

Appendix I

Radiological classification of pseudotumors

Pseudotumors can be detected by three types of radiological studies: MRI, CT, and ultrasound. They have been classified by radiological studies and in particular by metal artifact reduction sequences (MARS) MRI methods, such as multiacquisition with variable-resonance image combination (MAVRIC), slice encoding for metal artifact correction (SEMAC), short inversion time inversion-recovery (STIR), and view-angle tilting (VAT), usually performed before any tissue is available for histological analysis at implant revision time, unless the patient is subject to a US guided core needle or arthroscopic synovial biopsy.

Three MRI classifications have been proposed in the literature [1-3] which have been compared in a study performed on a MoM THA with a 38 mm fixed size femoral head [4, 5]. Other MRI studies of the pseudotumors by a single group of investigators have also provided features of pseudotumors with variable descriptive terms instead of a classification and correlated with histological ALTR/ARMD grading systems [6-8] and also with visual assessment of implant wear [9]. Their rationale for not using a classification has been the use of a data construct applied to machine learning (random forest) to predict the outcome for specific patients based on various MRI features and to be dynamic to a continuous set of new cases uploaded into the system [9]. A CT scan-based classification has also been developed [10] and good sensitivity and specificity for detection of pseudotumors with ultrasound has also been reported [11, 12]. The MRI and CT classifications and the various features of the pseudotumors used in other studies are summarized in [Table 1](#).

Table 1 MRI and CT classification of ALVAL

MRI Grading System	Description
Anderson (2011)	
A	Normal or acceptable seromas and small hematomas
B Infection	Fluid filled cavity with high signal T2 wall; inflammatory changes in soft tissue bone marrow edema
C1 Mild MoM disease	Periprosthetic soft tissue mass <5cm; no hyperintense T2W fluid signal or fluid-filled cavity
C2 Moderate MoM disease	Periprosthetic soft tissue mass >5cm or: 1. Muscle atrophy or edema in any muscle other than short external rotators; 2. Bone marrow edema: hypertense on short T1 inversion recovery (STIR)
C3 Severe MoM disease	Fluid filled cavity extending through deep fascia, tendon avulsion, intermediate T1W soft tissue cortical or marrow signal, fracture
Hauptfleisch (2012)	
Type 1	Thin-walled cystic mass <3mm
Type 2	Thick-walled cystic mass >3 mm
Type 3	Predominantly solid

Matthies (2012)

1 Thin walled	Fluid like: T1-hypointense T2-hyperintense [fluid] Shape flat: walls mainly in apposition
2a Thick walled/irregular	T1-hyperintense T2-hyperintense [proteinaceous] Shape: Not flat with >50% walls not in apposition
2b Thick walled/irregular	Atypical fluid: T1-hyperintense T2-variable [solid]
3 Solid mixed signal	Any size low signal T2 [Metallic Debris?]

Hayter (2013)

Synovitis volume: Fluid, Debris, Mixed, Other
Osteolysis volume: Femur, Acetabulum, Both
Extracapsular Disease volume: Fluid signal, Intermediate to low signal
Neurovascular compression: femoral, sciatic, obturator

Nawabi (2014)

Synovitis (volume and synovial thickness): fluid, solid, mixed
Osteolysis: areas of osseous resorption of intermediate or low intensity signal
Skeletal muscle disruption, tendon involvement, neurovascular compression

Burge (2014)

Synovitis (volume and thickness): fluid (hypertense signal), solid (intermediate signal), mixed (combined signal) and capsular dehiscence with decompression
Osteolysis (volume): well-margined areas of osseous resorptions of low and intermediate signal surrounding the femoral and acetabular components
Presence or absence of extracapsular metal debris as deposits of low-signal intensity
Evaluation for local lymphadenopathy and neurovascular impingement

Koff (2017)

	Synovial thickness and volume Osteolysis volume
Synovitis	
Normal	Thin capsule with low signal intensity
Mild	
ALTR	Thickened, hyperintense capsule +/- poor zone of demarcation from soft tissue/muscle indicative of necrosis
Metallosis	Low signal intensity deposits intra or extracapsular
Polymeric	Foci of particulate, intermediate signal intensity intra or extracapsular
Infection	Lamellated synovial lining with pericapsular edema

