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INTRODUCTION TO NUCLEAR MEDICINE AS MOLECULAR IMAGING IN ONCOLOGY

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Abstract

The management of cancer requires an interdisciplinary approach in which items related to diagnosis and treatment must intervene in the early diagnostic phase, staging, follow-up and monitoring of oncologic patients. In this context, nuclear-medicine (NM), based on original pathophysiological premises which define the best feasibility in humans of a molecular imaging, produce diagnostic data more strictly connected with prognosis and therapy. Allowing morph-structural images a better anatomical and loco-regional evaluation, an implemented information is obtained when NM machines (PET or SPECT) may be associated in a single gantry with CT or MRI , in the so called hybrid devices (PET/CT, SPECT/CT, PET/MRI), that have revolutionized diagnostic imaging. At the present, a major role in oncology is connected with PET/CT using ^{18}F- Fluoro-deoxyglucose (FDG), which is by now a pivotal diagnostic tool either in the pre-therapeutic and post-therapeutic evaluation, thanks to the growing evidence of a favorable cost/effectiveness respect to alternative procedures.

Keywords: Nuclear Medicine, Molecular Imaging, Hybrid Machines, Oncology

Currently the management of cancer requires an interdisciplinary approach in which items related to diagnosis and treatment must intervene in the early diagnostic phase but also in staging, follow-up and monitoring. A close integration between radiologist , pathologist, nuclear physician and specialists involved in the therapeutic strategy, such as oncologist, surgeon, and radiotherapist, is mandatory to individuate the most cost/effective diagnostic/therapeutic tree.

In this context, the nuclear-medicine approach is original and unique, being characterized by a pathophysiological essence having the ability to express information only achievable in a living being; in this way , diagnostic data are more strictly connected with a prognostic content, having also the capability to give useful data in connection with therapy. This constitutes a great difference in opposition to the standard morph-structural imaging, which does not detect differences between living or dead; as consequence, a lower capability to fill the clinical information with a supplementary content than that exclusively diagnostic is achievable. Nevertheless, allowing the morph-structural image a better anatomical and loco-regional evaluation, an implemented information is obtained when both forms of imaging are involved in a unique approach, as it happens in hybrid devices, that have recently revolutionized diagnostic imaging.

Hybrid machines

Hybrid systems are characterized by the concomitant presence in the same gantry of a component acquiring morph-structural data, together with an associated device allowing nuclear medicine (NM) imaging. The unit for morph-structural imaging is typically a Computed Tomograph (CT), having been more recently utilized also Magnetic Resonance (MR) scanners. With respect to the NM component, or a Positron Emission Tomograph (PET), providing images obtained after the administration of radiotracers labelled with positron emitters, or a Single Photon Emission Computed Tomograph (SPECT), producing images when using gamma emitters may be included in the gantry. [1]

The final result given by hybrid systems is not only the sum of individual contributions produced by both approaches, when separated. Multiple advantages are achievable when the capability to acquire almost simultaneously functional and morph-structural information is present in the same machine. At first, a higher diagnostic accuracy in terms of specificity and sensitivity may be obtained, as result of a better localization and interpretation of functional images inside the well defined anatomic context provided by CT. Moreover, the morph-structural information can reveal alterations undetectable by NM, increasing sensitivity and also providing a more specific characterization respect to the one obtained by radionuclide procedures alone. [2-4]

The hybrid imaging has also additional advantages, allowing to evaluate and implement diagnostic and therapeutic strategies respect to those feasible with separate tools. Typical examples are the improvement obtained by PET/CT respect to a CT standalone in making a biopsy or in defining a radiotherapeutic (RT) target. While CT doesn't allow the discrimination in a heterogeneous tumour mass between the malignant part respect to necrotic and/or fibrotic areas, PET and SPECT have typically the ability to characterize only the viable component, being absent a radiotracer's uptake in the absence of cells. Nevertheless, a PET (or a SPECT) standalone doesn't allow to perform a biopsy, failing anatomical landmarks mandatory to precisely localize the lesion to be biopsied. Indeed, the radiotracer's uptake is the major determinant in directing the needle to the malignant part of the tumour, but this action may allow an optimal result only when using a hybrid machine. A similar advantage may be found in defining the tumour target in RT, in which PET/CT allows a more precise delineation of the malignant component of the neoplastic mass. [5-6]

More in general, although both information allowed by the two component of the hybrid machine are important in defining a correct diagnosis , the major contribution is generally given by PET or SPECT, being the "radiotracer" the most effective instrument in obtaining a whole body information, based on a functional and/or molecular alteration, i.e. to produce a molecular imaging.

Molecular Imaging

To understand the concept of molecular imaging [7,] we must remember that the human body is composed by bio-molecules in dynamic

equilibrium between them . The normal condition is defined "homeostasis" and is studied by physiology; its alteration, the disease, is object of study by pathophysiology.

When a label detectable from outside is bound to the molecule of interest in that peculiar process, it becomes possible to "trace" its in vivo distribution; in this way a molecular alteration into the body may be individuated through a detector placed outside of the organism itself. Labelled molecules may therefore act as "tracers" of a molecular process, when detectable from outside.

