive Hp with a bleeding of 100- 500 ml in the 24h (9) causing desaturation, so an interventional radiology (IR) procedure was indicated.

The patients' characteristics are shown in Table 1.

Imaging

All patients were evaluated with a MDCT angiography before the procedure (Fig. 1)

Table 1. The patients' characteristics

Patients	Age	Sex	Cause	Grade	Pre-procedure Diagnostic Workup (CTA/FOB)	Time since embolization (months)
1	40	M	Bronchiectasis (Kartagener Syndrome)	Massive	CTA	3
2	30	M	Bronchiectasis	Massive	CTA	4
3	37	F	Bronchiectasis	Massive	CTA	5
4	46	M	Bronchiectasis	Massive	CTA	6

CTA=Computed-Tomography Angiography

MDCT angiography was carried out to:

- Localize the site of the bleeding and establish if there was a mono or bilateral bleeding
- Find the origin of the bronchial artery "incriminated" and measure its calibre
- Establish if there was an "active bleeding"
- Decide the type of the treatment and the choice of the catheter.

After that, we performed the procedure using a SeQure® microcatheter, that let us perform a superselective and target embolization.

Technique

After local anaesthesia (lidocaine 2%), a 5French sheath is inserted into the right common femoral artery. Using a 5F diagnostic catheter (Cobra or Simmons) on a Terumo (0.035 inch) guidewire, catheterization of the bronchial artery is performed. Once catheterized the right artery, angiography is performed in PA and oblique projections (Fig. 2). That is to study the pathological vessels, collateral arteries (intercostal a., costo-cervical a.) and the potential presence of AV

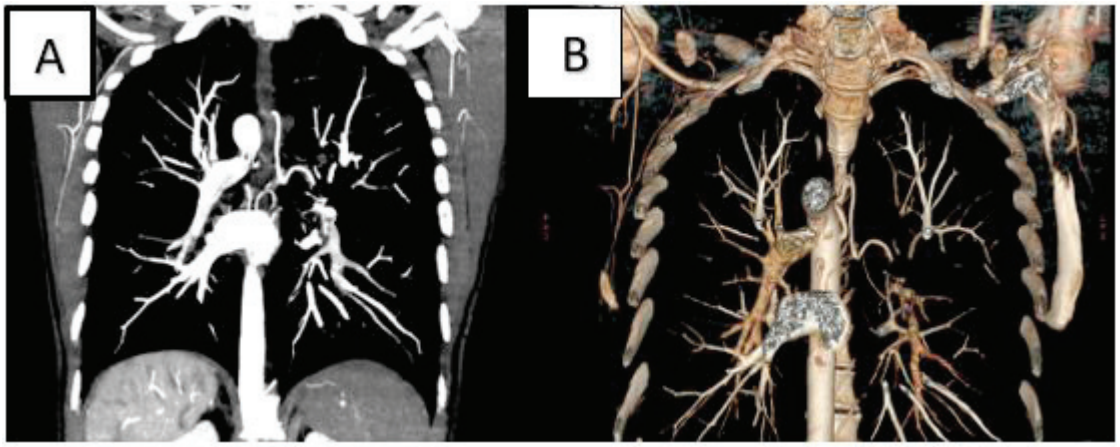

Figure 1. A) coronal section of a MDCT angiography. B) 3D reconstruction of a MDCT angiography.

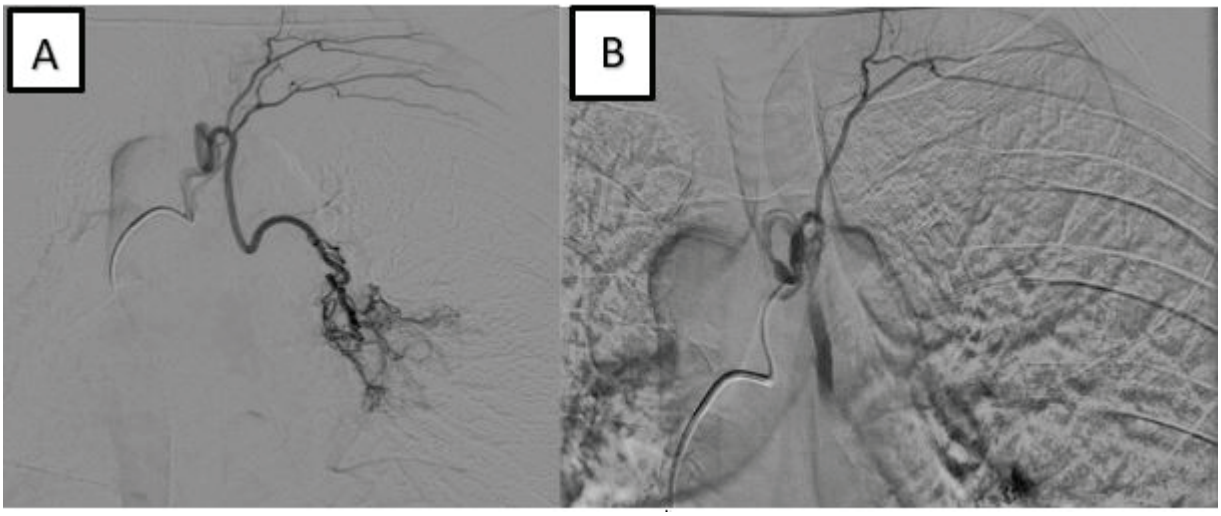

Figure 2. A) PA projection of an intraprocedural angiography. B) oblique projection of the angiography.

fistula or malformation. Moreover, it is important to exclude the presence of anteriors spinal arteries performing a lateral projection too.

In fact, the accidental embolization of this artery can lead to paraplegia which is one of the worst complications related to this intervention.

Once studied the angiographies, the 2.8Fr SeQure® microcatheter is advanced on a 0.016 guidewire into the bronchial artery, beyond the collateral arteries to avoid non-target embolization (eg costal arteries). Another angiography is performed from the microcatheter to better study the vessel. Then the embolization is performed using microparticles Embozene (Boston Scientific Corporation) 500 or 700 micrometers, prepared with contrast media and saline solution (1:1). The injection is performed slowly. Only the contrast media exits from the lateral holes at the tip of the SeQure®, creating a turbulence that avoids reflux and non-target embolization. The injection is performed avoiding reflux of contrast beyond the proximal marker of the SeQure®, preventing non-target embolization. Injection is stopped when the blood flow in the vessel is nearly to stop.

Final angiography demonstrates good result of the embolization.

Outcomes

After performing the BAE, for each patient we evaluated the parameters below:

- Technical success (TS): was defined as the possibility to arise the bleeding vessel and carry out a target embolization.
- Immediate clinical success (ICS): was defined as the cessation of bleeding within 24 h of BAE or within the same admission.
- Hp recurrence rate (HRR): was defined as a significant Hp occurring after discharge, requiring either hospital admission, medical management, or repeat intervention of BAE in the time of two month.
- Safety in reducing reflux complications

All complications were recorded and classified as minor and major; they were assessed according to SIR Criteria (31).

Results

Patient's results are showed in Table 2.

Table 2. Patient's results

Patients	Age	Sex	TS	ICS	RR	Major complication
1	40	M	Yes	Yes	No	0
2	30	M	Yes	Yes	No	0
3	37	F	Yes	Yes	No	0
4	46	M	Yes	Yes	No	0

In this study, 4 consecutive patients who underwent BAE were retrospectively analysed. The median patient age was 38 years and 75% were men.

All BAEs were carried out with SeQure® microcatheter using transfemoral access.

Technical success (TS) rate was 100% since every embolization was carried out targetly and a super selective injection of embolization material was performed. The immediate clinical success (ICS) rate of preventing massive Hp was 100%. There was no procedure-related mortality or morbidities. No major complication occurred during or after the procedure. Minor complications such as chest pain were observed in 1 patient (25%).

These patients showed good response after embolization with SeQure® microcatheter: recurrent Hp rate was observed in none of four patients (0%) within 2 months, and no repeat BAE is required.

In none patients (0%) a reflux complication was observed.

All the underlying pathologies for recurrent Hp were bronchiectasis (100%), in a case related to Kartagener Syndrome.

Discussion

The results of this study demonstrated that BAE with SeQure® microcatheter is a safe, effective treatment method for massive Hp with excellent short and medium-term outcomes. Hp is a potentially life-threatening occurrence, which requires prompt intervention.

Earlier, before the advent of BAE, the best method of controlling bleeding was surgery. It required patients many preparations such as chest CT, pulmonary function, even bronchoscopy to evaluate the patient's physical condition and determine the range of surgery; however, some preparations were impossible for the patients in emergency conditions (32).

BAE is a well-established procedure used to control Hp since it first performed in 1974 (33-35). Nowadays this procedure is widely used as a first-line management of Hp, because non-operable patients could be treated and other patients could be stabilized prior to surgery (36).

The use of certain complementary examinations is indispensable in patients with Hp.

The diagnostic workup for massive Hp should be undertaken as soon as possible and after the patient has been stabilized. Sometimes, the association of FOB and MDCT angiography, may be more effective than either alone.

However, the role of FOB is currently highly debated, in particular since the continuous evolution of CT. Several studies have compared MDCT with FOB (36-39). Revel and colleagues reported the comparison between MDCT and FOB in determining the site and the cause of life-threatening Hp. MDCT may be comparable to FOB for identifying the site of bleeding (70%

vs. 73% respectively), however MDCT has been found to be more efficient than FOB in identifying the cause of bleeding (77% vs. 8%, respectively, P<0.001) (37).

The MDCT angiography not only allows the study of pulmonary vascularization, but, at the same time, it allows an exhaustive study of the mediastinum and the parenchyma during the same acquisition (40). The MDCT identifies all of the catheterizable bronchial arteries in angiography, that are the source of the bleeding; as well as detects pulmonary arterial anomalies, avoiding useless bronchial angiographies and correctly indicating the therapeutic attitude (41,42).

Evertheless, the MDCT does not identify certain collateral bronchial arteries, in particular the anterior median spinal artery. Only the anterior lumbar spinal artery can be detected at this time (42).

While MDCT appears to have the highest diagnostic yield for life-threatening Hp, FOB remains invaluable for patients needing airway control.

A small parenthesis concerns Chest X-Ray (CXR), the latter represents one of the imaging modalities pertinent to the evaluation of massive Hp. Depending on the hospital, CXR could be still considered the initial imaging modality for evaluating a patient with Hp. It can assist in lateralizing bleeding and reveal a focal or diffuse lung involvement. Nevertheless, the sensitivity of CXR in this context is not high; CXR identified the bleeding site in 46% of cases, and the underlying bleeding cause in 35% (37).

In our series, all the patients underwent preprocedural MDCT, which localized the likely site of bleeding, so FOB was not performed. After performing MDCT, our patients were ready to begin the procedure. BAE should be performed as soon as possible after contrast-enhanced MDCT (and/or bronchoscopy).

The goal of BAE is reduction of the systemic arterial perfusion pressure in the bronchial arteries of the affected area in order to stop bleeding (43).

There are no absolute contraindications to BAE for the treatment of massive Hp. Coagulopathy, contrast allergy and renal failure are only relative contraindications.

A variety of agents have been used for bronchial artery embolization. We performed 4 procedures of BAE using the relatively new SeQure® microcatheter.

BAE must be carried out by an experienced interventional radiologist. The diameter of the bronchial arteries increases to several millimeters in patients with chronic inflammatory lung disease, especially cystic fibrosis (44).

Active bleeding is demonstrated in only 3.6 to 10.8% of cases (45,46).

Bronchial artery diameter >2 mm, tortuosity of the bronchial arteries, shunts, aneurysms, extravasation of contrast medium, and hypervascularized zones of lung parenchyma represent some features of pathological bronchial arteries that could be source of bleeding (27, 45, 47). Pathological artery identification is typically followed by embolization with the material of choice, how it happens in all IR procedures.

The choice of the embolization material is important to the success of the intervention and is dependent upon the size and site of the bleeding vessel, the ease of access and deployment of the occlusive material to the vessel, the size of the catheter being used, the durability of occlusion as well as the tendency for recanalization (30, 48, 49).

Before the beginning of the procedure, we need to evaluate the existence of branches supplying the spine or the existence of shunts between the bronchial arteries and the pulmonary arteries or pulmonary veins in order, to avoid a systemic embolism.

According to this, our results are very confident compared to literature which report an ICS of 70-99% (50).

The results of this study demonstrated that BAE performed using SeQure® microcatheter is a safe, effective treatment method for moderate or massive Hp with excellent short and medium-term outcomes.

In our study bronchial arteriography and embolization were well-tolerated by all patients.

We obtained a 100% of TS, carrying out 4/4 interventional procedures.

Of the 4 cases, an immediate control of bleeding was achieved with embolization in all patients (100%), with a full ICS. The procedural efficacy in controlling Hp was comparable to other studies.

Our short-term success rates evaluated through HRR was comparable to other studies, since HRR was 0%.

The study showed the procedure to be very safe.

In summary, Hp represents a significant clinical entity with high morbidity and potential mortality. Medical management (in terms of resuscitation and bronchoscopic interventions) and surgery have severe limitations in these patient populations. BAE procedures represent the first-line treatment for Hp arising from bronchial arterial source.

The most frequent side effects of BAE are transient chest pain (24 to 91%) and dysphagia (0.7 to 18.2%) (46). Nevertheless, one of the most severe complications is transverse myelitis. Unintended spinal cord ischemia, due to the embolization of spinal arteries (1.4 to 6.5%) (10, 46), leads to transient or persistent paraparesis or paraplegia (50). The spinal artery originates from a bronchial artery in 5% of patients. During the procedure of BAE, when spinal artery is founding, it's usually advised to use super-selective BAE to prevent the complication.

Another quite common complication is the reflux of embolic material into the artery. In this study, this type of complication has proved in some way to be avoidable thanks the use of SeQure® microcatheter.

The SeQure® microcatheter reduced the risk of non-target embolization to help maximize selective embolization, and above all, it seems to reduce significantly the reflux of embolic material. This microcatheter has a novel distal tip filter with side slits, allowing outflow of the embolic material, without passage of embolization beads. These features reduce non-target embolization and also reduce the risk of beads reflux at higher injection rates, enabling the injection of more embolic material until full stasis is achieved.

Our study has important practical implications. SeQure® microcatheter could represent a viable alternative to usually used microcatheter. It could reduce the risk of non-target embolization and it flow rate at reflux and bead accumulation in a flow model, compared to a standard microcatheter. All these features allow to reduce the risk of complication such as spinal cord ischemia or other unintended artery embolization.

The limitations of this study were its small patient population, availability of only short-term follow-up, its retrospective and observational nature, and it's conducted at single site.

A larger patient sample should be considered to ascertain a better efficacy and safety of this microcatheter.

A more prolonged follow-up may also establish long term prognosis in these patients.

Conclusion

This study demonstrates the safety and short/medium-term efficacy of BAE using SeQure® microcatheter. SeQure® ensured safe target-vessel embolization: it can reduce the risks of bleads reflux and, accordingly, the risk of non-target embolization events. BAE using SeQure® microcatheter can be a valuable therapeutic option for treating patients with haemoptysis.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent to the CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Flow diverting devices in acute ruptured blood blister aneurysms: a three centric retrospective study

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Summary. *Background*: Blood blister aneurysms (BBAs) are a rare tiny subset of intracranial aneurysms, located at the nonbranching site of an artery, representing a therapeutic challenge from both surgical and endovascular approach. Flow-diverting efficacy, by preserving flow through the parent artery, was approved for its use in unruptured cerebral aneurysms, but no consensus was reached on its use for BBAs ruptured in the acute setting. We report a multicenter experience of use of flow diversion in acute setting of ruptured BBA, to analyze the safety and efficacy of these devices. *Methods*: We performed a retrospective study of 6 consecutive intracranial BBAs treated with flow diverter devices (FDD) between 2018 and 2020 at 3 italian institutions. Materials, therapy used, complications, clinical and radiographic outcomes were reviewed. *Results*: We used different FDD, in all cases immediate change in contrast opacification at the end of the procedure was reported. Intraprocedural IIb/IIIa inhibitor agent was the major antiplatelet protocol administered. Any complications occurred. All patients showed complete BBA obliteration at 3 months follow-up. 5/6 patients achieved good clinical outcome (0–2 mRS) at 3 months, all of which were presented with low grade SAH (Hunt Hess I–III) and a lower Fisher grade. *Conclusion*: Our data support this endovascular technique as a safe and effective therapeutic modality for this pathology in the acute setting. (www.actabiomedica.it).

Keywords: flow-diverter, SAH, blister aneurysm (BBA), endovascular treatment (EVT), double antiplatelet therapy (DAPT), IIb/IIIa inhibitors.

Background

Blood blister aneurysms (BBAs) are a rare tiny subset of intracranial aneurysms, located at non branching site of an artery usually settled in the medial wall of the supraclinoid segment of the internal carotid artery (ICA) (1,2). BBAs are life treating, they typically occurred with acute subarachnoid hemorrhage (SAH), since they are characterized by morphological instability and high tendency to grow and rupture, due to their structural frailty (3), consisting in internal elastic lamina and media focal arterial wall defect, covered by a thin layer of fibrous tissue and adventitia (4), representing a therapeutic challenge from both surgical and endovascular approach.

Endovascular treatment (EVT) has been representing a promising alternative, showing lower morbidity and mortality compared with open surgical treatment (1,5), represented by clip reconstruction with or without aneurysm wrapping, reserving arterial bypass as a last resort option in selected cases, with high mortality and morbidity rates (6). In particular

flow-diverting efficacy, by preserving flow through the parent artery, was approved for its use in unruptured BBAs, however no consensus was reached for its use in the acute setting (7,8).

We report a italian multicenter experience of use of flow diversion in acute setting of ruptured BBA, to analyze the safety and efficacy of these devices.

Methods

From January 2018 to January 2020, 8 consecutive cases of ruptured BBA, treated with flow-diverter device, in the acute setting of subarachnoid hemorrhage, by three Neurointerventional Center were reviewed. Since data were retrospective reviewed, some follow-up data were missing, whereby only 6 cases were included in our three centric retrospective study. The study was approved by the institutional review board at each participating institution. Informed consent was obtained from the patient or legal representative for the EVT of BBA with use of the FDD.

The diagnosis of BBA was made by the treating physician at each contributing center based on clinical presentation and neuroradiological findings. Treatment of BBA was based on each operator preference, including timing of the procedure, vascular access, choice and number of devices, administration and dose of antiplatelet agents, and post procedure care.

All procedures were performed under general anesthesia and continuous infusion of heparin. The device was delivered in the standard fashion, through a microcatheter, having been navigated distally over a shaped microwire, often with the addition of an intermediate support catheter. The FDD was then deployed across the neck of the BBA under fluoroscopy. Angiograms ensured the right positioning. Post-embolization CT was chosen to detect periprocedural complications.

Patient demographic data (sex, age), presenting symptoms (Fisher scala, Hunt and Hess scala and Glasgow'Come scala) radiologic images (NCCT, CTA, MRI and DSA), operative reports such as flow diverter type and administration of antiplatelet agents, complications and postprocedural angiographic outcomes and follow-up were reviewed by local investigators at each participating institution and collected in an online database, without a central core laboratory. Two blinded physicians analysed the data.

Results

There were a total of 6 patients with BBA, treated with flow diverter devices in the acute setting of SAH, from three participating centers. Baseline clinical and imaging characteristics of these cases reviewed are shown in table 1.

Mean age was 45 years old, and there were no differences in sex among patients treated (3/6 were men). 4/6 patients had hypertension, and were admitted with mild GCS score (>13) and a Hunt and Hess score ≤2; 5/6 patients had a Fisher scale ≤2. Only one patient had a severe GCS score (GCS 6), with Hunt and Hess score of 4 and a grade 3 of Fisher scale.

A ruptured BBA was detected at admission in the 50% of patients after DSA study, while about 33% of BBA (2/6) was detected at the second DSA control after 7-10 days from SAH; only one BBA was detected on MRA.

3/6 patients showed a BBA of supraclinoid ICA, 2/6 patients showed BBA of basilar artery, one patient showed a BBA of middle cerebral artery. Median aneurysm size was 2 mm.

In all cases was used a single FDD. 3/6 were treated with the Pipeline Embolization Device (PED; Covidien, Irvine, California); 2/6 with the Flow-Redirection Endoluminal Device (FRED; MicroVention, Tustin, California); in one patient was used the Derivo embolisation device (DED; Acandis GmbH & Co. KG, Pforzheim, Germany).

