WHOLE-BODY INTEGRATED IMAGING FOR MULTIPLE MYELOMA: THE GOLD STANDARD

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ABSTRACT

The article aims to describe the study protocols of multiple myeloma with different imaging techniques. The guidelines of the major scientific reference societies for multiple myeloma - IMWG (International Myeloma Working Group) and NCCN (National Comprehensive Cancer Network) - provide for the study of CT WB, RM WB and PET / CT, which have completely outclassed traditional radiology. Each method contributes to acquiring an added value in the work up and follow up of patients suffering from multiple myeloma.

INTRODUCTION

In the world, the second most hematological cancer is the multiple myeloma whose costs are so substantial. The main features which make the cost increase are medication and hospital admissions (transplant, chemotherapy and skeletal fractures). Over the years, thanks to the evolution of the imaging methods, several protocols have been studied with the aim of diagnosing bone injuries early to reduce the incidence of pathological fractures. In 2020 the NCCN National Comprehensive Cancer Network published new recommendations for the imaging of this disease using different methods, which are: TC, RMI and PET/CT.

The multiple myeloma is the second most common hematologic cancer, caused by an alteration of a plasma cell clone of the bone marrow which begins to proliferate uncontrollably. The resulting secretion of a large quantity of immunoglobulins (above all IgG e IgA) and cytokines result in osteolysis, hypercalcemia or kidney failure. As a matter of fact, the clinical manifestations of the disease are characterized by high level of calcium, kidney failure, anemia and frequently painful bone involvement (with lithic lesions and osteopenia) predominantly in the axial and proximal appendicular skeleton, which can be summed up by the acronym CRAB (Calcium, kidney failure, anemia, bone injury). Although it accounts for only a relatively small percentage of all cancers, the costs associated with managing multiple myeloma are substantial. The available studies focus mainly on health care costs. According to a study published in 2013, in which the costs of treatment were analyzed on 236 patients (39 asymptomatic, 17%; 29 symptoms of autologous stem cell transplantation, 12%; 105 symptomatic receiving drugs, 44%; 63 plateau/remission, 27%) the average cost reached 19,267.1 - 25,078.6 (asymptomatic, 959.3 - 1091.6; symptomatic receiving drugs, 21,707.8 - 21,785.3; symptomatic treatment with autologous stem cell transplantation, 59,243.7 - 24,214.0; plateau/remission, 8130.7 - 15,092.5). The factors which make the total cost of the disease increase were

medicines and hospital admissions (46.1% and 29.4%, respectively). The cost of hospitalization funded by the Italian National Health Service was strongly influenced by transplantation (94.6%), chemotherapy and skeletal fractures of 1% and 2% respectively. The purpose of the study is to assess the gold standard of multiple myeloma skeletal imaging so as to increase the percentage of early diagnosis which results in the clear reduce of the cost for the disease treatment.

In 2014 diagnostic criteria for multiple myeloma were updated, which involved in reviewing the recommendations for diagnostic imaging modalities and the follow-up of the therapy response. As a result of these changes, the Conventional skeletal investigation was replaced by cross-sectional imaging techniques. For the initial diagnosis of bone lesions or bone marrow involvement that defines multiple myeloma, low-dose CT scans are recommended at low doses on the whole body and MRI throughout all the body. New guidelines for definitions of residual disease include also the assessment of focal lesions before and after treatment using PET/CT with 18F-FDG.

In 2019, international reference organizations "IMWG (International Myeloma Working Group)" disclosed a further redefinition of the study criteria of multiple myeloma bone lesions, which provided for a low-dose CT performed throughout the body to detect osteolytic lesions. MRI is the most sensitive technique for identifying bone marrow infiltration and it is recommended in studying diseases that can act as a precursor of multiple symptomatic myeloma that requires therapy, even in the absence of damage to bone mineralized. The diagnostic potential of PET/CT with 18F-FDG is mainly used for follow-up, therapy monitoring and response assessment.