CT Grading System		Description	
Boomsma (2015)			
A	I	Normal	Capsule thickening up to 6 mm
	II	Reactive	Capsule thickening >6 mm without bulging or exceeding neck of implant and without eccentric capsule enlargement
B	III	MoM disease (Mild)	Bulging capsule, anterior and posterior
C	IV	MoM disease (Moderate)	Eccentric capsular enlargement, predominantly inferomedial of the head
	V	MoM disease (Severe)	Bursitis mimicker with extensive filling of subtrochanteric bursa and/or iliopsoas bursa

The rationale of all the classifications has been to provide staging or grading of these reactive proliferations as a prognostic indicator for continuous clinical observation (mild), elective revision (moderate), and urgent revision (severe). All these studies are difficult to compare because they are not homogeneous for design, implant selection, MRI technology with different metal artifact reduction, correlation with histological analysis of the periprosthetic tissue, and implantation time of each case when the radiological examination is performed which can affect the MRI features of the reaction. All MRI and CT classifications for MoM THA and HRA pseudotumors have been performed on cross sectional studies and are based in large part on their appearance (cystic, solid, mixed). Threshold values for size (5 cm in one MRI classification) and thickness of the capsular wall (3 mm in one MRI and 6 mm in the CT classification) have been used as parameters for grading of severity, and features of the T1/T2 fluid signal when present for symptomatic and asymptomatic patients as well. The main features of MRI studies associated with prediction of severe/advanced soft tissue reaction identified with the acronym ALVAL have been found to be synovial thickness and synovial volume measured by manual segmentation from a method of MARS, coronal multiacquisition variable-resonance image combination (MAVRIC) or axial fast spin echo (FSE) images, although no threshold value for either category can be provided for the assessment of individual cases [7]. The features used either for classification or comprehensive analysis with histological correlation can vary during the implantation time. These changes can be explained at least in part by an increased amount of necrotic cell debris exfoliated in the synovial fluid and changes in thickness of the pseudocapsular/neosynovial wall due to increasing accumulation of the macrophage/lymphocytic infiltrate, accumulation of blood products secondary to hemorrhage, and invaginations of the neo-synovial membrane with formation of pseudocysts of variable size.

It is uncertain if the thickness of the capsular/neo-synovial wall and total volume of the pseudotumor can be considered the best parameters for the grading of severity of Type II pseudotumors, because if this type becomes predominant tissue necrosis and large fluid collection would occur quite infrequently. As a result, these parameters would not be useful for predicting the development of clinically significant bone involvement by macrophage infiltrate (aseptic loosening/osteolysis).

The identification of soft tissue necrosis by MRI examination is an important finding which often requires implant revision with removal of the damaged tissue and if present in cases of the same implant class or the same implant model, provides valuable information also to regulatory authorities and regional and national registries for the immediate monitoring, precautionary withdrawal, and eventual recall of the implant from the market. A noteworthy example is represented by the occurrence

of lymphocytic predominant ALTR/ARMD in the non-MoM CoCr DMNTHA configuration which was first reported in a short stem model in 2012 [13] and turned out to be remarkably similar to another short and long stem model reported in 2015 [14, 15], highlighting a problem of the implant configuration/composition to some extent independent from the manufacturer which could have been addressed earlier through a web based system of information sharing, potentially sparing thousands of patients worldwide from implant related complications and allow considerable savings to the health care system and to the implant manufacturing industry for litigation-related costs.

At last, a major pitfall of the three MRI and the CT classifications presented in [Table 1](#) is that there is no reported staging or grading of the osseous component of the ALTR/ARMD (bone necrosis) and also invasion by macrophage infiltrate (osteolysis) which develops more slowly and can become clinically significant and symptomatic only after many years of implantation time. The evaluation of osteolysis as a clinically relevant part of ALTR/ARMD has been assessed in detail in MRI studies with analysis based on pseudotumor features over classification and in which the volume of osteolytic areas is measured as the one of the soft tissue components by a method of manual segmentation from the coronal MAVRIC or FSE images [7-9]. It could become an important tool for the evaluation of late onset ALTR/ARMD in longitudinal studies of MoM LHTHA and MoM HRA cohorts, especially if serum levels of Co and Cr are raising and/or the patients become symptomatic.

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