In 4/6 patients, FDD were delivered with intraprocedural IIb/IIIa inhibitor agents, among which Tirofiban was the most used. Double antiplatelet bolus (clopidogrel and aspirin) was administered before the procedure in only one, while in the other case it was administered tirofiban together with clopidogrel. No intra-periprocedural complications were registered.

Patients were maintained on dual antiplatelet therapy (DAPT) after placement of flow diversion devices. A combination of aspirin and clopidogrel was the most common DAPT regimen after EVT, which was used in 5/6 of cases.

Table 1. Baseline Characteristics, Operative reports and Follow-up of patients with BBA treated with FDD in the acute setting of SAH

	Baseline Characteristics, Operative Reports and Follow-up	
Age at SAH		45 yo (21-57)
Male		3/6
Hypertension		4/6
Smoke		3/6
GCS baseline	>13-15	4/6
	9-12	1/6
	3-8	1/6
mFisher scale ≤ 2		5/6
Hunt-Hess scale ≤ 2		4/6
Diagnosis at admission		3/6
CTA+DSA at admission		4/6
Diagnosis with second DSA		2/6
Aneurysmal site	ICA	3/6
	MCA	1/6
	BA	2/6
Aneurysmal dimension ≤ 2 mm		5/6
Type of FD	PED	3/6
	FRED	2/6
	DERIVO	1/6
Intra-operative antiplatet therapy		5/6
Gp IIb-IIIa inibitors		4/6
Intraoperative complications		none
DAPT post EVT		5/6
DSA 7-10 days		4/6
DSA 7-10 days	stability	2/4
	growth	2/4
Re – treatment in 3 mo		1/6 (FRED Jr)
mRS at 3 mo	0-2	5/6
	6	1/6
Complete aneurysm occlusion at 3-4 mo DSA-MRA		6/6

Immediate change in contrast opacification at the end of the procedure described as no residual aneurysm filling or as reduced filling or contrast agent stasis inside the bleb, as a result of initial aneurysm flow exclusion was reported in all cases of treated blister aneurysms.

4/6 patients were submitted at 7-10 days DSA control, with 50% of angiographic results' stability and one 50% of dimensional BBA growth. One of these was retreated with a second FDD (Flow-Redirection Endoluminal Junior Device - FRED Jr; MicroVention, Tustin, California), with a telescopic technique.

Angiographic follow-up was performed for all patients, on average, 3,5 months after the treatment. All showed complete obliteration. There was one case of subintimal in-stent thickening recognized on follow-up imaging control, even patient remained asymptomatic.

Clinical 3 months follow-up showed good clinical outcome with modified Rankin Scale (mRS) score of 0-2 at 3 months for 5/6 patients, in patients that started with low grade SAH (Hunt Hess I–III) and a lower Fisher grade.

Discussion

This study evaluated 6 cases presenting with BBA at non-branching sections of the supraclinoid ICA, of BA and of MCA in the acute setting of SAH, which represents the main patient presentation, even it accounts for 0.5-2.0% of ruptured intracranial aneurysms (9).

BBAs are often undiagnosed at admission, above all due to their small size and broad-based shape, making the diagnosis on neuroradiological imaging challenging, so that DSA after CTA is often required, as in our study where 3/6 patients needed DSA after CTA, moreover 2/6 BBA were detected at the second DSA control at 7-10 days, probably due to their wall instability and morphological changes, and tendency to rupture which contributed also making them technically difficult to treat (3).

For all these reasons, FDD by redirecting blood flow along the normal course of the parent artery, has becoming widely accepted for the treatment of BBAs, as a safe and effective treatment for this subset of aneurysms, since induce intra-aneurysmal thrombosis

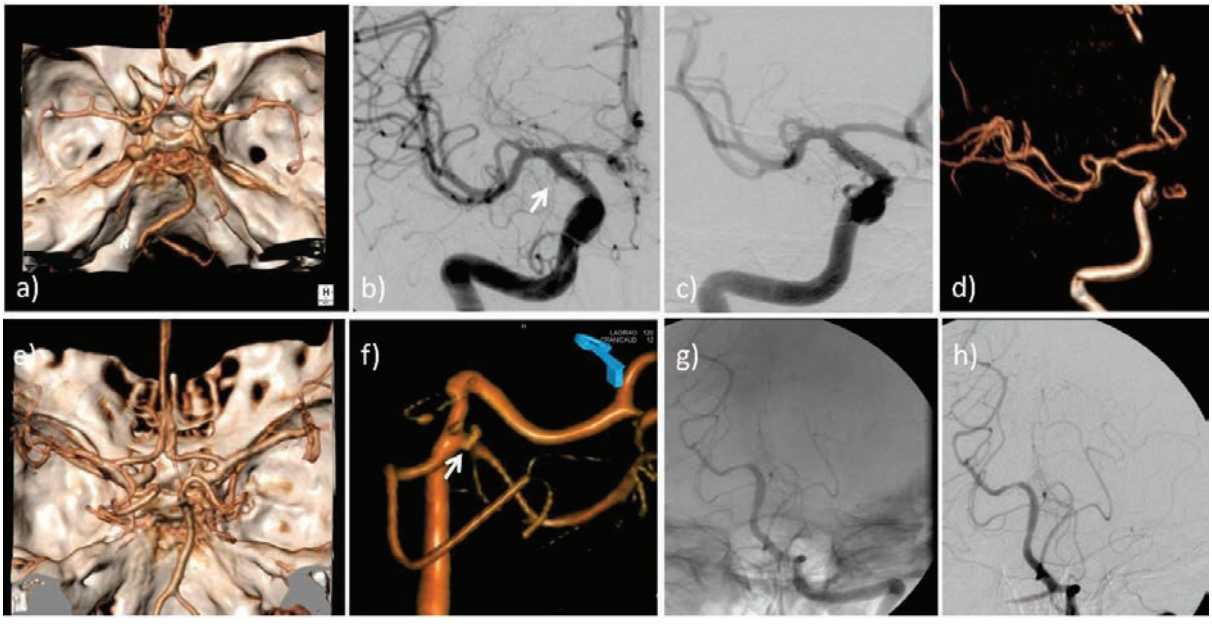

Figure 1. *On the top Case 1:* a) any aneurysm was detected on Angio-CT (VR reconstruction) at admission.
b) DSA of the right ICA: blood blister aneurysm of the right ICA (1 mm), was found at ICA C6 segment (white arrow). c) DSA of the right ICA post EVT: stenting of supraclinoid tract of the right ICA, after FRED insertion under fluoroscopy d) ANGIO-RM-TOF-3D sequence (VR reconstruction): at 3 months follow-up the BBA was excluded from the circulation. *On the bottom Case 2:* e) any aneurysm was detected on Angio-CT (VR reconstruction) at admission. f) DSA of left vertebral artery (VR reconstruction): 2 mm blood blister aneurysm was detected at the corner between SCA - P1 segment (white arrow). g) DSA of left vertebral artery after EVT: stenting with PED of the basilar trunk. At the end of the procedure no residual aneurysm filling was detected, as a result of aneurysm flow exclusion. h) 3 months DSA of left vertebral artery: at the follow-up the exclusion of BBA from circulation was confirmed.

with low re-rupture risk (3), indeed it has been reported to be associated with high rates of complete occlusion and good long-term neurological outcomes, even in the acute SAH setting (5).

In the last years, several evidences had been reported, supporting the safety and effectiveness of the use of FDD for ruptured BBA: in 2018 Mokin et al reported a multicenter experience with flow diversion exclusively for BBA of supraclinoid ICA, by including results of 32 BBA treatment, that supported the use of FDD with 87,5% of complete occlusion, and 68% of good clinical outcome at 3 months, with 5% of delayed complications, and only one case of fatal delayed rerupture after the initial treatment. (10). In 2017 Ryan et al retrospectively reviewed a serie of 13 patients with ruptured BBA treated with PEDs by reporting 77% of good clinical outcomes with no episodes of procedural or delayed aneurysmal rebleeding (7). In 2016, Linfante et al treated 10 patients with ruptured BBAs of the supraclinoid ICA using a PED, describing a 90% good clinical outcome rate with no procedural complications and no aneurysmal re-ruptures (11). In 2015, Aydin et al. in a series of 11 ruptured blister aneurysms, reported good clinical outcomes in 92%, cases treated with the Silk flow diverter. No aneurysmal re-ruptures, and a procedural minor ischemic stroke in 1 case (12). Another series in 2015, reported by Rouchaud et al., of 62 ruptured blister aneurysms treated with flow diversion, 86% achieved good clinical outcomes, and 17% suffered procedural complications including an almost 8% risk of procedural ICH (13). In 2014, Yoon et al. reported a 12-patient multicenter series of PEDs in ruptured ICA blister aneurysms with 83% of good clinical outcomes rate, and no procedural or post flow diversion aneurysm rerupture (14), while Chalouhi and colleagues reported 100% of complete aneurysm occlusion and an mRS score of ≤ 2 in all 8 patients in their series on PED treatment of blister aneurysms, with no procedural complications and no aneurysmal re-ruptures (15). Hu et al. all reported similar results (16). In 2013 Çinar et al. published a 7-patient ruptured blister aneurysm series with PED treatment and reported good clinical outcome in 71% and no procedural or postprocedural aneurysm rerupture (4).

In our study all the patients treated obtained immediate change in contrast opacification at the end of the EVT, as a result of initial aneurysm flow exclusion, with complete occlusion at 3 months follow-up, and good clinical outcomes, achieving 0-2 score of modified Rankin scale at 3 months, in 5/6 patients. These results were similar to all the three different flow diverting devices chosen, with PED resulting mainly used (see table 1). It is to note that PED is the most commonly studied flow diverting stent for the treatment of BBA, reported in literature (10). Any intra- or periprocedural complications were found, even in the issue of incomplete or delayed occlusion rates, or regrowth.

Although complete occlusion of BLA immediately following FDD placement has been demonstrated (16), the persistence or growth of the BBA often occurs after the placement of flow-diverting stents probably due to mismatching of the stent or insufficient stent expansion (1,4-5, 15).

Recent studies have not shown an increased rehemorrhage risk, even with confirmed residual aneurysm (10), such a low incidence of rebleeding in the immediate period can be explained by the reduction of jet inflow of blood and hemodynamic shearing stress on the aneurysmal wall (11,15).

Even for delayed occlusion cases or minimal increase, complete obliteration on follow-up angiography at 3.4 months was found, concurring with those previously reported where complete occlusion is usually observed in 80–90% of cases on follow-up (10,16).

Notwithstanding, it is important to note, that some intra and periprocedural complication have been reported in literature, such as side branch occlusion,stent thrombosis, vasospasm, intraoperative rebleeding, or post-procedural intracranial hemorrhage (1,3), these worsened by systemic heparinization and antiplatelet application, even if a comprehensive meta-analysis of the literature, showed how morbidity and mortality associated with BBA, treated with FDD, was lower than with surgical treatment, even in the presence of DAPT (17).

However the use of FDD in the acute setting remains a major issue since DAPT is needed to prevent thromboembolic events, however may be challenging in the acute phase, representing the major risk for the patient.

In the two patient in which BBA was detected at the second DSA, we used DAPT before procedure only in the patient clinically stable and IIb/IIIa inhibitor agent together with clopidogrel in the other one who showed worse clinical condition, while preferring intraprocedural IIb/IIIa inhibitor bolus in 4/6 cases in which BBA was detected at admission and promptly treated to avoid further hemorrhagic complications risk. None of our cases showed periprocedural intraparenchymal hemorrhage.

Some authors use and support the safety of tirofiban together with DAPT as protocol for patients with intracranial aneurysms who underwent flow diversion (18) while only a small series focused on the safety of IIb/IIIa inhibitor use in the case of ruptured aneurysm (19), so that consensus above antiplatelet therapy administration should be achieved.

Limitations of our study include the narrow number of patients, its retrospective nature, which is subject to the accuracy of case reporting, the lacking of treatment protocols at the participating institutions and the use of different FDD.

Further studies with large numbers of patients are needed to compare the effectiveness and safety of each kind of device since computational fluid dynamic analysis suggests that different flow diverters vary in their hemodynamic effects on cerebral aneurysms (20).

Conclusion

Endovascular flow diversion of intracranial blister aneurysms is a treatment that is increasingly practiced for this challenging subset of aneurysms, even if antiplatelet therapy is required and could represent a major limitation in the acute setting of subarachnoid hemorrhage presentation.

Our experience adds to previous reports other cases of ruptured BBA treated with the FDD in the acute setting of subarachnoid hemorrhage. Our data support this endovascular technique as a safe and effective therapeutic modality for BBA even in the acute setting. Larger studies are needed to compare flow diverters device efficacy.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Written informed consent to the interventions, CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Prostatic artery embolization in patients with benign prostatic hyperplasia: perfusion cone-beam CT to evaluate planning and treatment response

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Summary. This proof of concept is to evaluate the utility of perfusion cone-beam computed tomography (CT) in patients undergoing prostatic artery (PA) embolization (PAE) for benign prostatic hyperplasia (BPH) with moderate or severe-grade lower urinary tract symptoms (LUTS). PAE is a novel minimally invasive therapy and is both safe and effective procedure with low risks and high technical successes, making this procedure as the best alternative to surgery. A lot of technical changes would compromise clinical outcomes after procedure, including a variable prostate vascular anatomy, thin PA, and extensive atherosclerotic disease. The purpose of our study is to exploit the advantages of Perfusion Cone Beam Computed Tomography (CBCT) that could impact treatment and help interventional radiologists for treatment planning, diagnosis and for assessing the technical feasibility during PAE, mitigating the risk of nontarget embolization and suggesting clinical outcomes. Qualitative and quantitative clinical pre- and post-treatment values will be compared, to reach the best possible results. (www.actabiomedica.it)

Introduction

Benign prostatic hyperplasia (BPH) is the most frequent benign tumor in men and is present in > 50% of men ≥ 60 years old (1), associated with an increased incidence in advanced age: it is present in approximately 8% of men in the fourth decade of life but up to 90% of men in the ninth decade (2).

Proliferation of the glandular/stromal tissue in the transition zone of the prostate, located closest to the urethra, leads to a progressive bladder outlet obstruction and consequent lower urinary tract symptoms (LUTS) (3).

The International Prostate Symptom Score (IPSS), also known as the American Urologic Association Symptom Index (AUASI), is a validated instrument that quantifies patient's subjective urinary symptoms on a 35-point scale (4). The IPSS also incorporates urinary Quality Of Live score (QOL score), which assesses how the patient feels overall about his urinary symptoms (5). Scores characteristics are shown in Table 1.

In addition to diagnosis of BPH, the AUASI can aid in selecting initial therapy (Pharmacologic and Surgical Treatment) and monitoring the response.

Table 1. IPSS: International Prostate Symptom Score; QoL: Quality of Life

I-PSS: International Prostate Symptom Score							
In the past month:	**Not at All**	**Less than 1 in 5 Times**	**Less than Half the Time**	**About Half the Time**	**More than Half the Time**	**Almost Always**	**Your score**
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	

Total I-PSS Score ____

Score: 1-7: *Mild;* 8-19: *Moderate;* 20-35: *Severe*

Quality of Life (QoL) **Due to Urinary Symptoms**	**Delighted**	**Pleased**	**Mostly Satisfied**	**Mixed**	**Mostly Dissatisfied**	**Unhappy**	**Terrible**
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Medical and surgical therapies for BPH may be associated with major complications, including sexual dysfunction.

A number of surgical alternatives have been proposed in the past decades (6) to reduce the morbidity of surgical procedure for BPH. Minimally invasive surgical therapies (MIST) have been developed using mechanical and thermo-ablative strategies, but the role of minimally invasive surgical therapies in the treatment of BPH is still yet to be strongly defined (7).

Prostatic artery embolization (PAE) is emerging as a viable nonsurgical treatment for lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH). Embolization of the prostatic arteries leads to ischemic shrinkage of the prostate gland and a substantial IPSS and QOL improvement with a low incidence of serious adverse events (AEs) (8).

The PAE procedure requires the use of radiation for procedural guidance and would be limited by its technical challenges, including a variable prostate vascular anatomy, thin prostatic arteries (9) and may not always be technically feasible, especially in patients with extensive atherosclerotic disease (3).

The purpose of our proof of concept is to exploit the advantages of Perfusion Cone Beam Computed Tomography (CBCT) to analyze the detailed anatomy of male pelvic arteries that could be extremely helpful to avoid complications of PAE, which include nontarget embolization of surrounding organs, reduction of procedure time/radiation exposure, and achievement of the best clinical outcomes possible.

Methods

Patients selection

This single-center study, approved by the institutional review board, will include eligible patients who will be informed regarding the procedure and written informed consent will be obtained from all patients.

Inclusion criteria for PAE will be age > 50years, a diagnosis of moderate-severe lower urinary tract symptoms (IPPS ≥ 18 and QOL ≤ 3), Qmax ≤ 12 mL/s or Acute Urinary Retention (AUR) due to a BPH, refractoriness to medical treatment for at least 6 months, unfit to surgery and PV > 40 mL.

Exclusion criteria included malignancy, large bladder diverticula or stones, chronic renal failure, neurogenic bladder and detrusor failure, active urinary tract infection and unregulated and uncontrollable parameters.

Pre-treatment evaluation

Before the procedure, all patient will be evaluated clinically by an interventional radiologist and urologist using qualitative clinical values (IPPS, QOL score and the International Index of Erectile Function IIEF questionnaire) and quantitative clinical values (prostate volume PV, prostate specific antigen PSA level, Qmax and postvoid residual PVR in patients who did not have AUR).

Post-treatment follow-up

In the immediate postoperative period, pain assessment will be evaluated using a Visual Analog Scale (VAS): patients will rate their pain severity from 0 (no pain) to 10 (the worst pain).

Our study aims to evaluate outcome of patient with serial clinical and instrumental follow-up using IPPS, QOL and IIEF scores but also measuring PSA level, Qmax, PVR and PV.

Procedural Approach

The most technically challenging part of PAE is the identification and catheterization of prostatic arteries due to the variable origin of the PA (10) that sometimes could be variable between the left and right side (11). PAs are small arteries that may be difficult to identify with digital subtraction angiography (DSA) that increase procedure time and the risk of nontarget embolization, related to misrecognition of the target vessel, reflux or collateral flow to nontarget sites (12).

Cone-Beam CT is an advanced imaging capability based on the rotation of C-arm equipped with a flat panel detector; 2D projections are acquired with a

circular path covering at least 180° rotation, volumetric images are obtained with a 3D cone-beam image reconstruction, like shown in the Figure 1 (13).

Unenhanced CBCT has been largely used like a guidance for percutaneous approach in lung (14), liver (15), vessels (16), alone or in combination with fusion imaging (FI) techniques (17, 18).

An intra-procedural three-dimensional (3D) perfusion angiography CBCT is needed during PAE, to localize the prostate, identify PAs and their anatomic variants: the role of CBCT with automatic vessel detection (AVD) software (EmboGuide, Philips Healthcare) during PAE permits to assess the complex vascular anatomy after a single injection of contrast medium in the artery and may define vessels and perfused tissue territory, as an adjunctive technique to DSA (13).

CBCT must be performed with the catheter into the internal iliac artery (IIA) to evaluate the origin of the PAs. A new CBCT can be performed with the microcatheter in the PA, to avoid non-target embolization (19) (Figure 2).

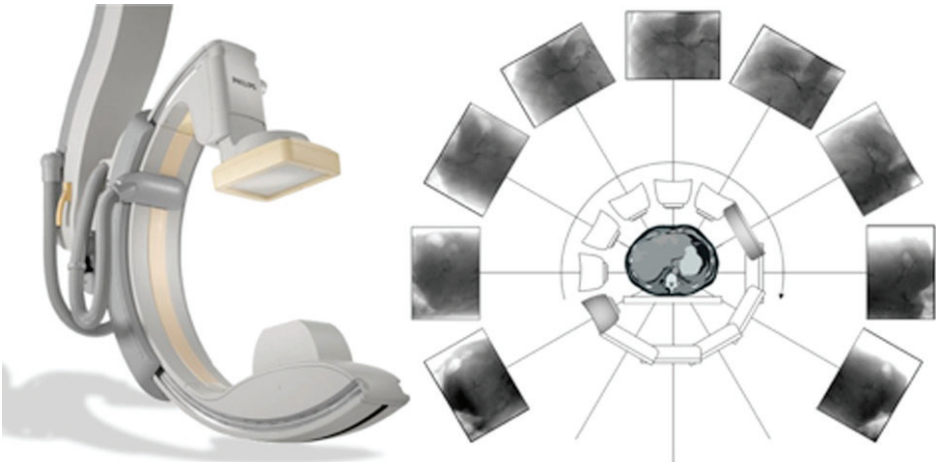

Figure 1. Cone-Beam CT imaging involves the rotation of a C-arm equipped with a flat panel detector around the patient (left image). Multiple 2D two-dimensional projections are acquired and reconstructed to generate a 3D three-dimensional volumetric data set (right image).