In 2020, the NCCN National Comprehensive Cancer Network published new imaging recommendations for multiple myeloma. For the initial diagnostic work up of patients with suspected MM, the lower sensitivity of traditional radiology was confirmed, compared to low-dose WB TC, which predominantly highlights

Fig. 1 - MIP reconstruction.

the destructive and/or reactive effects of the disease on the trabecular and cortical bone. There were no substantial differences regarding PET/TC, putting both methods on the same ET level. As far as WB MRI, however, showed greater sensitivity since the excellent contrast of soft tissues allows direct imaging of the bone marrow, resulting in increased sensitivity and early detection of MM. In addition, unlike TC WB and PET/CT with 18-FDG, MRI does not expose patients to radiation. For the follow-up of patients with multiple myeloma, the NCCN recommends advanced imaging (i.e. FDG-PET/CT on the whole body, low-dose WB TC, contrastless WB MRI) specifying and emphasizing to use the same imaging mode used during the initial work-up for follow-up assessments.

MATERIALS E METHODS

Having been used for the description of protocols:

- TC GE Light Speed VCT 64
- Rm Signa Voyager 1.5 T, n° 2 16 panel coil body anterior array, 1 32 panel antenna HNU (Head-Neck Unit) ed 1 32 panel phased-array SPINE HR integrated with patient-door cot.
- Biograph PET TC True Point True V Siemens with LSO crystals.

For the TC WB study, the patient is positioned on the supine, with the upper limbs place the hips, trying to keep them close to the body as much as possible, so as to fit them into the study volume. The lower limbs are stretched and fastened with a containment band to minimize any movement artifacts. Run the scout (AP-LL) from the vertex to the feet. Then acquire the entire volume, in a single acquisition, from the vertex to the feet, making the patient holding the breath only during the chest-abdomen passage. The whole scan lasts to the maximum 10 seconds. The TC WB is performed with FOV 50 KV 120 Mas from a minimum of 1 to maximum of 20 (depending on patient's body size) rot/sec 4/5. The study is acquired with standard 2.5 mm reconstruction, reconstructions are performed with a filter "bone" at 0.625 mm.

As regards the protocol for MRI, which has been optimized for the WB study of multiple myeloma, Two identical protocols were stored but with different FOVs for axial acquisitions to be adapted to the patient's size: FOV 47 for large patients and FOV 44 for small or medium patients. 4 coils are used to run the study, all of which are connected at the same time: 2 array anterior coils, 1 head neck unit and a 32-panel array phased antenna integrated with patient-door cot. Then move on to the positioning

Fig. 2 - Coils anterior array.

Fig. 3 - Coils anterior array .

Fig. 4 - DWI reconstruction

of the patient, who, after removing all the metal objects and everything that is not rm-compatible, will have to wear a cotton or disposable coat and a disposable hair cap. It is preferable that, given the long period of time of acquisition of the examination, the patient empties the bladder before being placed. The patient will be placed supine head-first, pay a lot of attention to the placement of patient, who must be laying in order that the patient is completely in axis and parallel to longitudinal line of the cot, with the upper limbs adopted along the body in order to avoid tipping artifacts being acquired, the lower limbs will have to be symmetrical and preferably locked with a containment band to avoid foot movements. Respiratory gating will be placed for apnea acquisitions, verifying proper operation through the monitor. The patient could be provided with audio headphones, through which apnea commands will be dictated and at the same time the noisy characteristic of the method will be reduced. Next, the coils will be placed. The head, which will have to be in axis with the body, will be inserted into the NHU antenna, while on the chest, abdomen and lower limbs, 2 coils anterior array will be placed, being careful to overlap them on the lower and lower limiters respectively.

After placing the coils, they must be connected once at a time, starting with the HNU. Afterword the link, it follows the recognition of the reel by clicking on the isocenter bar of the cot, then register the center. This procedure should be repeated for each antenna apart from the one integrated with patient-door cot. When all the coils are connected, register the centering through the “touch strip”, placed to the both side of the cot, which in our protocol corresponds to the vertex, press the reset button and bring the patient at the inner of the gantry.

The RM WB protocol provides axial acquisitions with 6-step DWI sequences, in order to cover from the vertex up to most of the lower limbs (until femurs for very high patients). At the end of each sequence, the program automatically provides for a pasting of the individual steps, so as to obtain a reconstruction on a single volume of the entire study. Multi b: 0, 800 and 1000. It is useful during the post-processing phase to invert the shades of grey which make the pathologic areas more highlighted.

The second sequence involves in an acquisition on the coronal plane in T2. This time the study will be acquired in a caudo-cranial sense, so that to minimize

Fig. 5 - T2 pasting coronal reconstruction

Fig. 6 - T1 FSE pasting coronal reconstruction

Fig. 7 - T2 pasting sagittal reconstruction

Fig. 8 - T2 FS pasting sagittal reconstruction

the excursions of the cot. During the chest-abdominal acquisition is provided an 18 second breath-hold sequence with the aim of reduce to the maximum the artefacts caused by respiratory movement.