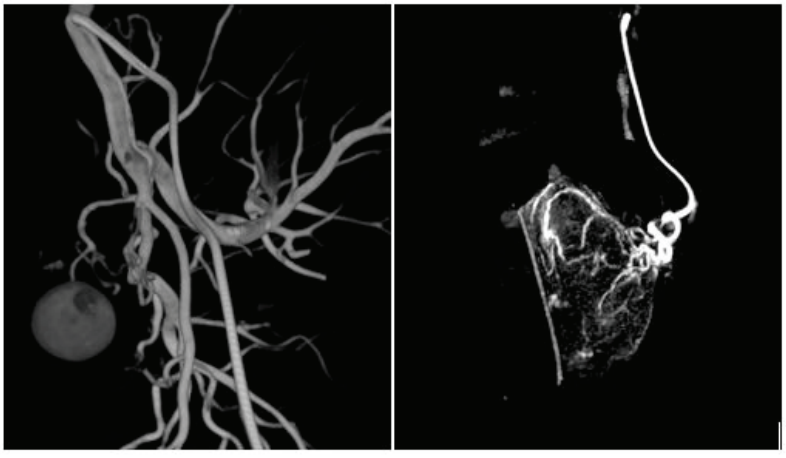

Figure 2. Non-selective cone-beam CT angiography was performed (left image): a Foley catheter is introduced into the bladder and filled with a mixture of iodinated contrast medium (20–30%) and saline solution. Selective catheterization (right image) permits parenchymal evaluation.

Software-assisted detection of prostatic vessels is feasible and collateral non-target vessels may also be successfully depicted on CBCT, to decrease risks and to increase operator confidence before embolization (13).

Acquired data could be enforced using a separate postprocessing workstation for volume rendering technique (VRT), multiple planar reformatted (MPR) and maximum intensity projection (MIP) reconstruction, resulting in a 3D layered images like CT scans during the procedure.

Those methods were already described in cerebral perfusion imaging and liver intraprocedural treatments (20–22) but also to detect vessels in endovascular treatments both for Endoleak (23) and in emergency transarterial embolization (24).

Postprocessing of acquired image data also permits to detect the presence of perfusion parenchymal blood volume (PBV) with contrast material in CBCT images, based on vascularization and enhancement, to generate color-coded perfusion maps. A recent study evaluates the utility of PBV before and after liver chemoembolization and suggests it like a surrogate biomarker to predict early success/failure of the procedure, helpful to optimize treatment following chemoembolization (25).

For these reasons we consider CBCT as an essential instrument for treatment planning, diagnosis and for assessing the technical feasibility during PAE: the direct visualization of prostatic parenchyma and his supplying arteries during prostatic angiography, can lead us to predict a technical success and clinical response.

Technical outcome

Technical success will be reached at least with one side prostatic arterial embolization. A pioneer study shows that unilateral embolization may lead to a technical success in a 50% of these patients, despite evidence suggesting a better clinical result after bilateral embolization (26).

Values for fluoroscopy time (in minutes), dose area product (DAP) totals, number of DSA series and cone-beam CTs will be recorder from the automated dose report.

Total contrast medium volume (in milliliters) will be calculated at the end of the procedure.

Possible complications

After treatment patients might suffer a postembolization syndrome, which can include pain, dysuria, frequency, and other irritative symptoms, that last less than 1 week and require only symptomatic management. AUR requiring temporary catheterization and urinary tract infection requiring oral antibiotic therapy (3). According to a recent meta-analysis study, major complications following PAE are rare and are potentially attributable to nontarget embolization (bladder, rectal or seminal vesicle injury), or to radiation-related skin injury (8).

Discussion

The prevalence of BPH increases with age; one fourth of men older than 70 years have moderate to severe LUTS (27).

Medical and surgical therapies for BPH may be associated with major complications.

Medical treatments are mostly alpha-1 blockers (AB), 5-alpha réductase inhibitors (5ARI) and phospho-diestérase inhibitors. Patients who cannot tolerate medical therapy or in case of failure, surgery can be indicated, after evaluation of the Bladder Outlet Obstruction (BOO) with urodynamic studies (28).

Prostatectomy via open surgery or transurethral resection of the prostate (TURP) is the standard treatment for benign prostatic hyperplasia (19) and is selected according to the size of the prostate, the expertise of the urologist and patient preference and is the standard treatment for benign prostatic hyperplasia (29).

TURP has been the Gold standard for treatment of prostate glands as large as 80-100 cm^3 but can be associated with a lot of morbidity, including ejaculatory and erectile dysfunction, incontinence, urethral stricture, urinary retention and infection (30).

Surgical treatment is very efficient for prostates larger than 80-100 cm^3 but carries frequent complications, more common than TURP, including

lymphocele, hematomas, major bleeding, incontinence, urethral stricture, urinary retention, sepsis, retrograde ejaculation which is very frequent and can compromise fertility and sexual pleasure (31, 32).

The scenery of BPH treatments is rapidly evolving, turning on minimally invasive therapies with mild side-effect profiles. PAE avoids transurethral access, anesthesia, and hospitalization, making it arguably the least invasive of the procedural therapies for LUTS (3).

A recent systematic review and meta-analysis investigate the efficacy and safety of PAE in the treatment of LUTS showing a significant outcome-improvements with a low risk of complications, especially in men with high risk of complications due to pre-existing medical conditions. Malling at all also assert that rates of clinical and technical success were reported between 76.3 to 100% and 76.7 to 100%, respectively (33).

Pisco et al evaluating 630 patients say that most clinical failures occurred during the short-term follow- up. As time increased after PAE, the incidence of clinical recurrence decreased. The cumulative clinical success rate at medium- and long-term follow-up were 81.9% and 76.3% (34).

Promising results are shown also by Unflackert et al. (8). After one year, PV decreased by 31.31cm3, PSA remained unchanged, PVR decreased by 85.54mL Qmax increased by 5.39 mL/s, IPSS improved by 20.39points, QOL score improved by -2.49 points, and IIEF was unchanged. They record a low incidence of serious AEs (0,3%) although minor AEs were common (32,93%), with no adverse effect on erectile function.

Multiple randomized trial compared PAE versus transurethral resection of the prostate (35, 36), and show a similar reduction of LUTS in the PAE-group compared to that of TURP (36).

Both procedures resulted in significant clinical improvements in the treatment of BPH. However, the advantages of the PAE procedure must be weighed against the potential for technical and clinical failures in a minority of patients (35).

To limit these failures, it has become increasingly necessary to identify innovative therapeutic strategies and to adapt that to every single patient.

DSA based on 2-dimensional projection provides excellent visualization of pelvic vessels, but its low sensitivity for soft-tissue contrast and, sometimes, to identify the prostatic arterial supply. CBCT consists in an angiographic unit equipped with a flat-panel detector that can provide volumetric tomographic 3D images. Wang et al. discovered that CBCT provided more informations than DSA in 64.2% of cases (37).

Recent studies have shown how CBCT could impact treatment and help interventional radiologists for treatment planning, diagnosis and for assessing the technical feasibility during PAE, mitigating the risk of nontarget embolization, and suggesting clinical outcomes. Bagla et al. found that CBCT provided information that could probably save the patient from complications or recurrence in 46% of cases (38, 39).

New applications of CBCT have been extensively studied in the literature: the new software allow to measure not only the immediate therapeutic effects but also to define and manage the optimal endpoint of an embolization.

The presented analysis describes positive therapeutic results in PAE, but for continued prospective outcomes studies and clinical trials are needed to increase his technical success.

Conclusion

Literature data confirming that PAE is safe and effective treatment for BPH with good long-term results on almost all measured outcome parameters. The minimally invasive nature of the technique results in very low morbidity also in patients with other medical comorbidities.

The goal of our proof of concept is to evaluate the usefulness of perfusion imaging using CBCT, obtained during PAE in patients with BPH, for evaluating prostatic arterial anatomy that could be extremely helpful to avoid complications of PAE, reduction of procedure time/ radiation exposure and to reach the best possible outcomes. For this purpose, qualitative and quantitative clinical pre- and post-treatment values will be compared, to reach the best possible results.

Human and Animal Rights and Informed: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Original article

In-bore MRI targeted biopsy

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Summary. Clinical suspicion of Prostate Cancer (PCa) is largely based on increased prostate specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) and/or positive imaging and, up today, biopsy is mandatory to confirm the diagnosis. The old model consisted of Standard Biopsy (SBx), that is random sampling of the prostate gland under ultrasound guidance (TRUS), in subjects with clinical suspicion of PCa. This involves the risk of not diagnosing a high percentage of tumors (up to 30%) and of an incorrect risk stratification. Multiparametric Magnetic Resonance Imaging (mpMRI) has transformed the diagnostic pathway of PCa, not only as an imaging method for detecting suspicious lesions, but also as an intraprocedural guidance for Target Biopsy (MRI-TBx), thus bridging the diagnostic gap. Several single and multicenter randomized trials, such as PROMIS, MRI first, PRECISION and that reported by Van der Leest et al. have confirmed the superiority of the "MRI pathway", consisting of mpMRI and MRI-TBx of suspicious lesions, over the "standard pathway" of SBx in all patients with elevated PSA and/or positive DRE. MRI-TBx appears to be advantageous in reducing the overall number of biopsies performed, as well as in reducing the diagnosis of clinically insignificant disease while maintaining or improving the diagnosis of clinically significant PCa (cs-PCa). Moreover, it shows a reduction in the diagnosis of ins-PCa, and therefore, of overdiagnosis, when using MRI-TBx without sacrificing performance in the diagnosis of cs-PCa. In light of these results, the European Association of Urology (EAU) has introduced the concept of MRI-TBx into its guidelines for the PCa diagnostic process, with a specific indication to perform prostate mpMRI before any biopsy (level of evidence IA); in the clinical practice of our Institute, in-bore MRI-TBx is the preferred technique, as it allows even very small lesions to be sampled, detects more cs-PCa and less ins-PCa than SBx, and have a lower percentage of upgrades after surgery. (www.actabiomedica.it).

Keywords: prostate cancer, multiparametric Magnetic Resonance Imaging (mpMRI), MRI-Targeted Biopsy, in-bore biopsy

Background

Clinical suspicion of Prostate Cancer (PCa) is largely based on increased prostate specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) and/or positive imaging and, up today, biopsy is mandatory to confirm the diagnosis.

The old model consisted of Standard Biopsy (SBx), that is random sampling of the prostate gland under ultrasound guidance (TRUS), in subjects with clinical suspicion of PCa. This involves the risk of not diagnosing a high percentage of tumors (up to 30%) and of an incorrect risk stratification (1).

Multiparametric Magnetic Resonance Imaging (mpMRI) has transformed the diagnostic pathway of PCa, not only as an imaging method for detecting suspicious lesions, but also as an intraprocedural guidance for Target Biopsy (MRI-TBx), thus bridging the diagnostic gap.

Several single and multicenter randomized trials, such as PROMIS (2), MRI first (3), PRECISION (4) and that reported by Van der Leest et al. (5) have confirmed the superiority of the "MRI pathway", consisting of mpMRI and MRI-TBx of suspicious lesions, over the "standard pathway" of SBx in all patients with elevated PSA and/or positive DRE. MRI-TBx appears to be advantageous in reducing the overall number of biopsies performed, as well as in reducing the diagnosis of clinically insignificant disease while maintaining or improving the diagnosis of clinically significant PCa (cs-PCa).

In particular, comparison between the MRI-TBx and SBx pathways, followed in the PRECISION study by 252 and 248 patients, respectively, has demonstrated cs-PCa in 38% of patients with MRI-TBx vs. 26% with SBx. The percentage of patients with findings of insignificant PCa (ins-PCa) was 9% with MRI-TBx vs. 22% with SBX. Moreover, this improved performance was accompanied by a 28% reduction of biopsies (MRI-TBx vs SBx), because men with negative mpMRI did not receive prostate biopsy (4).

Similar results have been obtained in the MRI FIRST study (3) and the study by Van der Leest et al. (5)setting, and population: A prospective, multicenter, powered, comparative effectiveness study included 626 biopsy-naïve patients (from February 2015 to February 2018, both of which showed a reduction in the diagnosis of ins-PCa, and therefore, of overdiagnosis, when using MRI-TBx without sacrificing performance in the diagnosis of cs-PCa.

In light of these results, the European Association of Urology (EAU) has introduced the concept of MRI-TBx into its guidelines for the PCa diagnostic process, with a specific indication to perform prostate mpMRI before any biopsy (level of evidence IA) (6). Highlighting the risk of missing cs-PCa (4.9%) (5), they recommend that suspicious lesions at mpMRI in biopsy naïve patients undergo MRI-TBx along with SBx. The most practical technique to perform such a combination of biopsies is with mpMRI-US fusion, as it allows both targeted and systematic sampling within the same sitting.

For patients with a previous negative SBx and positive mpMRI, on the other hand, only MRI-TBx need be performed (7). In this case, in-bore MRI-TBx is the preferred technique in the clinical practice of our Institute, as it allows even very small lesions to be sampled, detects more cs-PCa and less ins-PCa than SBx, and have a lower percentage of upgrades after surgery (8).

In-bore Technique

A manual system for in-bore MRI-TBx (DynaTRIM® Targeted Trans-Rectal Interventional MRI, Invivo, Gainsville, FL, US) first entered use in our Institution in 2014. As illustrated in Fig. 1, during the use of this system the patient assumes a prone position on MRI bed, the introducer is put into the rectum and then connected to the device. The movement of the introducer is determined by an imaging registration software that forms part of the system. After MRI image acquisition, the software indicates how many degrees to rotate the introducer around each of two axes, and how far to advance longitudinally in order to guide the needle into the target lesion. Positioning of the introducer in this way however, is not always precise due to the limits of the system (related for example

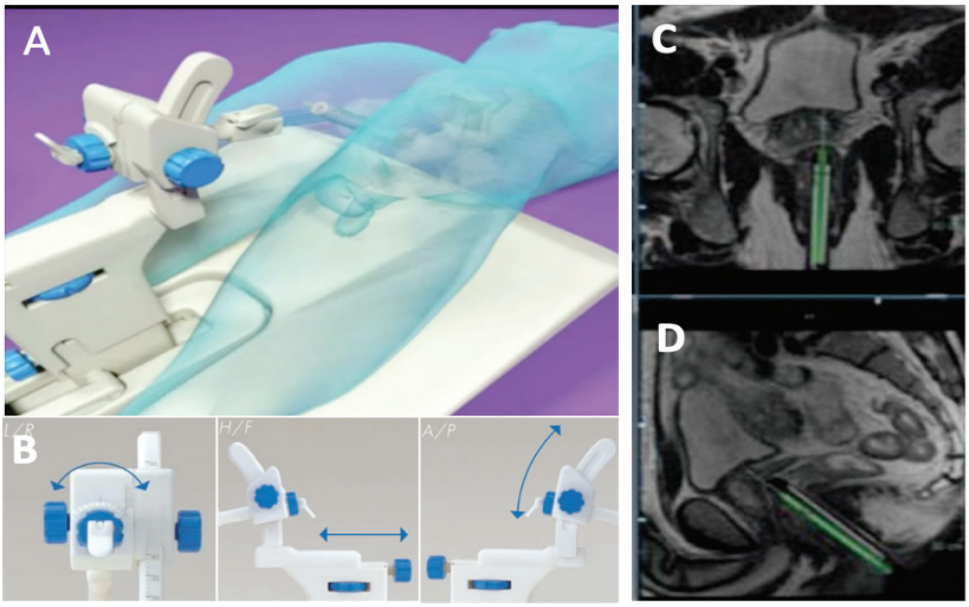


Fig. 1 "Manual System for In-Bore MRI-TBx" – Insertion of introducer in rectum of patient in prone position (**A**); Device movement determined by applying two rotations and longitudinal translation (**B**); Axial (**C**) and para-sagittal (**D**) T2 weighted (T2W) images are obtained for initial guidance. These images were sent to a dedicated planning workstation where the radiologist identifies the current needle guide position and the target lesion. The software then calculates the adjustments needed to reposition the needle guide such that the needle trajectory arrives at the target lesion.

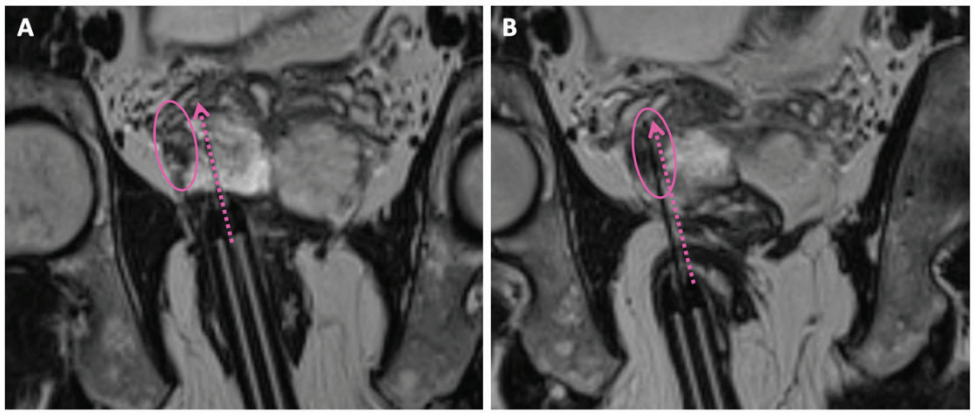


Fig. 2 "Manual adjustment of needle trajectory" - Manual in-bore MRI-TBx performed in Patient with the target lesion located on the base of the right Peripheral Zone (PZ) of the gland. Note the needle guide pointing at the suspicious lesion and, from left (**A**) to right (**B**), with fine manual adjustments, it has been possible to sample the most suspicion area of the lesion.

to resistance to movement by the rectum, and operator variability in applying the indicated rotations and translation), but the operator can manually adjust the trajectory to better orient the introducer and needle towards the target identified on the MRI (Fig. 2). In our experience, we have found that relative to applying the rotations indicated by the software further manual adjustment increases the percentage of samples with PCa diagnosis by 92.3% (9).

In 2018, a second, robotic device for in bore MRI-TBx (Soteria RCM® Remote controlled manipulator, Soteria Medical, Arnhem, The Netherlands) was

introduced into our practice. It has a pneumatic robotic arm, that provides more freedom of movement for manipulating the introducer, and an imaging registration software able to directly move the introducer. It also provides a projection of the needle trajectory, based on post-movement images to verify the correct orientation towards the target, allowing greater confidence in the procedure and thus saving time (Fig 3, 4).

Key Indications

Patients with previous negative biopsy and positive mpmri (Clinical Case 1)

According to EAU Guidelines (Level of evidence IIA) (6), patients with previous negative biopsy and positive mpMRI should undergo only a MRI-TBx. This is because it has been demonstrated that adding

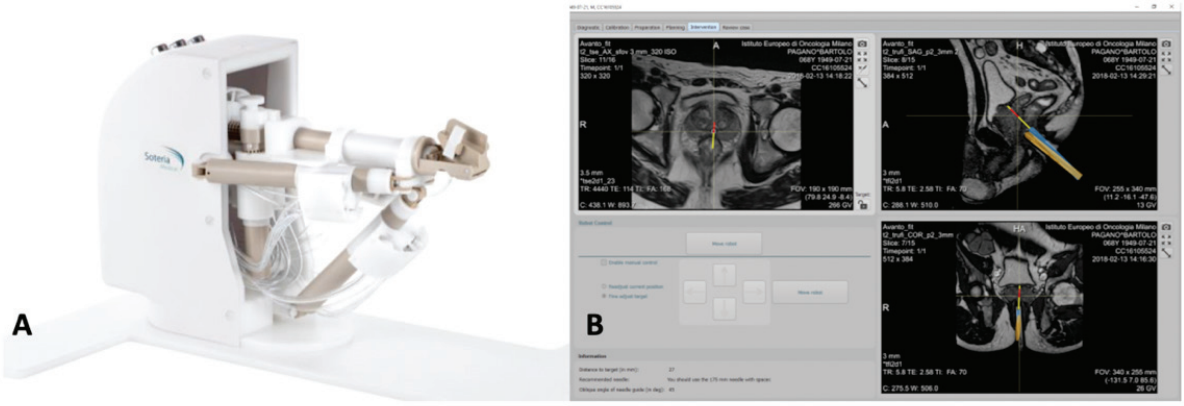


Fig. 3 "In-bore Robotic System" – **A.** Robotic arm; **B.** The same initial planning images are obtained and sent to the dedicated workstation where the radiologist indicates the needle guide and target lesion locations. On command from the radiologist, the robot then repositioned the needle guide to point in the direction of the lesion.

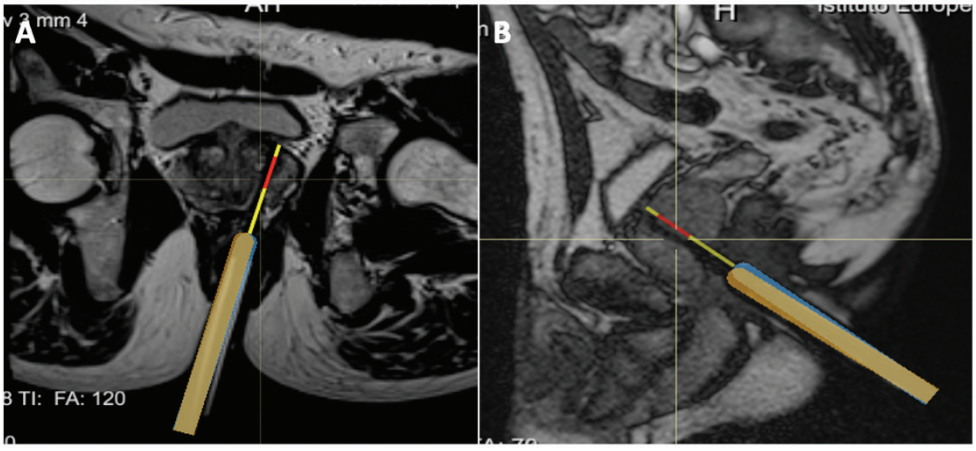
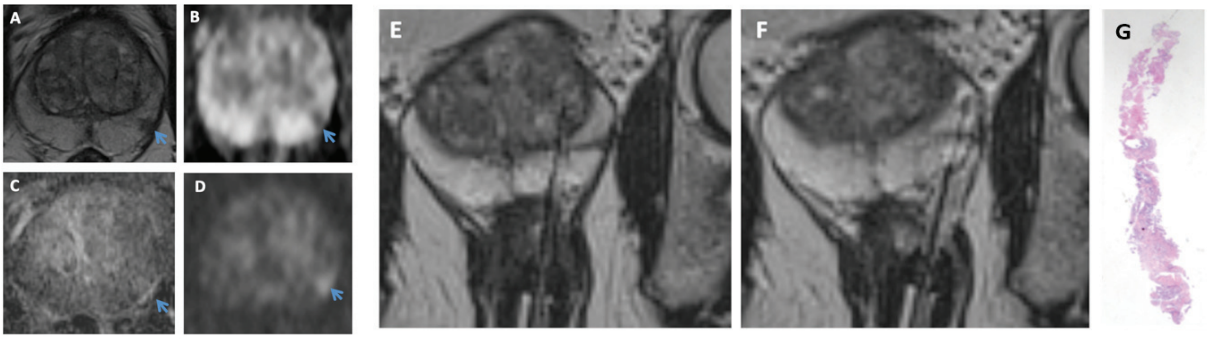


Fig. 4 "Robotic adjustment of needle trajectory" – The software automatically simulated the predicted needle position and overlaid this on the images, providing an estimate of position of the sampling part of the needle relative to the lesion without having to insert the needle. After the movement of the robot, further images are acquired to check if the projection of the sampling part of the needle is correctly positioned within the lesion (totally or at least in part) (**A, B**). If the predicted needle position did not correspond to the lesion, the radiologist could repeat the above procedure of target definition and repositioning of the needle guide until an acceptable correspondence was reached

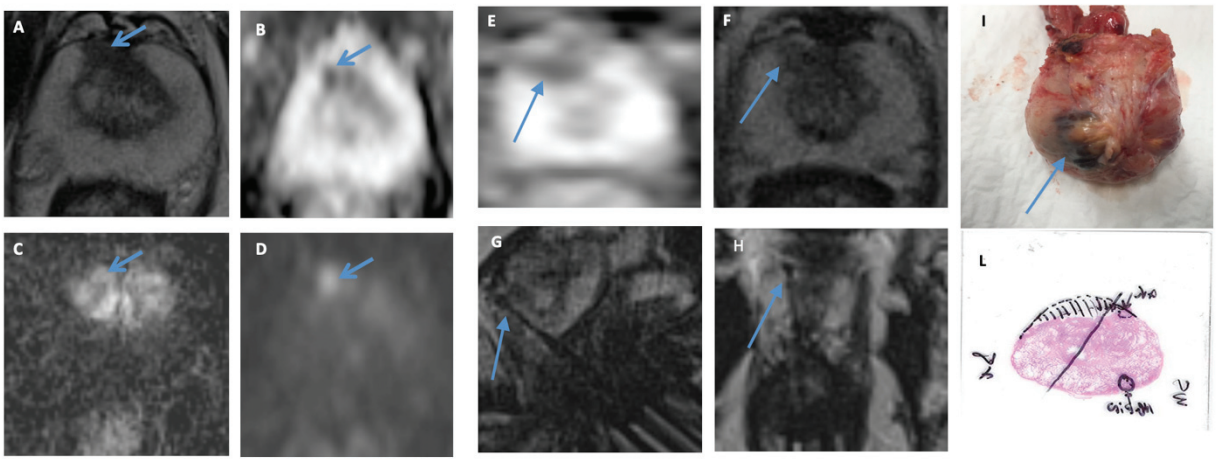


Clinical Case 1. 70-year-old man, with PSA 9.2 ng/mL, negative DRE and Atypical Small Acinar Proliferation (ASAP) finding at TRUS-SBx in 1/14 cores. At pre-biopsy mpMRI a 4 mm lesion, with a Prostate Imaging Recording and Data System (PI RADS) score of 4, was found in the left PZ, characterized by circumscribed hypointensity <15mm on T2W sequence (**A**), focal markedly <15mm hypointensity on Appearent Diffusion Coefficent (ADC) map/ hyperintensity on Diffusion Weight Images (DWI) high b-value image (**B, D**) and no focal early enhancement (**C**). An in-bore MRI-TBx was performed: the first core was acquired near the lesion, with pathological next result of normal parenchyma (**E**); after manual adjustment, the second core was acquired directly into the target, with the following pathological result of 70% of Adenocarcinoma, Gleason Score (GS) 3+4 (**F, G**).

SBx, the cs-PCa detection rate increases only of 2.7%, such that detecting a single cs-PCa at least 37 additional SBx have to be performed (10).

Biopsy naïve patients, only in selected cases (Clinical Case2).

In biopsy naïve patients, EAU Guidelines recommend both SBx and MRI-TBx on the suspicious lesions. However, in selected groups of patients, those with PI RADS 3, 4 and 5 lesions and/or lesions of less than 10 mm and/or lesions located in anatomical sites difficult to reach with biopsy (anterior apex or cranial zone), in-bore MRI-TBx may play a role. Of course, the patients should be carefully selected because the risk of missing cs-PCA when using just MRI-TBx in biopsy naïve patients rises to 4.9%; in other words, every 20 SBx procedures an additional cs-PCa is diagnosed (9).



Clinical Case 2. 65 years old man, with PSA 3.2 ng/mL steadily increasing, negative DRE and no previous biopsy; at pre-biopsy mpMRI a 5mm PI RADS 4 lesion was found in the right anterior PZ, with circumscribed hypointensity <15mm on T2 (**A**), focal markedly <15mm hypointensity on ADC map/hyperintensity on DWI (**B, D**) and focal early enhancement (**C**). During pre-biopsy MRI, the lesion was firstly identified on ADC map and axial T2W plan (**E, F**), then reached by the needle (**G, H**), with a final diagnosis of GS 4+3. Final histology after prostatectomy disclosed a pT3aN0 stage and confirmed the GS 4+3 (**I, L**).

In a meta-analysis of 29 studies (including 13,845 patients) however, Goldberg et al. argued that by avoiding SBx, the percentage of ins-PCa is reduced without affecting the ability to diagnose cs-PCa, underlining the potential of MRI-TBx alone (11).

Reclassification (Clinical Case 3)

In patients with mpMRI features suggesting the presence of a primary GS 4 (for example: reduced ADC values, large volume lesion, undiagnosed extraprostatic extension), but SBx only shows a GS 3+3 (12), in bore MRI-TBx should be performed for possible reclassification, in order to personalize treatments (13,14).

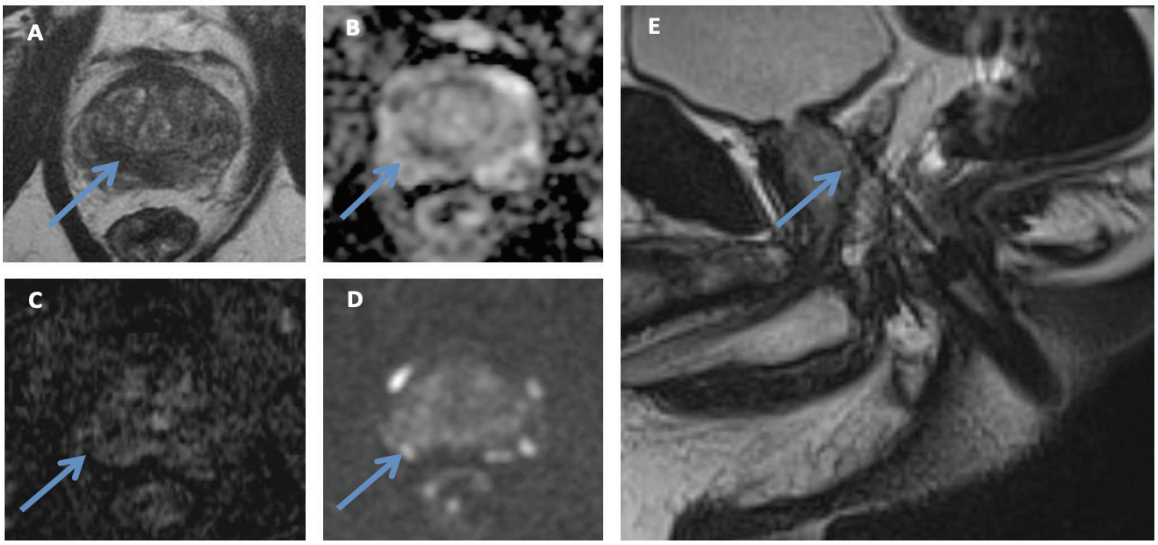
Controversial Areas

Number of cores

There is currently no agreement in the literature or in the urological and radiological communities on the number of cores needed to correctly diagnose PCa, on the best target sampling path or on the best spatial distribution of intra-target cores.

In their latest document, the PI-RADS Steering Committee (15) suggest trying to resolve these issues by introducing the concept of "focal saturation" to indicate the sampling of the target lesion and its "penumbra" in biopsy naïve patients or in patients with previous negative SBx. While not precisely described in the text, the term "penumbra" is presumably meant to refer to the area around the target.

To test the suggested approach, we retrospectively evaluated all 219 of the 414 in-bore MRI-TBxs performed with manual device, all 81 of 283 in-bore MRI-TBx performed with robotic system that satisfied criteria for focal saturation in the ata archive of our institution. With the manual system, 100% of the diagnostic rate was obtained with the first four samples and no additional PCa diagnosis was obtained beyond the fifth core, while with the robotic system, 100% of the diagnostic rate was obtained with the first three samples, that is no additional PCa diagnosis was obtained beyond the fourth core. Therefore, from our



Clinical Case 3. 70 years old man, with PSA 7.98 ng/mL, negative DRE and diagnosis of GS 3+3 in 3/14 at SBx, suitable to Active Surveillance (AS, <20% +ve cores, <50% core involvement, GS 3+3, PSA <10ng/mL, cT1c) [6]; at pre-biopsy mpMRI a 15mm PI RADS 5 lesion was found in the right Central Zone (CZ), with circumscribed hypointensity > 15mm on T2W images(**A**), focal markedly > 15mm hypointensity on ADC map/hyperintensity on DWI (**B, D**) and focal early enhancement (**C**), with suspicious seminal vesicle infiltration. After discussion of the case at multidisciplinary team, a MRI-TBx was perfomed (**E**), resulting in a GS 4+3 and thus fitting the patient for surgery, with a final staging of pT3b N0 M0.

experience, the optimal number of samples needed for focal saturation to diagnose PCa with a 100% diagnostic rate is 4 for the manual system and 3 for robotic procedures.

Biological equivalence

Accurate risk stratification is a cornerstone of modern PCa management (16, 17), and the introduction of MRI-TBx into the diagnostic pathway has raised the question as to whether the risk of upgrading of the GS, after radical prostatectomy differs between MRI-TBx and SBx.

In a recent study, published in 2020 by Ahdoot et al. (18), 404 patients undergoing prostatectomy were analyzed to compare the histopathological results of SBx and MRI-TBx with the final histopathology obtained after surgery. They was observed that, for the same patients, the degree of GS upgrade was 41.6% with SBx, 30.9% with MRI-TBx and 14.4% if both SBx and MRI-TBx were considered. These results are in agreement with existing data in the literature, where the median percentage of GS upgrade after surgery is 20-30% when comparing in bore MRI-TBx with whole-mount histopathology (5, 19-21).

From our experience with 168 patients, the overall agreement was 30%; considering only those with GS 3+3 at in-bore MRI-TBx, however the upgrade rate was high (64.3%) from biopsy to radical prostatectomy. We concluded that for GS 3+3, this indicates the necessity to integrate biopsy GS with mpMRI results before adopting a less invasive treatment. A lower rate of upgrading was observed for patients with a diagnosis of GS 3+4 and 4+3 (19.6% and 4.8% respectively) which suggest a safely plan active treatment.

A possible risk introduced by MRI-pathway is the so-called "*Will Rogers phenomenon*", the potential displacement of patients with less aggressive high-grade PCa from a group with classically favourable outcomes to a group with less favourable ones. In this way, the first group becomes less "contaminated" by patients with high-grade PCa, improving the overall outcome. Similarly, the second group will present a potentially more favourable high-risk disease, improving outcomes in this group as well.

This could have clinical implications, especially for men who are suitable for AS or radical treatment, so the validation of risk calculators using this data from targeted biopsies, as the technique becomes widely adopted, will be mandatory (22).

Patient acceptability

A final, controversial area relates to the acceptability by the patient of different biopsy procedures. To better understand these views, we assessed 47 patients with an ad-hoc questionnaire with 11 questions on a visual analog scale (VAS) of points from 0 (not satisfied) to 10 (very satisfied). Feedback was positive regarding MRI-TBx, particular for the perceived usefulness (9.2) and perceived possibility to ask questions (9.0), though a few patients complained about pain (21%), immobility (10%) and duration (4%). Out of 47 patients enrolled, 24 had previously had SBx. In 10 questions provided, the results were in favour of in-bore MRI-TBx; only for duration was there a preference for SBx. In addition, 75% of the respondents stated, if necessary, that they preferred in bore MRI-TBx instead of SBx.

Conclusions

MRI-TBx is a procedure practicable within a reasonable time and it is based on a specific clinical assumption. Future studies to answer emerging clinical questions are mandatory.

Human and Animal Rights and Informed: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Authors Contribution: Each author has contributed to conception and design, analysis and interpretation of the data, drafting of the article, critical revision and final approval.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Branch vessel occlusion in aneurysm treatment with flow diverter stent

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Summary. Flow diverter placement for treatment of intracranial aneurysms gained growing consensus in the past years. A major concern among professionals is the side branch coverage which leads in some cases to vessel occlusion. However, the lost vessel patency only infrequently is accompanied by a new onset of neurological deficits secondary to ischaemic lesions. A retrospective analysis of all patients treated with flow diversion at our hospital was aimed to better understand this phenomenon in order to formulate a hypothesis about the causes. We concluded that vessel occlusion occurs due to a reduced blood pressure gradient in those vessels with a strong collateral or anastomotic vascularization that refurnishes the same distal vascular territories. Indeed, we detected no new brain infarction since blood flow was always guaranteed.

Keywords: aneurysm, branch vessel, patency, side branches occlusion, flow diversion, flow diverter stent

Introduction

In recent years Flow Diverter Stents (FDS) gained growing consensus as an alternative treatment option for intracranial aneurysms (1-13) in response to extensive in vitro and in vivo studies (14-16) and encouraging clinical experiences. The placement of this device across the aneurysm neck alters intra-aneurysmal flow patterns redirecting flow away from the aneurysm and back into the parent vessel (17-20). This results in aneurysm thrombosis because of stagnating blood, followed ideally by shrinkage of the aneurysm as the clot organizes and retracts. One of the major concerns related to the use of flow diverters is the potential occlusion of side branches, with secondary ischemic complications.

Although the fate of the different major side branches of the distal internal carotid artery (ICA) has been examined in different small studies the overall literature regarding this topic is still scarce (21). Most studies focus only on one branch at a time whereas the minority (22,23) takes into consideration more side branches, simultaneously also including the posterior circulation aneurysms (24-26). Since the concerns about safety of FDS, especially regarding the patency of the covered side branches, are still ongoing, we aimed to contribute with an insight of the data collected on a large group of patients in our institution.

Material and Methods

The protocol for this single-centre retrospective study was approved by the Ethics Committee review board of the Policlinico Maggiore Hospital.

Medical records from consecutive patients with intracranial aneurysms treated with at least one flow diverter between 2009 and 2018 were reviewed retrospectively from a prospectively maintained database to obtain demographic data (including age and sex) as well as data regarding clinical presentation, complications, and outcome. We included all patients treated with at least one of the five following different types of flow diverters: the Pipeline Embolization Device (PED) (Medtronic, Irvine, California, USA), the Silk Flow Diverter (SFD) (Balt Extrusion, Montmorency, France), the Flow-Redirection Endoluminal Device (FRED) and FRED Jr systems (MicroVention, Tustin, California, USA), and the DERIVO embolization device (DED) (Acandis GmbH, Pforzheim, Germany). Both, anterior and posterior circulation aneurysms were taken into account. From this database we selected those patients with at least one covered side branch in addition to the parent vessel.

Our protocol for FDS deployment requires the procedures to be done under general anaesthesia. Distal access on the right femoral artery was obtained using a tri-axial access system consisting in a Neuron 6 French 105 cm long sheath (Penumbra, Alameda, California, USA); Vista Brite Tip 8 French Guiding Catheter (Cordis Corporation, Bridgewater, NJ, USA); and a microcatheter with sizes varying from 0,021 – 0,027 Inches to obtain distal access. The appropriate size of FDS was selected after measuring the parent artery and was deployed to cover the aneurysm neck.

All patients received dual antiplatelet therapy (Aspirin 300 mg and Clopidogrel 75 mg, both once daily) for 5 days prior to the procedure. When the procedure was done in an emergency setting (due to aneurysm rupture) the patient received Aggrastat (Tirofiban) (dose adjusted to body weight) intravenously in 30 min and a maintenance dosage for the following 24 hours, followed by oral antiplatelets drugs. In all scenarios the postprocedural antiplatelet therapy consisted in dual antiplatelet regimen of Aspirin 300 mg daily and Clopidogrel 75 mg daily for the first three months following the procedure. Afterwards single antiplatelet therapy with ASA 300 mg daily was continued until the 12 months follow-up.

Control digital subtraction angiography (DSA) was performed immediately following FDS placement and follow-up DSA was performed between 3 and 6 and at 12 months. At the one year follow-up, the patient performance status was scored with the Modified Rankin Scale (MRS). Furthermore, all patients that showed a reduced or absent blood flow in the covered side branches were subsequently evaluated by a neurologist.

All pre-procedure and post-procedure angiographic data, including aneurysm location (carotid-ophthalmic segment, MCA, ACA, posterior circulation, distal sites), type (saccular or dissecting) and size (small, large and giant); number and type of FDSs deployed (in combination with coiling or not), and patency of anterior and posterior circulation branch vessels (OphA, PComA, AChoA, ACA (A1), ACoA, M2, PICA, AICA, SCA, callosomarginal artery, pericallosal artery and PCA (P2-P3)) were reviewed by two different investigators independently. When, in the same patient with multiple aneurysms, more than one was treated with flow diversion, they were considered as different cases. At the first angiographic follow-up at 3 – 6 months we evaluated the change in flow (reduction or absence) and the calibre (due to intimal hyperplasia) of the covered side branches; at 12 months, again, we looked for side branch patency and exclusion of the aneurysm.