Even the third sequence is acquired on the coronal plane, but in weighing T1 ESF, always having hold the breath during the study of the chest-abdominal region, in this case the study is acquired in a cranio-caudal sense.

The fourth sequence is captured on the axial plane with LAVA Flex 3D sequence (DIXON -GRE 3D

double echoes in phase- out phase in weighing T1). The study is performed all in apnea, except for the first acquisition on the head-neck region.

The examination is completed with acquisition on the sagittal plane of the entire spine in weighing T2, T2, FS and T1 FSE.

The PET/TC study involves the PET study in co-recording with CT. Unlike other imaging techniques, the patient who has to undergo the PET/TC exam, needs preparation: the night before the examination is invited to take foods lacking of certain sources

Fig. 9 - T1 FSE pasting sagittal reconstruction

Fig. 10 - Pet/TC

of carbohydrates (grains, rice, potatoes, flour and legume derivatives) and sugars. Moreover, the patient should fast in the six hours prior to the test. Diabetic patient will anticipate breakfast and drug therapy six hours before the examination (patients with insufficiently controlled blood sugar, i.e. > 160 - 180 mg/100ml, cannot perform the examination). Before administering the radio-marked tracer, a blood glucose test is performed. make the pz relax in an armchair at least 15 minutes before the examination, and then inject the dose prepared by TSRM. After administration, the patient must stay in an adjoining room, in a convenient not cold environment comfortably seated and relaxed, abstaining from non-essential motor activities, recommending drinking 4-5 glasses of water. At the end of the uptake, before the examination is performed, the patient is invited to urinate without contaminating, sometimes a catheterization associated with hydration and diuretics (10-20 mg of furosemide) may be necessary. PET/TC begins 60minutes after the injection of the radiopharmaceutical. The patient is supine, with the upper limbs place the hips, trying to keep them as much as possible adhesive to the body, so as to get them back into the study volume. The lower limbs are stretched and held on with a containment band to minimize any movement artifacts.

The CT protocol provides a low-amperage scout to optimize positioning and a subsequent spiral CT scan, essential for the correction of attenuation. The following data are used for the scout: 130 KV and 50 mA, 1.85 sec scan time and a 3 sec delay, scanning is performed in a cranio-caudal direction (operator's choice) from the vertex to the feet. For the TC: 110-130 KV and 30 mAs, 4.0mm slice and pitch 1.5, the CAREdose (for modulated dose optimization) is inserted, FOV 70 cm. PET is performed in co-recording with CT, in order to avoid misalignment of PET/TC scans a 4 mm slice is used. The verse of acquisition is cranio-caudal (operator's choice), indicate the isotope (^{18}F) and the drug (FDG), dose administered to the patient (in MBq) in relation to weight, date and time of the administration, nth° bed in relation to the height of the patient (12 bed per a volume of acquisition include between 175/180 cm with acquisition time per bed of 2 - 3 minutes, each bed measures 21 cm: area more wide, less radiation for the patient, more accurate choice of FOV). The

technique is performed in normal respiratory acts trying to immobilize the patient and without requiring apnea.

CONCLUSIONS

Several studies have shown the role of different imaging techniques for the assessment of focal lesions: WB magnetic resonance imaging is a sensitive and non-invasive imaging technique that can detect bone involvement especially in the spine and provide details about soft tissue disease and possible infiltration of the marrow (normal, focal point, widespread or heterogeneous), but the excessive duration of the study (about 50/60 minutes) and the contraindications related to the method limits its use. The TC WB is sufficiently sensitive and in addition its easy and fast execution within the widespread presence of the equipment make it fundamental for

Fig. 11 - Pet/TC

work up and during the follow up for patient affected by multiple myeloma.

PET/TC with 18- FDG can be used to analyze the vitality of focal lesions and it is therefore, at present, the gold standard for post-therapeutic residue assessment and extra-medullary localizations. It is in the experimental study the PET / CT 11C-metionin, which showed a more sensitiveness than pet/TC

18-FDG in the detection of focal lesions, both inside and outside the bone. More data are needed in a homogeneous patient population to understand whether this tracer could be an alternative to 18-FDG in detecting the disease residue after treatment. Other tracers targeting membrane lipids (e.g. choline, acetate) and CXCR4 are currently being examined.

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