Results

We identified 137 patients with 147 aneurysm who were treated with flow diversion for aneurysms in the anterior and posterior circulation between 2009 and 2018 at our institution. Twenty-five patients were excluded from the analysis for reasons of no branch vessel coverage seen on angiography (n = 19) and lack of follow-up due to various reasons as acute parent vessel occlusion or death during acute treatment (n = 6). Therefore, we included 112 patients with 119 aneurysms in our subsequent analyses. Out of these 112 patients, 87 were females (78 %) and 25 were males (22%). The mean age was 54.8 ± 12.25 years. In terms of aneurysm dimensions the average aneurysm fundus size measured 11.2 ± 12.25 mm, including 8 giant aneurysms (diameter > 25 mm). In regard of the aneurysm type 92 were saccular berry aneurysms, 25 were dissecting aneurysms

and 2 were blister aneurysms. The carotid-ophthalmic segment was the most frequent location for aneurysms in our series (81.51%). Baseline characteristics for these patients including demographics and aneurysm characteristics are presented in Table 1.

A total of 214 instances of branch vessel coverage were identified in the 112 patients with 119 aneurysms. These included 87 OphAs, 57 AChoAs, 32 PComAs, 19 ACAs, 6 ACoAs, 3 PICAs, 2 SCAs, 2 AICAs, 3 callosomarginal arteries, 2 pericallosal arteries, and 1 PCA (Table 2). Out of the 139 FDS used in total, the most utilized were the PED (n=113), followed by FRED (n=9), FRED Jr (n=9), SFD (n=5), and DED (n=3) (Table 3). Fifteen patients were treated with more than one FDS, however no patient had different types of FDS implanted simultaneously. Forty-three patients experienced a subarachnoid haemorrhage (SAH) due to aneurysm rupture and thus received adjunctive coils treatment.

There was evidence of branch vessel occlusion immediately after flow diverter deployment in 5 cases (2 OphAs, 2 PComAs, 1 A1). On follow-up angiography (at 3/6 and 12 months), we identified 22 and 23 branch vessel occlusions, respectively. At 3/6 months the occluded vessels were 4 OphAs, 10 PComAs, 5 A1, and 3 ACoAs. At the 12 months follow-up the occluded vessels were 5 OphAs, 10 PComAs, 4 A1, and 4 ACoAs.

Three ophthalmic arteries that were completely occluded at the three months follow-up were again patent at one year.

The OphA was occluded in 7 of 87 instances (8.04 %), the PComA was occluded in 11 of 32 instances (34.38 %), the ACA (A1 segment) in 5 of 19 instances (26.32 %), the ACoA in 5 of 6 instances (83,33 %). No instance of other vessel occlusion was observed on follow-up angiography. Subgroup analysis of PCoA vessel patency showed no occlusion when the PCoA was fetal-type. Branch vessel patency and occlusion are displayed in Table 4.

Thirty-three patients developed endothelial hyperplasia (30 mild, 3 severe) at the three months follow-up. At one year, five patients with mild hyperplasia showed complete vessel occlusion and two reduced flow. All three patients with severe hyperplasia had complete artery occlusion.

Table 1. Demographics and clinical characteristics

Characteristics	Results
No. of Patients	112
Mean age ± standard deviation (years)	54.8 ± 12.25
Sex	
Female	87 (78%)
Male	25 (22%)
SAH at presentation	43 (36.13%)
Aneurysms	119
Morphology	
Saccular	92 (77.31%)
Dissecting	25 (21%)
Blister	2 (1.68%)
Size (mean, mm)	11.2 ± 12.25
Size Maximum diameter	
<10 mm (small)	67 (56.3%)
>10-25 mm (large)	44 (36.97%)
>25 mm (giant)	8 (6.72%)
Location	
carotid-ophthalmic segment	97 (81.51%)
MCA	3 (2.52%)
ACA	3 (2.52%)
Posterior circulation	11 (9.24%)
Distal sites	5 (4.2%)
Aneurysm occlusion at 12 months (success rate)	93 (78.15 %)
Complete exclusion	83 (69.75%)
Reduction 70-80%	10 (8.4%)

Table 2. Covered branch vessels

Characteristics	Results
No. of branches covered	214
Anterior circulation	
OphA	87 (40.65%)
AChoA	57 (26.64%)
PComA	32 (14.95%)
ACA	19 (8.88%)
ACoA	6 (2.8%)
Posterior circulation	
PICA	3 (1.4%)
SCA	2 (0.93%)
AICA	2 (0.93%)
PCA	1 (0.47%)
Distal sites	
Callosomarginal artery	3 (1.4%)
Pericallosal artery	2 (0.93%)

Table 3. Flow Diverter Stents

Characteristics	No. of FDS	No. adjunctive coils
Tot. FDS	145	40 (33.61%)
PED	117 (78.4%)	34
SFD	6 (4.8%)	1
FRED	10 (8%)	4
FRED Jr	9 (6.4%)	1
DED	3 (2.4%)	0

Taking in consideration the patients that showed branch vessel occlusion due to the implantation of the FDSs and excluding those patients with acute procedure-related complications, only one presented with clinical symptoms. It is the case of a patient who experienced three episodes of amaurosis following the occlusion of the ophthalmic artery. However, the symptoms ceased one year after the procedure and did not represent. We observed no adverse clinical sequelae in the remaining patients who experienced branch vessel occlusion.

The number of aneurysms occluded at follow-up were 93 out of 119 (83 complete exclusion, 10 reduction 70-80%) (success rate 78.15 %).

Discussion

As the name suggests, the primary mode of action of FDS is diversion of blood flow from the aneurysm which is obtained by change in intra-aneurysmal flow and tissue growth across the aneurysm neck (2). Even though endothelization seems to be the dominant predictor of long-term occlusion, it is observed with a certain delay when compared to the intra-saccular thrombosis.

While FDS induce disruption of blood flow near the aneurysm neck, inducing thrombosis into the aneurysmal sac, they should preserve physiological blood flow in the parent vessel and adjacent branches. However, it has been increasingly reported that coverage of some side branches by the device might cause flow reduction and moreover their occlusion (2). The concerns regarding potentially secondary ischaemic lesions seem not to be supported by the investigations conducted so far.

A series of in vitro studies on models reproducing conditions in which a flow diverter is placed across aneurysmal neck and collateral branches has demonstrated that flow through the collaterals is usually preserved. Coverage of the collateral vessel inlet area greater than >90% resulted in a flow reduction of less than <10% (30,31). These results are not unexpected because flow through the collateral is driven by a pressure gradient even if the porous flow diverter is interposed. In vivo, this mechanism is encountered when taking in examination the patency of smaller vessels such as the **anterior choroidal** and **lenticulostriate arteries** and **perforating vessels** with no distal collaterals. These vessels may maintain flow due to a pressure gradient across the ostium and are more likely to remain patent (32-35). This is according to our findings as we experienced no occlusion of vital vessels due to the FDS implantation.

On the other hand, larger vessels such as the posterior communicating artery **PComA, A1, ACoA** and the **ophthalmic artery** usually have well-developed distal collaterals and anastomoses which makes them more prone to occlusion following placement of the flow diverter. This may be due to the insufficient pressure gradient across the device to maintain flow within

Table 4. Branch vessel coverage and occlusion rates

Side Branches	No. of Side Branches	Occlusion at 3/6-Mo Follow-Up	Occlusion at 12-Mo Follow-Up	Overall occlusion rate
Tot of branches covered	214	22	23	28
OphA	87 (40.65%)	4	5	7 (8.04%)
AChoA	57 (26.64%)	0	0	0
PComA	32 (14.95%)	10	10	11 (34.38%)
ACA (A1)	19 (8.88%)	5	4	5 (26.32%)
ACoA	6 (2.8%)	3	4	5 (83.33%)
PICA	3 (1.4%)	0	0	0
SCA	2 (0.93%)	0	0	0
AICA	2 (0.93%)	0	0	0
PCA	1 (0.47%)	0	0	0
Callosomarginal artery	3 (1.4%)	0	0	0
Pericallosal artery	2 (0.93%)	0	0	0

the artery caused by the opposing effect of the distal collateral flow (36,37).

- A1: The A1 also called the "pre-communicating" segment of the ACA originates from the terminal bifurcation of the ICA and terminates at the anterior communicating artery (ACoA), where the A2 (or "post-communicating") segment originates. The A2 segment receives blood from the ipsilateral A1 segment and from the contralateral A1 segment via the ACoA that connects the two ACAs. Therefore, the blood supply to the vascular territory of the ACA is preserved even if the A1 segment is occluded on one side and morphological variants of their absence exist in the general population.
- ACoA: The ACoA arises between the A1 and A2 segments of the anterior cerebral artery and acts as an anastomosis between the left and right anterior cerebral circulation but does not directly play a role in delivering blood to the brain parenchyma. Again, its occlusion is not vital, as it does not interfere with blood flow in the ACA, and in 5% of the population the ACoA is even absent (38).
- PComA: Also the PComA has as major role in the connection of two circulation districts, namely the anterior and the posterior circulation. It runs between the PCA and the C7 (communicating) segment of the ICA forming part of the Circle of Willis. PComA hypoplasia is a relatively common finding with an incidence of approximate 35%
- Ophthalmic artery: The preprocedural angiography of the patient shown in Fig. 1.A shows the ophthalmic artery (arrow) originating from the aneurysm site. At the 3 months follow-up, the same artery is not more visible at angiography (Fig. 1.B). The angiographic study of the external circulation clearly shows a retinal blush with the retinal artery being refurnished by the anastomoses with the branches of the internal maxillary artery (Fig.2). This communication is one of the best known anastomotic connections between the circulation of the internal and external carotid artery. The retina receives blood primarily via the intracranial circulation (ICA

and ophthalmic artery) but it is also refurnished by the external circulation by the meningolacrimal artery via foramen of Hyrtl and the infraorbital artery via the foramen Rotundum. As expected, the patient did not report any symptoms following the procedure and the aneurysm showed a complete exclusion at the 12-month follow-up. The reported case is in our eyes explicative in regard of the phenomena of blood flow inversion due to pressure gradient alterations observed after flow diverter placement.

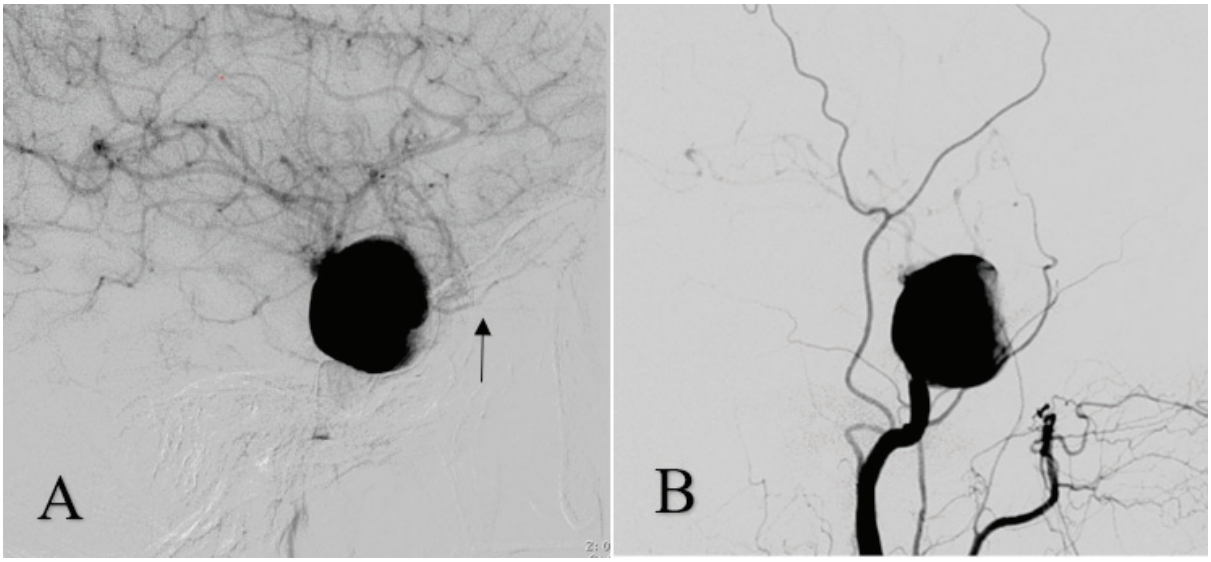

Figure 1. A. Preprocedural angiography shows the ophthalmic artery (arrow) originating from the aneurysm site. B. At the 3 months follow-up, the same artery is not more visible.

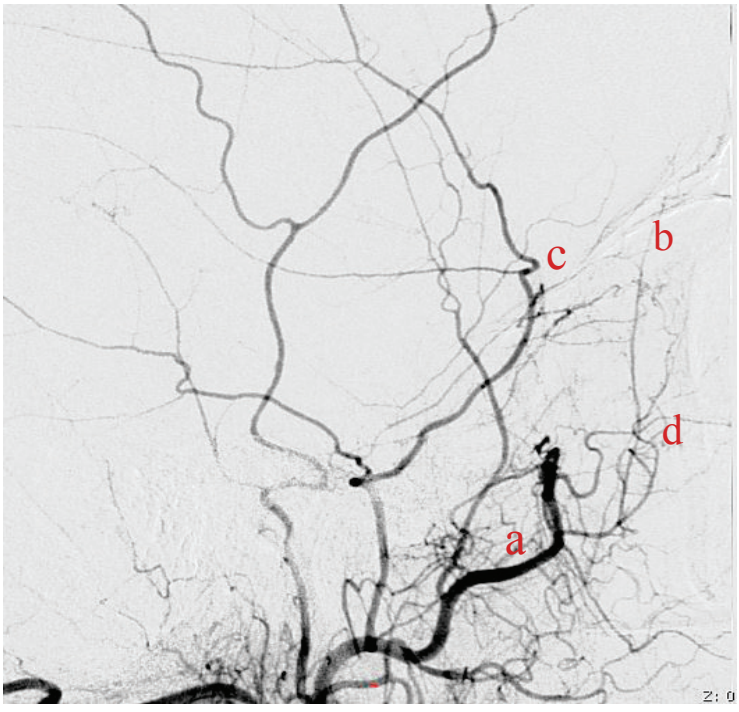

Figure 2. Angiographic study of the external circulation depicting the maxillary artery (a) that refurnishes the retinal artery (b) via the lacrimal artery (c) and the infraorbital artery (d).

ACoA and PComA showed the highest occlusion rates among all the collateral branches. The higher rate of ophthalmic artery patency after flow diversion (8.04%) when compared to PComA (34.38%) can probably be attributed to a higher continued physiological demand. Furthermore, because both systems have an adequate collateral circulation, clinical symptoms do not usually develop in these occluded arteries or in arteries with diminished flow.

Conclusion

Even though occlusion and diminished flow are common following FDS treatment, they are not clinically significant in most cases. Vessel occlusion in our series was not accompanied by any kind of deficit in the long term. The branches most commonly occluded were those arteries that are not indispensable due to their strong collateral blood supply that efficiently shunts the occluded portion and are namely PcomA, A1, AcoA and OphA. This is accompanied by a high success rate in treating the aneurysms with flow diversion and a low complication rate. Therefore, we conclude that FDS placement with coverage of side branches is safe as flow is only interrupted in the covered segment if the blood supply is maintained by collateral circulation.

Abbreviations

OphA: Ophtalmic Artery
PComA: Posterior Communicating Artery
AChoA: Anterior Choroidal Artery
ACA: Anterior Cerebral Artery
A1: First segment of Anterior Cerebral Artery
ACoA: Anterior Communicating Artery
M2: Second segment of Middle Cerebral Artery /division
PCA: Posterior Cerebral Artery
P2-P3: Second and Third segment of the Posterior Cerebral Artery
PICA: Posterior Inferior Cerebellar Artery
AICA: Anterior Inferior Cerebellar Artery
SCA: Superior Cerebellar Artery
ICA: Internal Carotid Artery
FDS: Flow Diverter Stent
DSA: Digital Subtraction Angiography
MRS: Modified Rankin Scale
SAH: Subarachnoid Haemorrhage

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Written informed consent to the interventions, CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Case report

Glue embolization of a pial arteriovenous fistula of the spinal artery

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Summary. There are no clear guidelines about the treatment Pial Arteriovenous Fistulae (PAVF). For high-risk and severally symptomatic fistulae surgery is the first choice of treatment, including feeding artery ligation, surgical resection, radiosurgery and endovascular embolization techniques. We described a case of a patient with a symptomatic PAVF at the craniocervical junction fed by the anterior spinal artery, successfully treated with endovascular approach consisting of glue embolization of the feeding vessel. (www.actabiomedica.it).

Keywords: pial arteriovenous fistula, spinal cord, fistula, embolization glue

Background

Pial arteriovenous fistulae (PAVF) account for less than 2% of all arteriovenous fistulae (AVF) (1). They are fed by parenchyma vessels in contrast with dural AVF which are typical fed by dural arteries (2). The origin of PAVFs is unclear, being reported as congenital, traumatic or iatrogenic, while the location is typically supratentorial. Clinically PAVF can be silent for all life or manifest with haemorrhage, epilepsy, mass effects, cranial nerve deficits or congenital heart failure (3). If untreated, mortality is reported up to 63% (4).

There are no clear guidelines about the treatment; asymptomatic fistulae may heal spontaneously thus conservative approach is recommended. Low-risk minimally symptomatic fistulae should be cautiously monitored. High-risk and severally symptomatic fistulae are usually treated with surgery, including feeding artery ligation, surgical resection, radiosurgery and endovascular embolization techniques.

We described a case of a patient with a symptomatic PAVF at the craniocervical junction fed by the anterior spinal artery, successfully treated with endovascular approach consisting of glue embolization of the feeding vessel.

Case Presentation

A 38 years old man, with no previous history of head trauma, was admitted to our emergency department after the onset of an intense pulsing neck pain associated with nausea and vomiting. Fifteen days before the patient suffered a middle-intensity headache during his usual gym training for which he went to another hospital where clinical examination and brain computed tomography (CT) scan did not detect any abnormality.

Investigations

Upon the admission to our emergency department the patient was alert, without motor and sensory deficits.

Brain CT scan showed haemorrhage in the basal cisterns and in the fourth ventricle (Figure 1). No lesions of the brain parenchyma were found. The ventricle system had normal dimensions. The three-dimensional CT angiography did not show any clear vascular anomaly. A further contrast-enhanced Magnetic Resonance scan confirmed these findings (Figure 1).

The patient underwent angiography under general anaesthesia to further assess any vascular malformation. Through a transfemoral approach with a 6 French (F) introducer, a 6F Envoy catheter (Cordis Endovascular, Miami Lakes, Florida, USA) was guided into the right vertebral artery over 0.035 inch Terumo guidewire (Terumo, Tokyo, Japan) under road-map guidance. The angiography showed a small PAVF fed by one branch of the anterior spinal artery with the venous drainage into the perimedullary veins of the cervicomedullary junction (Figure 2).

Treatment

Considering the unfavourable angle of the right origin of the anterior spinal artery, the 6F Envoy catheter was positioned in the left vertebral artery. A 3x10 millimetres (mm) Hyperglide balloon was positioned and inflate in the basilar artery to reverse the blood flow. A 1.2F Sonic microcatheter (Balt, Montmorency, France) was guided into the right anterior spinal artery over 0.08 inch Mirage microwire (Irvine, California, USA) using the road-map guidance. To reach the feeder of the PAVF 1 mg of Nimodipine (Nimotop, Bayer Healthcare, Germany) was administered from the microcatheter into the anterior spinal artery. After the vasodilatation occurred, the microcatheter was guided into the feeder of the PAVF over the microwire and 0,2 ml of a 50% mixture of glue GLUBRAN 2 (Gem Srl, Italy) and Lipiodol was injected (NBCA-LUF)

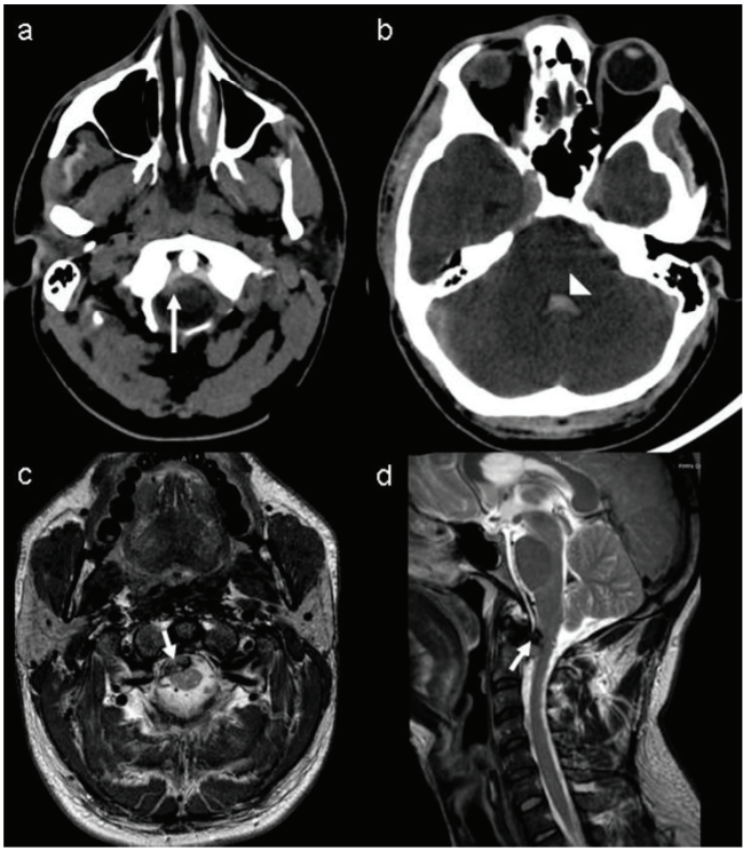

Figure 1. CT and MR scans at admission: axial CT scans (a,b), axial T2-weighted MR image (c), sagittal T2-weighted MR image(d). CT shows subarachnoid haemorrhage in the bulbo-medullary space (long arrows) and in the fourth ventricle (arrowhead). MR shows blood (short arrows) in the subarachnoid space at the front of the bulbo-medullary junction.

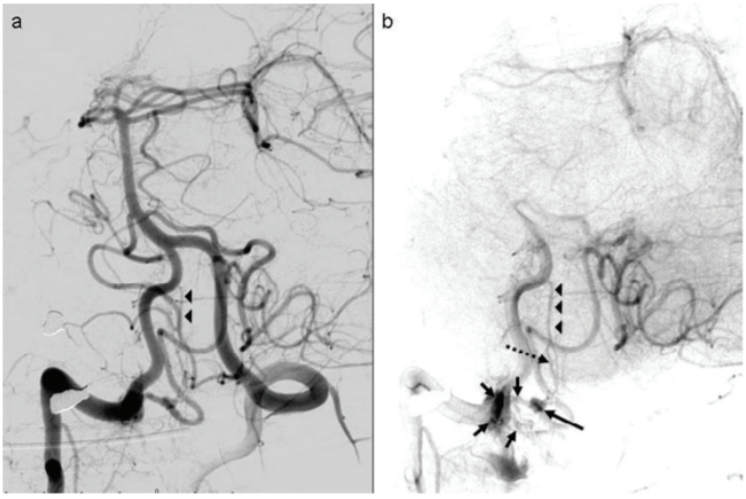

Figure 2. pre-treatment DSA: right oblique view in initial phase (a), right oblique view in late phase (b). DSA shows a branch (dotted arrow) of a prominent right anterior spinal artery (arrowheads) feeding a PAVF with pseudoaneurysmal dilatation (long arrow) in the bulbo-medullary space with drainage into the perimedullary veins (small arrows).

(Figure 3). At the end of the procedure, an angiogram through the catheter did not show any residual PAVF (Figure 4).

Outcome and Follow-up

No procedure-related complications were reported. After 10 days, the patient was discharged without any neurological signs and symptoms. At three-month and one-year follow-up the angiographies excluded any recurrence and clinical examinations confirmed the absence of any neurological deficits (Figure 5).

Discussion

We reported the case of an embolization of a PAVF fed by the anterior spinal artery, located at the level of the cranio-cervical junction and causing a subarachnoid haemorrhage.

The aim of the treatment is to occlude the fistulous connection of the PAVF in order to prevent further bleedings, preserving the blood supply of the spinal cord and avoiding ischemic myelopathy (2). For low-risk minimally symptomatic PAVFs can heal spontaneously thus a conservative approach is recommended, while high-risk or severely symptomatic PAVFs require a immediate treatment, which can be surgical, endovascular or both. The surgical approach, that sometime is guided by intraoperative fluorescence angiography, can occlude the arterial feeder of the PAVF and remove the varicose vein causing mass effect. Surgery is now limited to those cases in which the endovascular procedure is considered dangerous because the arterial feeder is a small branch of a cortical or spinal artery and cannot be occluded (3). The endovascular treatment consists in the embolization of the fistolous connection with coils or liquid embolic agents like n-butyl cyanocrylate (NBCA) or Onyx (3). The positioning of coils can be performed with a better control and is more successful when the fistoulous connection is not so big. Different authors report the use of coils to embolize intracranial PAVFs, in particular Alshekhlee et al. succeeded to embolize a PAVF of the cranio-cervical junction releasing a 1.5 mm by 2 cm coil in the left arterial spinal artery without any complications (2). The use of embolic agents (NBCA or Onyx) is more safe when the size of the feeder vessels allow the distal catheterization, with the superselective catheterization of the feeder vessels having a mortality up to 10% (5). In literature some cases of intracranial PAVFs embolized with NBCA (6,7) or Onyx (8,9) have been reported. Among these cases there is no one

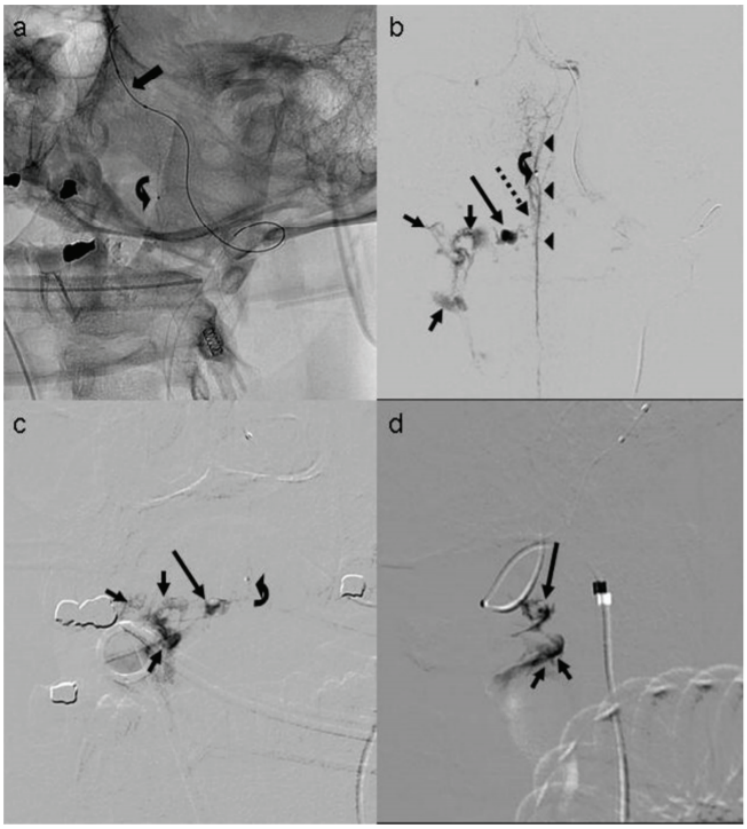

Figure 3. embolization procedure: unsubstracted frontal view (a); frontal view of PAVF after the injection from the microcatheter in the spinal artery (b); frontal view of the superselective catheterism (c) lateral view of the superselective catheterism (d). A balloon Hyperglide 3x10 (thick arrow) was located and inflated in the in the basilar artery to reverse the blood flow and the tip of the microcatheter (curved arrow) was positioned into the anterior spinal artery (arrowheads). Microcatheter injection confirms a branch (dotted arrow) of the anterior spinal artery (arrowheads) feeding a pseudoaneurysmal dilatation (long arrow) with drainage into the perimedullary veins (small arrows).

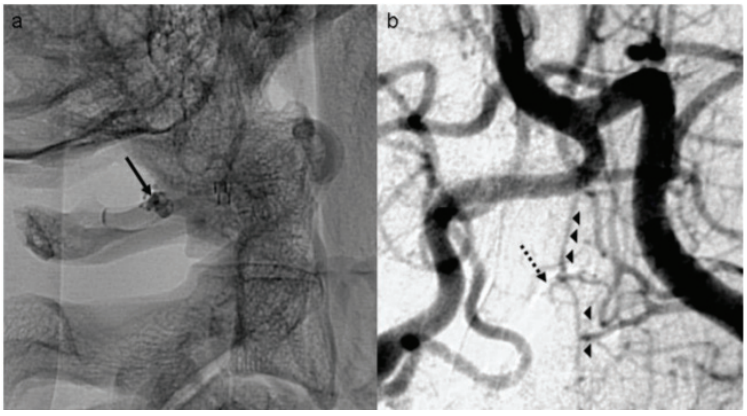

Figure 4. post-treatment DSA: unsubstracted lateral view (a), magnified frontal view (b). The unsubstracted lateral view shows the glue (arrow) within the pseudoaneurysmal dilatation. DSA shows the occlusion of the vessel (dotted arrow) feeding the PAVF and the preservation of the anterior spinal artery (arrowheads).

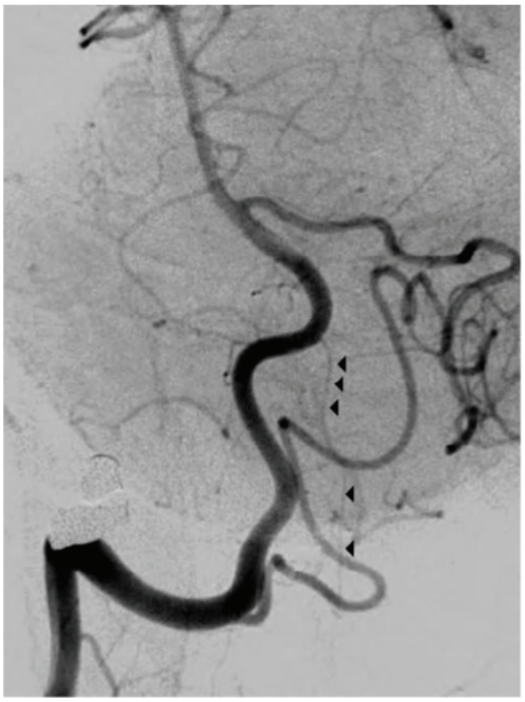

Figure 5. DSA at one year follow-up showing the preservation of the anterior spinal artery (arrowheads) without evidence of the PAVF.

reporting PAVF of the anterior spinal artery located at the cranio-cervical junction.

We decided to obtain a 50% NBCA-LUF to reach the pseudoaneurysmatic dilatation and to reduce the amount of reflux. The use of different embolization materials, as Onyx, was considered unsuitable for the risk of poor distal progression and of reflux. In relation to the small size of the feeder vessel, we avoided coils for the risk of not occlude the pseudoaneurysmatic dilatation and to induce the development of new feeder vessels. The surgical treatment was avoided because of the lack of experience of our neurosurgeons in the treatment of this pathology.

Learning Points/Take Home Messages

- PAVF of the cervicomedullary junction can cause haemorrhage in the basal cisterns and in the fourth ventricle.

- The administration of Nimodipine from the microcatheter into the anterior spinal artery can be useful to navigate the vessel.

- PAVF of the cervicomedullary junction, fed by branches of the anterior spinal artery, could be embolized with Glue.

Informed Consent: Written informed consent to the interventions, CT and the MR exams was obtained from all subjects in this study.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Case report

Cooled radiofrequency ablation technology for painful bone tumors

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Summary. Bone metastases are a common cause of cancer-related debilitating pain, especially when localized in the vertebral column and not responsive to standard treatment. In such cases, various treatment options are available; among these is Radiofrequency, whose role has been rapidly growing over the past few years. In this study, we used the innovative Osteocool RF Ablation System (Medtronic) on a patient with a painful bone metastasis localized in the 5th lumbar vertebra, with encouraging results. The radiofrequency ablation of bone metastases with palliative aim represents an excellent treatment option, as it is a minimally invasive and safe procedure, and can be repeated multiple times. (www.actabiomedica.it).

Keywords: radiofrequency, bone tumors, ablation, treatment

Introduction

After the lungs and liver, the skeletal system is the third most common localization of metastases, with around 70% of primary tumors originating from the prostate or breasts (1).

One of the more involved segments is the vertebral column, where around 70% of all bone metastases are localized (2); these can be either osteoblastic or osteolytic, single or multiple.

Although they are often asymptomatic, vertebral metastases are an important cause of morbidity and can decrease life quality; around 80% of patients experience serious pain before adequate treatment is planned (3, 4). Pain associated to bone metastases may be due to neural compression, pathological fractures or biological mechanisms which are not yet completely understood (cytokine production by the tumor, stimulation of nociceptors by periosteum stretching, nociceptor production by leukocytes) (5).

In case surgery cannot be performed, many types of palliative treatments are available: the most common therapies involve the use of analgesics such as bisphosphonates, but also external radiotherapy, cryotherapy and radiofrequency (3, 6). In particular, there has been a recent surge in the applications of

radiofrequency, whose indications include the treatment of benign primitive bone lesions (7) - most notably osteoid osteomas for which it represents the best treatment choice (8) - and the palliative treatment of bone metastases (7, 9); furthermore, it is also employed for coagulation and ablation during surgical procedures, and in all cases where conventional treatment is not indicated. As reported by Di Staso et Al. (10), radiofrequency and radiotherapy are not mutually exclusive, as RFA can be performed after RT to reduce eventual pain from bone metastases.

RFA systems are based on the flow of an alternating current through a probe positioned inside the lesion, resulting in tissue death by coagulative necrosis (11).

The aim of the study is to highlight advantages of bipolar radiofrequency systems internally cooled by water circuits in the treatment of bone metastases, with a particular focus on lesions localized in vertebral soma, as they often represent a treatment challenge.

Device Description

Bone radiofrequency devices have been studied for the treatment of benign bone tumors and for palliative care of bone metastases. Many different types are in commerce; at our Centre, we employ the Osteocool RF Ablation System produced by Medtronic, which consists of a bipolar coaxial probe containing a water cooling system which is inserted into the lesion through a osteointroducer. The advantage of a bipolar probe consists in the presence of both the active electrode and the grounding electrode on the same probe, as opposed to traditional bipolar systems which necessitate of two different probes (12). Moreover, bipolar systems can decrease the ablation time and power, and are less susceptible to the heat sink effect (11).

The internal water cooling system avoids carbonization of surrounding tissues by better dissipating heat and by enlarging the ablation area.

Moreover, if the recorded temperature exceeds a predetermined value, the system automatically adjusts the RF power in order to avoid eventual damage to surrounding organs (13), such as the spinal cord or nerve roots.

The generator produces 40w of power (20w for each channel), allowing the tip of the probe to reach and maintain a temperature of 70°C for a given period of time, thus letting the energy pass to the surrounding tissue and resulting in coagulative necrosis (8, 14). Additionally, additional probes capable of measuring the temperature of surrounding tissues can be independently connected to the system, so as to monitor critical areas such as nerve roots.

Once the ablation procedure is completed, the resulting void can be filled through the osteointroducer with a balloon kyphoplasty or a vertebroplasty, in order to support the pathological vertebral body and avoid its collapse.

Bone Lesions Treatment Indications

There are two main indications for radiofrequency: treatment of benign bone tumors and treatment of bone metastases (15). In the first case there is a curative aim: Santiago at Al. (8) reported that RFA of osteoid osteomas has a high success rate, with few complications and a short recovery time, and can therefore be considered the first-choice treatment for most osteoid osteomas localized in the vertebral column and pelvis.

For what concerns bone metastases, treatment often has a palliative aim (7) and is limited by the size of the lesion. A study by Thanos et al. (16) described the possible contraindications of RFA, which include a distance of less than 1 cm between the lesion and the spinal cord, lesions involving the posterior wall of vertebral soma, and lesions causing cortical destruction with involvement of surrounding soft tissues; however, positioning a thermocouple near the dural sac or the peripheral nerve roots reduces the risk of damaging nervous structures (13).

Moreover, during the same procedure it is possible to perform also a kyphoplasty or vertebroplasty. It is worth mentioning that a vertebroplasty is contraindicated in all patient who have a proven allergy to concrete, and in those with an interruption of the posterior wall of the vertebral soma because of the high extravasation risk (17), although the latter is a relative contraindication as it depends on the operator's experience (3).

Case Description

The procedure was performed on a 55-years-old male patient who had already been operated of a primitive lung tumor localized in the right superior lobe and had later developed a single bone metastasis in the 5th lumbar vertebral body, which caused severe pain and did not respond to common antalgic therapy nor to chemo-immunotherapeutic treatment. The lesion had a mixed ostesclerothic-ostheoblastic appearance and was confined to the vertebral body, without destruction of the posterior wall or infiltration of nerve roots (Fig. 1). The case was discussed by a multi-disciplinary team who evaluated the feasibility of the procedure, in particular whether it was possible to reach the tumor with the osteointroducer and the radiofrequency probe without damaging the surrounding structures, and assessed the haematochemical status of the patient and his coagulation pattern.

In consideration of the lesion's characteristics and of the procedure's aim, we utilized the Osteocool RF Ablation System (Medtronic).

An adequate ultra short antibiotic prophylaxis was administered before the procedure by injecting 2g of Cephazoline i.v.

The procedure was thoroughly explained and informed consent was obtained, then the patient was positioned on the table of an angiography platform (Philips Azurion) also capable to acquire a CT cone beam for lesion alignment. Once the patient was sedated with the anesthesiologist's support, the correct access point was located under angiographic guidance and a local anaesthetic (mepivacaine 2%) was injected to alleviate the discomfort caused by the osteointroducer and RF probe placement (Fig. 2).

With the help of a sterile hammer, a 13G osteointroducer was advanced in the cranio-caudal and latero-medial direction through the transverse process of the 5th lumbar vertebra. The CT cone beam showed the correct alignment of the lesion (18). After its placement, the osteointroducer remains in the same position for the whole procedure, as it is not only useful for the ablation procedure but it is also employed to obtain a preliminary bioptic sample to send to the laboratory for future histo-pathological comparison.

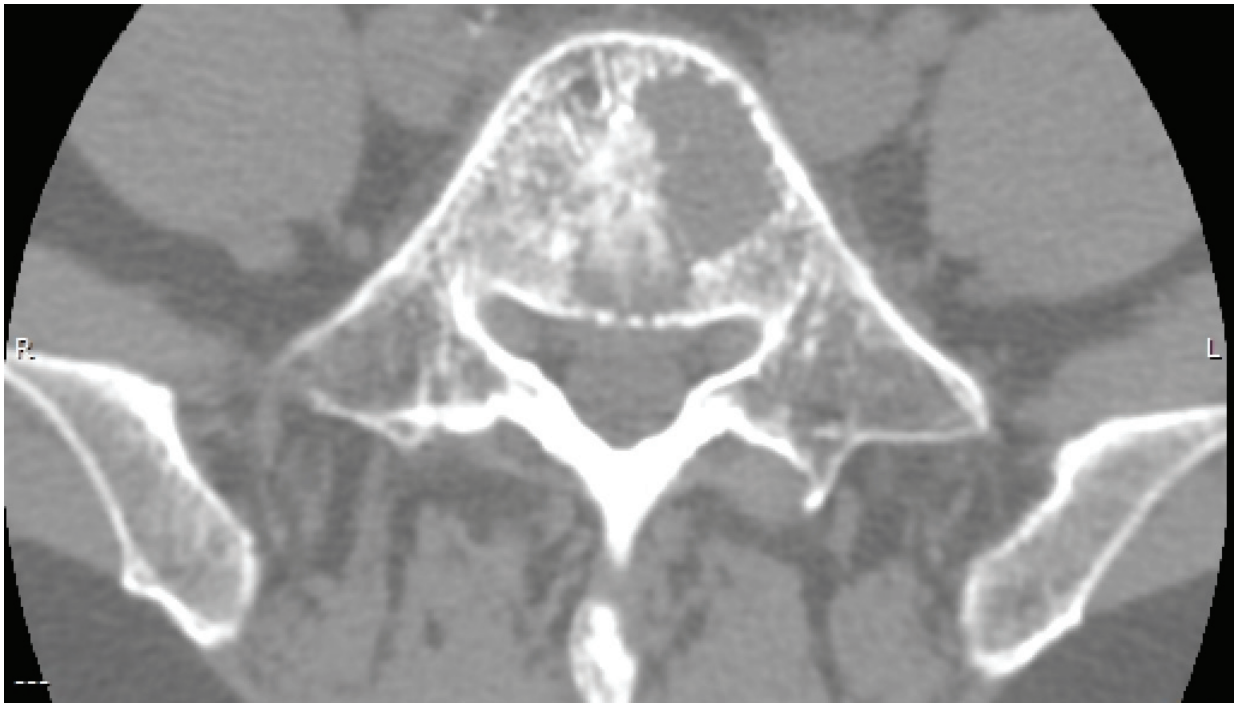

Fig. 1 Pre-procedural CT showing a predominantly osteolytic bone lesion in the soma of L5, with diameters of 27x19mm.

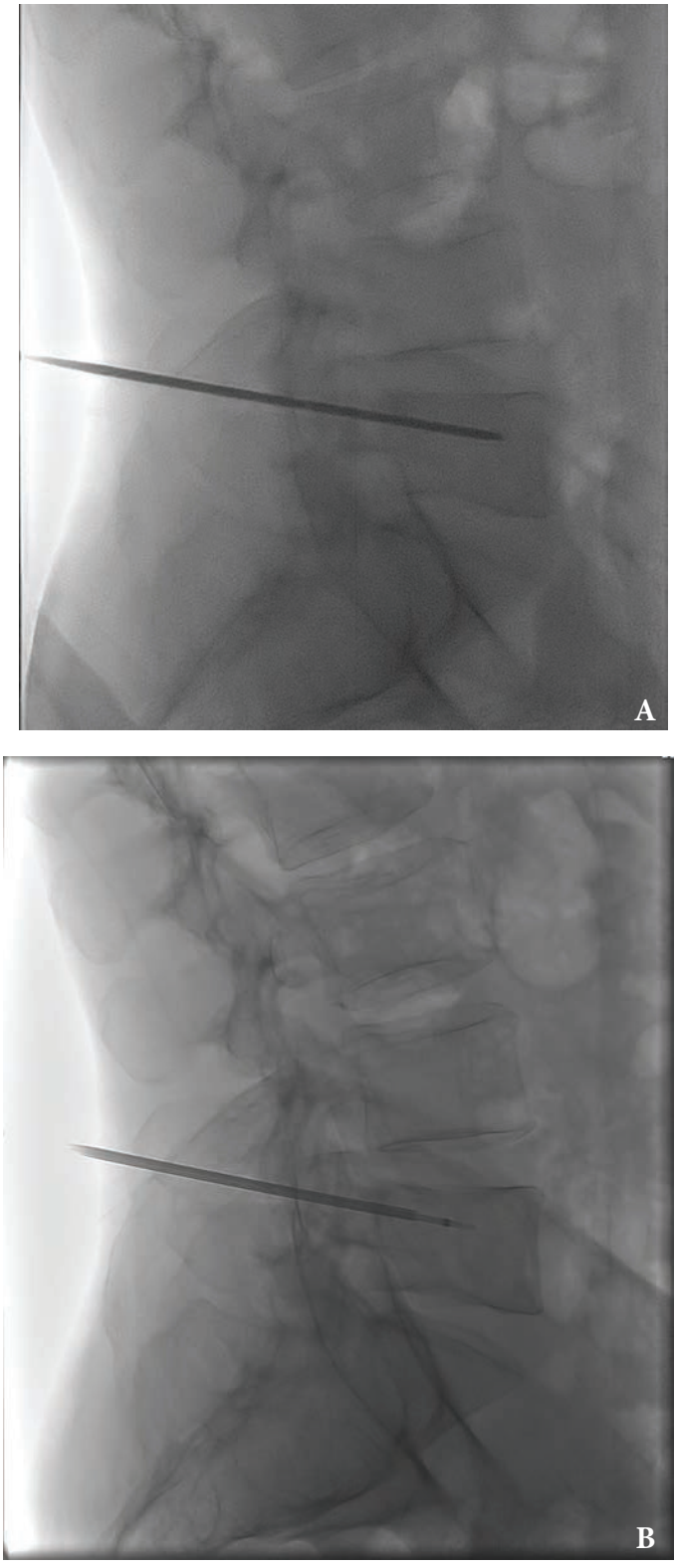

Fig. 2 Intraprocedural fluoroscopic image (latero-lateral projection) showing correct placement of the osteointroducer (2A) and radiofrequency probe (2B).

The ablation system consisted in a 40 W generator (20 w per channel) which can be connected to 2 radiofrequency probes and to 2 independent thermocouples for real-time temperature monitoring of the surrounding tissues.

The ablation was performed through a single bipolar probe with an active 7 mm tip with a diameter of 20G, resulting in an ablation area of 29x21 mm around the probe protruding 2.5 mm from the probe tip; a default ablation time of 6.30 minutes was necessary, as advised by the production company.

The radiofrequency energy is progressively transferred by the ablation system to the lesion until a temperature of 70° is reached and then maintained constant for the rest of the ablation time; the energy is regulated by the system according to the impedance encountered (2).

A 28G thermocouple was positioned into the epidural space near the posterior vertebral wall in order to measure the temperature outside the lesion to avoid damage to nervous structures; if the temperature exceeded 45°, the system would then stop the energy output.

After the procedure was over, the RF probe was removed and vertebroplasty was performed via the osteointroducer: 4 ml of concrete were injected under fluoroscopic guide. The CT cone beam demonstrated the success of the procedure and the absence of concrete spillage along the posterior vertebral wall (Fig. 3).

There was no periprocedural complication.

Already in the first hours after the procedure, the patient had a clear improvement of symptoms with a decrease in VAS (visual analogue scale) grading from 8 to 2.

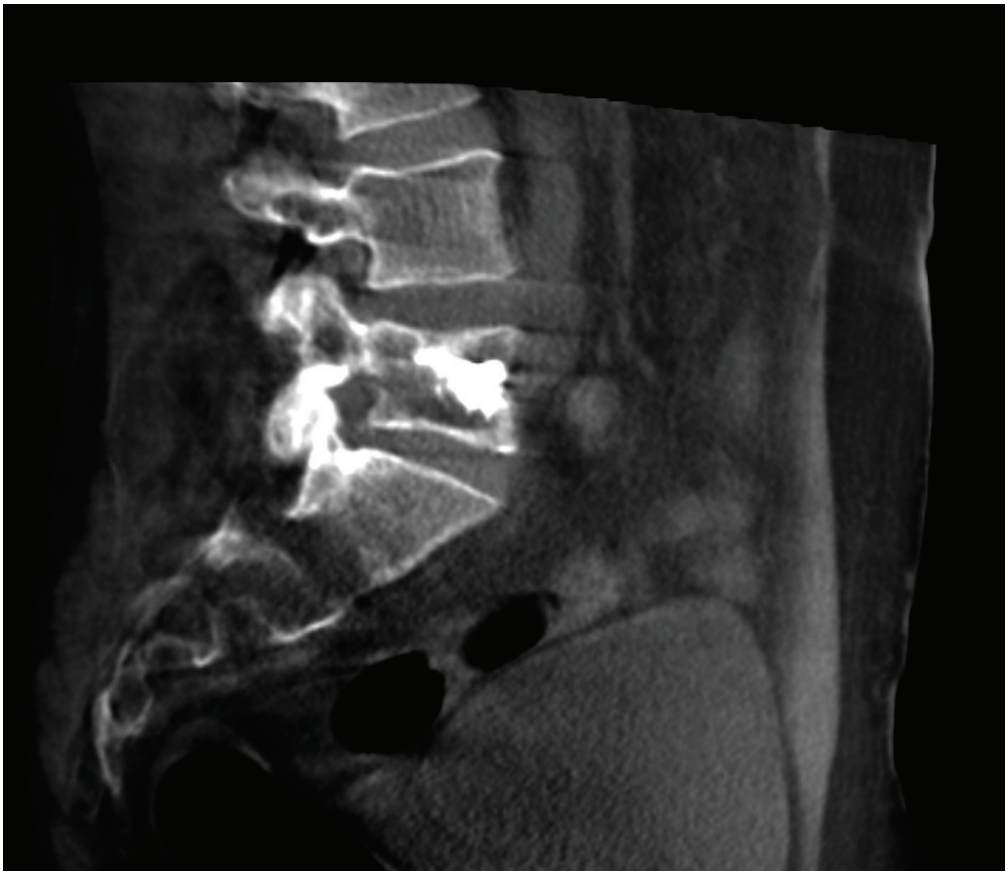

Fig. 3 Post-procedural cone beam CT showing successful vertebroplasty results with concrete injection in the 5th lumbar vertebra.

Discussion

Many studies in literature describe the possible applications of radiofrequency systems for curative treatment of benign bone tumors and palliative treatment of bone metastases (7, 8). Goetz et al. (19) reported successful employment of RFA in alleviating pain in patients with osteolytic metastases who did not benefit from standard therapies. Our study analyzes the efficacy of a new ablation system, which has considerable advantages over other commercially available devices.

In particular, many systems consist of monopolar probes and need either the application of a grounding electrode on the patient's skin or the use of a second separate probe in order to produce a dipole. On the contrary, the system we used consists of a single probe containing both the active and grounding electrodes, thus generating a dipole on a single probe; moreover, the internal water cooling system is able to avoid tissue carbonization and to increase the ablation area. Additionally, this RF generator allows the simultaneous connection of two RF probes in order to further enlarge the ablation area: in this case, with each probe introduced through a vertebral pedicle and their tips positioned 8-10 mm from each other, it is possible to create a large predefined ablation area.

Moreover, a great advantage is the possibility to perform RF procedures either alone or after failed RT procedures or simultaneously with RT. As described by Di Staso et Al. (10), RF associated with successive RT is safe and can significantly reduce cancer-related pain in patients with bone metastases, therefore decreasing the need for analgesics.

The reduction in pain has been documented by many authors with the help of VAS (visual analogue scale); in particular, a study by Nakatsuka et Al. (20) demonstrated a VAS reduction from 8.4 ± 2.4 to 1.1 ± 1.8 in a group of 13 patients with pain refractory to standard therapies. Goetz et Al. (19) reports good results of RFA on painful bone metastases, with a significant decrease in symptoms even in patients in which standard treatments failed.

In order to choose a RFA treatment, a multidisciplinary evaluation is mandatory, with a team of radiologists, oncologists and surgeons.

Possible complications include damage to underlying tissues, pulmonary embolism, thermal damage to nerve structure, damage to the spinal cord and nerve roots with risk of radiculopathy, paresis or paralysis; studies on animals demonstrated that damage to adjacent soft tissues depends primarily on bone cortex thickness, treatment length and distance between lesion and periosteum (7). However, Kam et Al. (3) reported that RFA utilization before vertebroplasty results in a thrombosis of paravertebral and vertebral plexi, thus reducing the embolization risk associated to the procedure itself.

Conclusions

Patients with bone metastases often have a poor quality of life and a considerable expenditure of both economic and human resources (medicines, assistance). The radiofrequency ablation system represents an excellent treatment choice in the palliative care of bone metastases as it is a minimally invasive and safe procedure (21), and can be repeated multiple times. Moreover, it does not exclude the possibility of a successive RT in case of treatment failure.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent to the CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Case report

Giant intracranial aneurysm following radiation therapy: literature review with a novel case discussion

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Summary. *Background:* The aim of this paper is to report the results of our review of the literature of published cases of intracranial aneurysms appearing after radiotherapy, and to present our case to add it to the current literature, in order to discuss the role of inflammation. *Methods:* We searched the PubMed database using combinations of the following MeSH terms: intracranial aneurysm, radiosurgery, radiotherapy, inflammatory changes in aneurysmal walls from 1967 to 2019. *Results:* 51 studies, for a total cohort of 60 patients, are described. The median latency between the radiation treatment and the diagnosis was 9,83 years, ranging from a minimum of 0,33 to a maximum of 33. The modality of rays' administration was variable, and the dosage ranged from a minimum of 12 grays to a maximum of 177,2 grays. The anterior circulation appeared to be more frequently involved, and the most compromised vessel was the internal carotid artery. Radiation-induced vascular diseases have already been described in literature as well as RT-induced cellular and structural changes such as necrosis, macrophage or mononuclear cell infiltration, and several data support the role of inflammation in the development and remodelling of intracranial aneurysms, that, on one hand, favours them and, on the other, is necessary to their healing after endovascular treatment. *Conclusions:* Our team suggested a new insight in the management of these vascular lesions, which corresponds to a lower threshold when deciding whether or not to treat, and a longer and stricter follow-up.

Keywords: aneurysm, Giant, radiation therapy, radiosurgery, intracranial aneurysm, changes in aneurysmal walls

Introduction / Background

During the past years, the use of radiation for both diagnostic and therapeutic purposes has largely increased. Moreover, thanks to advances in multidisciplinary treatment, life expectancy of cancer patients is also increasing. This allows the observation of long-term complications/consequences of patients that underwent radiotherapy (RT).

Radiation-induced vascular diseases have already been described in literature, with a focus primarily on occlusive stroke and atherosclerosis (1,2), but various articles have also reported the formation of intracranial aneurysms. Even if it is hard to state whether or not there is a direct correlation between the exposure to ionizing radiation and the formation of intracranial aneurysms, and no clear pathognomonic findings have been described up to date, different authors report similar findings from a histopathological point of view when analysing vessels and aneurysmal walls. These findings include well known RT-induced cellular and structural changes such as necrosis, macrophage or

mononuclear cell infiltration, intimal fibrosis, and intraluminal thrombotic material (3,4,5). In fact, there are several data supporting a role of inflammation in the development, remodelling, and rupture of intracranial aneurysms (IA), which add a further layer of complexity in IA pathogenesis (6,7). In this paper we report the results of our review of the literature of published cases of IA appearing after RT, and we present our case to add it to the current literature.

Methods

We reviewed the literature for published articles reporting IA documented via neuroimaging in patients that underwent RT. We searched the PubMed database using combinations of the following MeSH (Medical Subject Headings) terms: "intracranial aneurysm", "radiosurgery", "radiotherapy", "brain aneurysm and inflammation", "vessel wall imaging in IA", "inflammatory changes in aneurysmal walls", "ankylosing spondylarthritis brain aneurysm". We also conducted a research with Google Scholar with the same MeSH terms. We considered only full papers and excluded abstracts. We did not exclude papers based on publication language.

Results

We chose to include 51 studies, for a total cohort of 59 patients plus an additional one described here. Age, sex, type of lesion requiring radiation therapy, vessel from which the aneurysm arose, latency between first radiation and diagnosis of aneurysm, presentation, dosage and modality of radiation treatment were registered. Mean age at diagnosis was 44,86 years (Min: 5; Max: 83), comprehending 38 females and 22 males. The most common lesion was nasopharyngeal carcinoma, accounting for up to 13 cases, followed by 8 medulloblastomas, 6 gliomas (5 LGG and 1 HGG), 6 vestibular schwannomas, 4 optic gliomas, 4 adenomas, 4 arteriovenous malformations, 3 craniopharyngiomas, 3 meningiomas, 2 metastases, 2 Ewing sarcomas, one germinoma, one chordoma, one chondrosarcoma, one retinoblastoma, and one lymphoma. Generally, the involvement of the anterior circulation appeared to be more frequent: the vessel from which the aneurysms arose was mostly the internal carotid artery (ICA), accounting for 25 cases, followed by the middle cerebral artery (MCA) and the anterior cerebral artery (ACA), each affected in 7 cases, and the anterior communicating artery (ACoA), implicated in 5 cases. Instead, the aneurysm arose from the anterior inferior cerebellar artery in 7 cases, from the posterior cerebral artery (PCA) in 6 cases, from the basilar artery in 3 cases, from the posterior inferior cerebellar artery (PICA) in 2 cases, and from the superior cerebellar artery (SCA) in only one case. In 39 of the cases the diagnosis was made following the rupture of the aneurysm. The median latency between the radiation treatment and the diagnosis was 9,83 years, ranging from a minimum of 0,33 to a maximum of 33 years. The modality of rays' administration consisted in involved-field radiation therapy (IFRT) in 29 cases, whole-brain radiation therapy in 12 cases, gamma-knife in 11 cases, stereotactic radiotherapy in 4 cases, and brachytherapy in one case. The dosage ranged from a minimum of 12 grays to a maximum of 177,2 grays. (Tab. 1)

Case Presentation

In this paper we present the case of a 69-year-old female who referred to our Institution in April 2017 because of diplopia, left eye ptosis, and anisocoria with the left pupil wider than the right one. Neurological examination showed no other symptoms. On admission, the patient underwent brain Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI) with and without contrast, and MR Angiography (MRA), showing the presence of an aneurysm (27 x 20 mm) of the supraclinoid segment of the left carotid artery (Fig1b). The multidisciplinary decision-making process brought us to recommend endovascular treatment (ET).

The patient's medical history was characterized by ankylosing spondylarthritis treated with methotrexate and adalimumab, both reduced few months prior to hospitalization. In 2005, the patient underwent surgery for the treatment of gastric cancer, followed by chemotherapy with a negative follow-up. The patient

Table 1. Showing the results. HGG: high grade glioma; LGG: low grade glioma; NF: nasopharyngeal; MET: metastasis; OG: optic glioma; VS: vestibular schwannoma; RB: retinoblastoma; AVM: arteriovenous malformation.

ARTICLE	AGE	SEX	LESION	VESSEL	LATENCY	RUPTURE	GRAY	TYPE
Aichholzer et al., 2001	11	M	LGG	ACoA	11	YES	54	IFRT
Akai et al., 2015	65	M	AVM	MCA	15	NO	40	GKS
Akamatsu et al., 2009	83	F	VS	AICA	8	YES	12	GKS
Aoki et al., 2002	20	F	OG	ICA	19	YES	90	IFRT
Benson and Sung, 1989	21	M	MEDULLO	PCA	10	YES	47,2	WBRT
Benson and Sung, 1989	31	F	MEDULLO	PCA	17	YES	45	WBRT
Benson and Sung, 1989	14	M	MEDULLO	PCA	9	YES	50	WBRT
Casey et al., 1993	65	F	LGG	MCA	3,5	YES	60	IFRT
Casey et al., 1993	44	M	AVM	MCA	21	YES	40	WBRT
Chen et al., 2004	55	M	NF CARCINO	ICA	0,33	YES	81,8	IFRT
Cheng et al., 2001	59	M	NF CARCINO	ICA	7	YES	120	IFRT
Cheng et al., 2008	57	M	NF CARCINO	ICA	3	YES	128,4	IFRT
Cheng et al., 2008	37	M	NF CARCINO	ICA	2	YES	120	IFRT
Dho et al., 2017	27	M	AVM	MCA	10	YES	36,5	GKS
Endo et al., 2011	62	M	ADENOMA	ICA	17	YES	90,2	GKS
Fujita et al., 2014	29	M	ERWING	ICA	4	YES	162	SRS
Fujita et al., 2014	61	M	MENINGIOMA	ICA	11	YES	59,6	SRS
Gabriel et al., 2004	60	F	ADENOMA	ICA	29	NO	--	BRACHY
Gomori et al., 1987	47	M	NF CARCINO	BASI-LAR	3	YES	--	IFRT
Gonzales-Portillo and Valdivia, 2006	12	M	RB	ACA + ICA	12	YES	103	IFRT
Gulati et al., 2014	30	M	NF CARCINO	ACA	8	YES	60	IFRT
Holodny et al., 1996	62	F	MET	BASILI	7	YES	31,8	WBRT
Huang et al., 2001	19	F	AVM	ACA	9	NO	37,5	SRS
Hughes et al., 2015	57	F	VS	AICA	10	NO	39	GKS
Huh et al., 2012	77	F	CHONDRO	ACoA	8	YES	59,4	IFRT
Jensen and Wagner, 1997	9	M	MEDULLO	ACA	0,8	YES	48	WBRT
John et al., 1993	55	M	NF CARCINO	ICA	5	YES	66	IFRT
Kamide et al., 2016	17	M	MEDULLO	PICA	8	NO	55,8	WBRT
Kellner et al., 2015	68	F	MENINGIOMA	SCA	10	NO	16	GKS
Lam et al., 2001	47	M	NF CARCINO	ICA	8	YES	116	IFRT
Lam et al., 2001	55	M	NF CARCINO	ICA	7	YES	66	IFRT
Lam et al., 2001	65	M	NF CARCINO	ICA	12	YES	111	IFRT
Lau and Chow, 2005	53	M	NF CARCINO	ICA	12	NO	60	IFRT
Liu et al., 2009	5	M	CRANIOFAR	ICA	2	NO	58,8	IFRT
Louis et al., 2003	61	M	LYMPHOMA	ICA	27	NO	43,5	IFRT
Mak et al., 2000	72	F	NF CARCINO	ICA	6	YES	--	IFRT

ARTICLE	AGE	SEX	LESION	VESSEL	LATENCY	RUPTURE	GRAY	TYPE
Maruyama et al., 20004	15	M	OG	ACA	14,6	YES	110	IFRT
Matsumoto et al., 2014	39	M	GERMINOMA	ICA	31	NO	60	--
Moriyama et al., 19924	51	F	ADENOMA	MCA + PCA	1	YES	50	IFRT
Murakami et al., 2002	30	M	CRANIOFAR	PCA + BASIL	19	NO	50	IFRT
Nanney et al., 2014	38	M	MEDULLO	PICA	33	NO	79,66	WBRT
Nishi et al., 1987	57	M	ADENOMA	ICA	9	NO	50	IFRT
Parag et al., 2016	40	F	LGG	MCA	3	NO	60	IFRT
Park et al., 2009	74	M	VS	AICA	5	YES	18	GKS
Pereira et al., 2002	19	F	CRANIOFAR	ICA	5	NO	54	IFRT
Sciubba et al., 2006	24	M	MEDULLO	MCA	15	NO	55,8	WBRT
Scodary et al., 1990	59	M	LGG	ACA	12	YES	65	WBRT
Sunderland et al., 2014	60	F	VS	AICA	10	YES	25	GKS
Takao et al., 2006	69	F	VS	AICA	6	YES	18	GKS
Tamura et al., 2013	29	M	ERWING	ICA	4	YES	177,2	IFRT
Twitchell et al., 2018	37	M	LGG	ACoA	12	NO	--	WBRT
Twitchell et al., 2018	38	F	CHORDOMA	PCA		YES	--	--
Vogel et al., 2011	16	F	OG	ICA	1	YES	54	GKS
Woodin and Phatouros, 2018	53	M	NF CARCINO	ACoA	2	NO	66	IFRT
Wu et al., 2014	68	F	MET	ICA	3	NO	60	IFRT
Wu et al., 2016	17	M	MEDULLO	AICA	12	YES	132,5	WBRT
Yamaguchi et al., 2009	73	F	VS	AICA	6	YES	50	SRS
Yoon et al., 2011	57	M	HGG	ACA	0,8	YES	59,4	IFRT
Yucesoy et al., 2004	48	F	OG	ACoA	6	NO	--	--
Present study	69	F	MENINGIOMA	ICA	18	NO	60	GKS

also underwent surgery in 1999 for an incomplete removal of a left tentorial meningioma; further treatment of the lesion was achieved with gamma-knife at the isodose of 55%. Neuroimaging follow-up showed, up to 2009, the optimum outcome regarding the residual meningioma and the absence of any vascular malformation (Fig1a).

Endovascular Treatment (ET)

Due to the absence of headache and of bleeding signs in the pre-procedural neuroimaging, we decided to treat the patient endovascularly with Flow-Diverter and coils. Administration of antiplatelet drugs (ASA 300 mg/die and Plavix 75 mg/die) was started five days before the procedure.

Under general anaesthesia, in triaxial technique (Vista Brite Tip 8F 95cm J&J and Neuron 6F 105cm Penumbra), the M2 segment was reached with a microcatheter Headway 27 (Microvention) and Traxcess microwire 0.014 (Microvention). Due to the difficulty of reducing the microcatheter loop, we changed it with a Scepter XC 4x11 balloon (Microvention). Inflating the balloon, we were able to straighten the system. Then, after deflating the Scepter, we removed it and changed it with a microcatheter Headway 27. Thus,

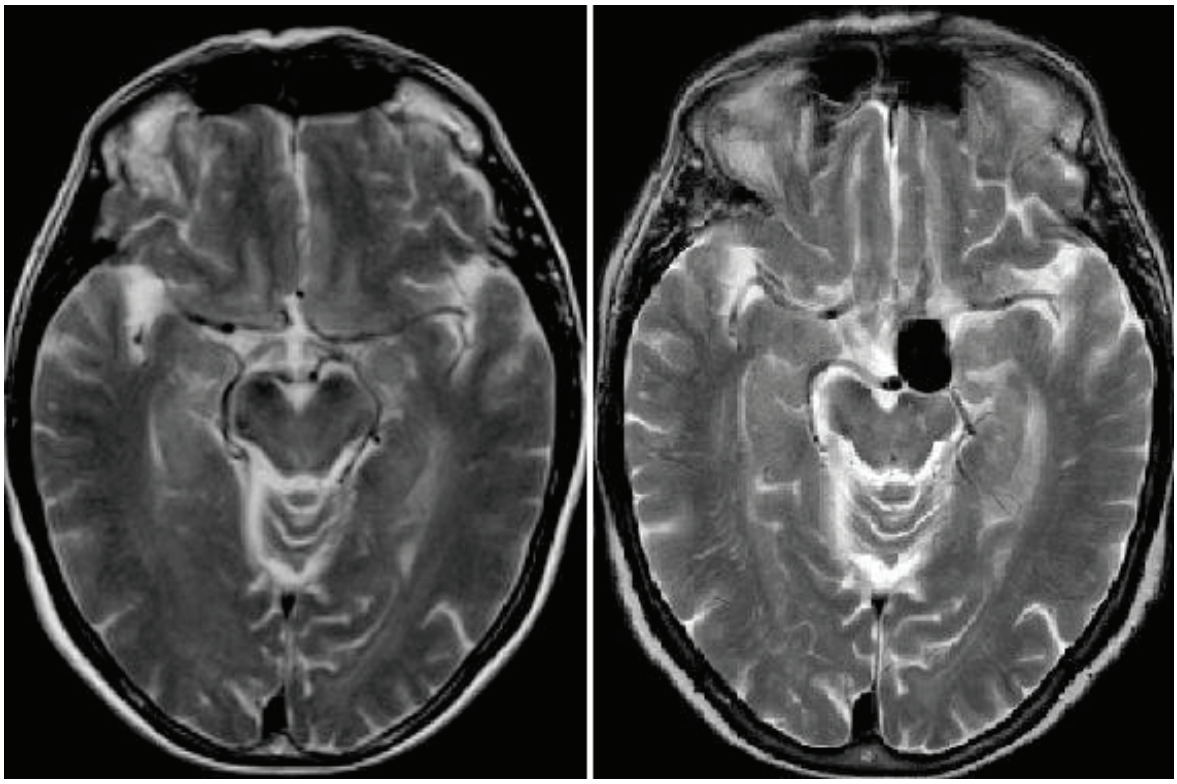

Figure 1. a) T2-weighted image in 2009. No presence of Aneurysm in the left carotid artery; b) T2-weighted image in 2017. Giant Aneurysm in the left carotid artery

the microcatheter Headway Duo (Microvention) with Traxcess 0.014 microwire (Microvention) was placed inside the aneurysm. A Fred stent 5x26 was deployed at the supraclinoid and intracavernous segments of ICA. Finally, in "jailing technique" we put coils into the aneurysmal dilatation (Fig2).

Post-procedural observation showed no further new neurological deficits.

Two days after treatment, the patient suffered from a lipothymic episode with head trauma. A brain CT scan revealed a left sylvian subarachnoid haemorrhage (SAE) (Fig3). No sign of recent haemorrhage was detected in the perimesencephalic space, whereas emergency angiography showed the stability of the treated aneurysm. The sylvian space bleeding was interpreted as a possible periprocedural complication due to a very distal vessel perforation or as a post-traumatic haemorrhage, and not as a rupture of the aneurysm. Therefore, given the good neurological state, the follow-up was observational, and a brain CT scan obtained 10 days later showed complete resolution of the haemorrhage.

Five months after the successful endovascular treatment, the patient referred again to our Institution and was subsequently hospitalized. Brain MRI and MRA showed once again stability of the treated aneurysm, with signs of thrombosis in the aneurysmal sac, aneurysmal wall enhancement (AWE), enlarged ventricles, and signs of transependymal oedema. Because of the concurrent presence of symptoms related to hydrocephalus, such as gait impairment, together with the previously known ptosis and anisocoria, a ventriculo-peritoneal shunt with adjustable valve was placed (VPS) (Polaris - Sophisa set at 150 mmH_2O).

Radiological and clinical 3-year follow-up showed smaller ventricles, absence of transependymal oedema, and regression of the neurological deficits: isocoria, normal eyelid movements, and no gait impairment. At

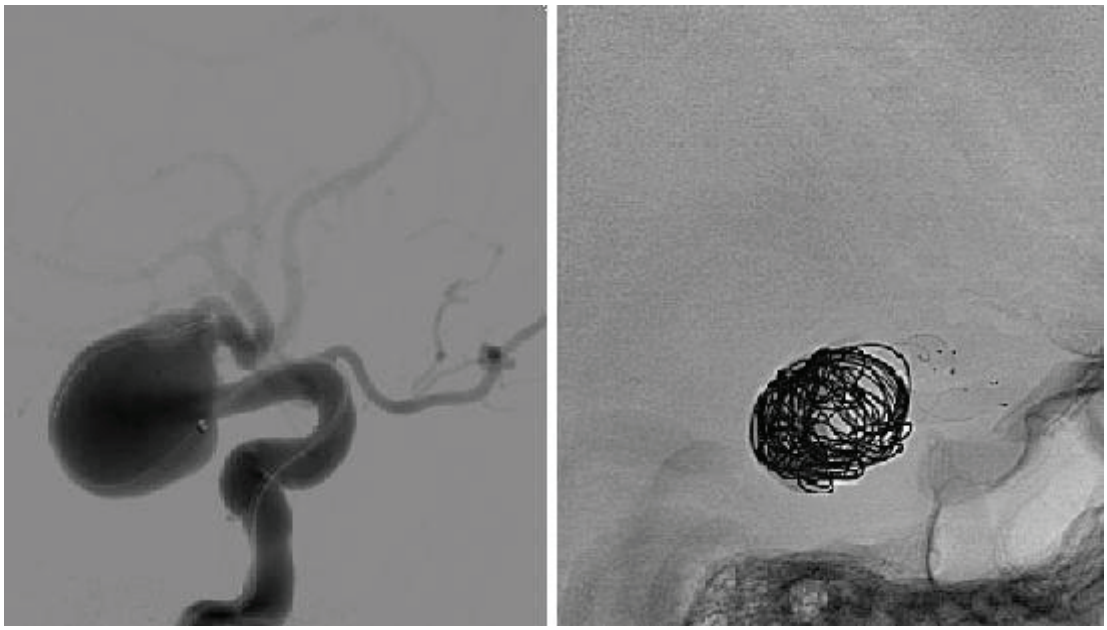

Figure 2. a) DSA lateral view. Working projection shows the loop of the microwire inside the Aneurysm; b) DSA lateral view shows the deployment of the Fred stent and the coils inside the Aneurysm

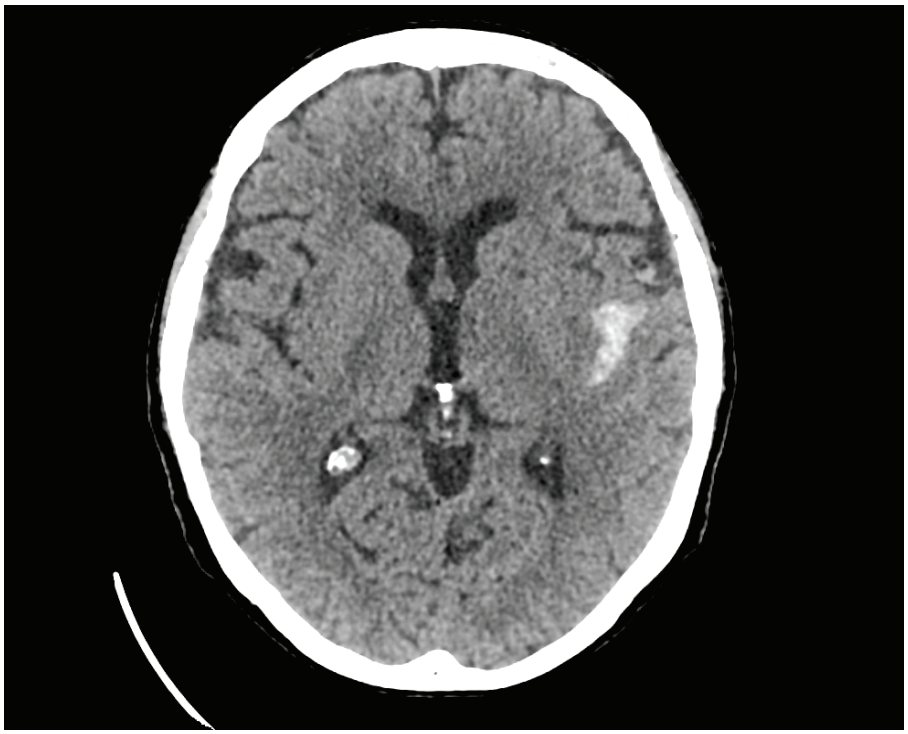

Figure 3. CT scan revealing left sylvian SAE

angiographic follow up, the treated aneurysm resulted completely excluded, the indirect sign of inflammation, AWE, was also reduced, and the aneurysmal sac was completely filled with coils and thrombotic material (Fig4a and 4b).

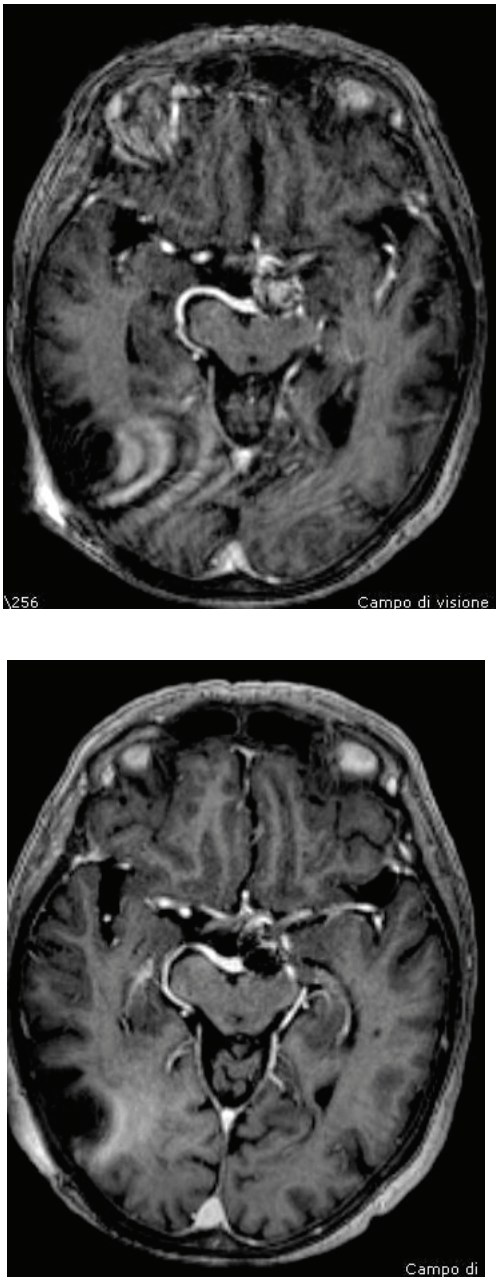

Figure 4. a) T1-weighted image in 2017. The enhancement inside the Aneurysm is the sign of inflammation; b) T1-weighted image in 2020. Strong reduction of the enhancement inside the Aneurysm and strong improvement of neurological symptoms

Discussion

Vernooij et al. report an incidence of stenoocclusive changes after RT of 1.8% (9), while Omura et al. report an incidence as high as 19% (10). The first case of IA following RT was reported in 1967, and since then few case reports and very short case series have been described. Adib et al. underline how the problem of radiation-induced aneurysms could be at the same time underreported, because of the cease of the novelty, and overreported, because of the unique type of presentation. Therefore, the real incidence of aneurysms emerging after RT is yet to be established, but a recent nationwide study conducted over a 10-year follow-up found that RT was a significant risk factor for IA development (11).

Cerebral aneurysms that arise in previously irradiated fields appear to be more susceptible to rupture; this consideration must be taken into account in the decision-making process when facing an incidental aneurysm. Although there is no clear causal connection between RT and the formation of IAs, some authors hypothesize that the integrity of the parent artery wall is degraded by radiation, making it more vulnerable to shear stress (5). In addition, histopathological examinations showed changes in the cellular composition of irradiated vessels. Lubimova and Hopewell demonstrated reduction in endothelial cells within 24 hours of radiation in a rat brain irradiated with 25Gy (7). Another study showed how large cultures of endothelial cells exposed to radiation were more likely to adhere to neutrophils and platelet cells (8). Endothelial dysfunction is related to IA formation in experimental models, and partial or total de-endothelialisation is associated with human IA rupture (12). Chronic inflammation has become understood as an important phenomenon in IA wall pathobiology (13), with a role in probable biological processes leading to IA formation, growth and rupture.

Inflammation is a proapoptotic state, but chronic inflammation seems to have multiple functions in IA wall, favouring both IA wall degeneration and reparative mechanisms.

Radiation may also induce an inflammatory cascade, including the release of cytokines and growth factors necessary for tissue healing (14).

The inflammation of the aneurysmal sac, which is considered a sign of instability, is common in aneurysms that arise following radiotherapy. It appears in fact that common denominators in the histopathological analysis of these aneurysms are the presence of active macrophages, neovascularization and decreased elastin (3,4,5).

Several studies have suggested that aneurysmal wall enhancement (AWE) on MRI may help in identifying unruptured intracranial aneurysms with a higher risk of rupture, since aneurysms exhibiting AWE have been shown to be significantly more prone to be unstable than those which do not display it (15,16,17). Recent systematic review and meta-analysis have demonstrated that aneurysms which demonstrate AWE are significantly more likely to be unstable than those which do not exhibit wall enhancement (18).

In our case, even if a histopathological examination was not achievable due to the chosen treatment, the indirect sign of the aneurysmal wall inflammation, which is represented by the AWE (17), was present at the MRI study right after treatment, and was significantly reduced after treatment during the 3-year follow-up.

It should however be mentioned that ET could have local or global intracranial effects. Early AWE was previously reported to likely represent the normal healing process of early acute inflammatory reactions (19). AWE is a phenomenon that in most cases remains stable over years (20,21), and several studies conclude that it should be considered an expected post treatment finding (19,20,22).

It is interesting to notice that, in our case, symptoms appeared only few months after the patient's immunosuppressant therapy for the treatment of spondylarthritis was reduced. The MRI acquired after the ET but before the placement of VPS showed effects of chronic inflammation: the aneurysmal sac was filled with thrombotic material and enhanced after administration of gadolinium; the symptomatic hydrocephalus with enlarged ventricle and the transependymal oedema were also registered as effects of chronic inflammation (19).This case is peculiar because the patient presented a chronic systemic proinflammatory state on top of which the radiating therapy added its effects locally, resulting in a giant aneurysm and in the further development of hydrocephalus. In support of our thesis, the clinical and radiological findings were recorded only few months after the patient's immunomodulating therapy was reduced, and they were found to be significantly reduced after ET when corticosteroid therapy was reintroduced (20). The inflammatory process happening inside the treated aneurysm, induced by the presence of the flow-diverter, permits the healing of the aneurysm; therefore, systemic immunosuppressive therapy could potentially interfere with and favour the healing process. On the other hand, when a chronic inflammatory state is present, and an RT-induced aneurysm is detected, corticosteroid drugs could find a use in the follow-up of these patients. We are well aware that a single case does not allow to obtain an ultimate truth, but it is enough to raise doubts and ask questions.

Conclusion

Different theories have incorporated a combined explanation for IA formation, that includes haemodynamic stress, endothelial dysfunction, and inflammation (15,23,24), which all contribute to the production of the pro-inflammatory phenotype. Intracranial aneurysms that arise from previously irradiated fields are an uncommon long-term complication when compared to other vascular issues such as stenosis or atherosclerosis. These aneurysms are particularly fragile and tend to have a higher risk of rupture, and therefore a more dramatic type of presentation. Thus, it is of primary importance to warrant special attention to RT-induced aneurysms when diagnosed. Our team suggested a new insight in the management of IAs, which corresponds to a lower threshold for treatment indication of these incidental unruptured aneurysms, and a longer and stricter follow-up, moreover given the high level of wall instability associated with the already described inflammation state a peri-procedural steroid administration would be advisable. The decision of the optimal treatment, either surgical or endovascular, should be done case by case.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards

of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Written informed consent to the interventions, CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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