This constitutes the basis of molecular imaging, which may be performed with all the most important techniques, even if with some limitations. For example, a molecular imaging can be obtained with CT using a molecule conjugated to a iodine atom, at the base of CT contrast media; with MRI, using paramagnetic molecules; with US using micro-bubbles. In addition, it can be realized a highly accurate imaging by optical techniques, which are based on the addition as label of fluorescent substances emitting light radiation. Finally, the molecular imaging can be obtained through the application to the molecule of a radioactive label, as it happens in NM. [8]

For studying a particular biological process, to avoid alteration of the system to be studied and/or toxic effects, it is necessary to use a very small quantity of tracing molecules, in a much smaller number than the native ones. This condition can be exclusively realized with the administration of ponderal quantities of the labelled tracers in the order of picomoles or nanomoles. At present this eventuality may be only realized with optical imaging (OI) or NM, being necessary a higher quantity, in the order of micromoles or millimoles, when using contrast media for CT or MRI, therefore usable in the study of a very limited number of molecular processes; at the opposite , most complex events of biology up to proteomics and genomics may be better studied with OI, which is the best technique in defining molecular mechanisms in their most evolved processes; very effective and reliable for these purposes in the large majority of cases are also radionuclide procedures.

In summary, molecular imaging is only occasionally feasible by CT and MRI, having the latter more potential in this direction compared to CT, which objectively seems devoid of a capacity of molecular imaging. In this direction, MRI is addressing on a path that allows the investigation of molecular processes, but is still in research rather than in clinical application.

In producing molecular imaging NM presents a major advantage in opposition to OI. If it's true that the latter is superior in the imaging at genomics and proteomics level, conversely it may perform an analysis only on superficial layers, as in experimental models or, in humans, on skin, eye or mucosa, when using endoscopic techniques. This may be useful, especially in dermatology, in the endoscopic evaluation of the digestive system or as intra-surgical procedure, but it is evident that OI will never give an in vivo information on the presence and characterization, for example, of liver metastases in their three-dimensional complexity.

Nuclear Medicine as Molecular Imaging

Therefore, the only technique that fully provides such information in humans is NM, which from its birth has demonstrated to be an excellent candidate for this type of imaging. In fact, starting from Georg Charles von Hevesy, who firstly defined the concept of radiotracer, molecular imaging is at the base of NM. As example, ^{131}I-iodine, the first radiotracer clinically used both in diagnosis and in therapy, gives a molecular information useful not only for diagnosis, but also for prognosis and as premise to a therapeutic strategy. In fact, in the restaging of a person operated for well differentiated thyroid cancer, a whole body scan with radioactive iodine may allow diagnosis of metastasis or recurrence; individuate a favourable prognosis , being the uptake only possible in still differentiated lesions; define a rationale recruitment of the patient for a radionuclide therapy , because in this patient is possible to administer ^{131}I at significantly higher doses for an effective and well tolerated therapeutic action. Actually it can be attributed to this uptake also a strictly genomic meaning. In fact, the tumour's concentration of radioactive iodine (^{131}I, ^{123}I or ^{124}I) individuate the expression of the iodine symporter's gene also in metastatic cells. [9]

Premises to the Clinical role of Nuclear Medicine

The above considerations are clinically relevant, because NM may allow an early diagnosis,

being the functional and/or molecular alteration earlier than the morph-structural one. In addition, being the concentration linked to pathophysiological mechanisms, these procedures have the possibility to better define a connection with prognosis and therapy, permitting an individual approach to the patient, as premise to the so-called tailored medicine. [10]

Nevertheless, if tailored medicine is the new paradigm better characterizing the patient, it is not yet widely diffuse in the clinical practice. Therefore at the present in oncology a traditional approach is still more frequently applied.

In the present scenario, a diagnostic imaging is required initially to detect a lesion and to determine its malignant potential. Furthermore, information defining position, relations with nerves, vessels, surrounding organs, on dimensions and structural characteristics of the lesion is crucial either to give a differential diagnosis and to define a therapeutic strategy. [11]

Nevertheless, most of the information achievable when using PET/CT is due to FDG or to radiotracers beyond FDG, essential either in oncology and in many non oncologic diseases.

For example, in a DOTA-PET [12] scan (using somatostatin analogues labelled with ^{68}Ga, [13] targeting somatostatin receptors hyper-expressed in neuroendocrine tumors), [14] NM has the major role in detecting pathological areas distributed trough the body, in diagnosing a neuroendocrine tumour, in staging or re-staging, having the possibility to individuate primary tumour, recurrence and metastases; furthermore, a DOTA-PET positivity express a prognostic value, as the concentration is linked to the presence of a differentiated tumour, being this prerogative lost in dedifferentiation. Such information is also useful to decide a therapeutic approach since patients positives at DOTA-PET may be recruited for a metabolic therapy with somatostatin analogues labelled with high doses of β- radionuclides; in this way, as it happens since decades in patients with thyroid carcinoma using radioiodine, by identifying the pathological concentration of the tracer in the diagnostic phase , it is possible to predict a priori a therapeutic efficacy in that individual patient, on the basis of the presence of an effective theranostic model. [15] However, it remains the need to configure this accumulation in a morph-structural context for a correct surgical or radiotherapeutic approach, and/or for increase diagnostic accuracy. This is information is only obtainable thanks to the relevant and mandatory contribution allowed by CT.

PET/MRI

PET/CT is companion of a technique that is now entering in the diagnostic setting, PET-MRI, characterized by greater complexity, higher costs and thus a lower spread than PET/CT, limiting its utilization mainly to research in a few academic structures. [16] PET/MRI has a great clinical potential, permitting a better evaluation of territories in which MRI is better than CT, as it happens in areas in which the morph-structural alteration is defined by small changes in structural density. The most important advantages for MRI, and therefore for PET/MRI, could be found in the pelvis, especially in the post therapeutic evaluation, in the head and neck region, in brain demyelinating diseases, in diagnosis of breast cancer. [17]

Thanks to the absence of ionizing radiations, MRI is also advantageous in terms of dosimetry, issue highly important for certain groups of patients such as in paediatrics. For this reason, a greater cost-benefit ratio and therefore a clinical appropriateness could be obtained in many pathological conditions as in the evaluation of inflammatory diseases.

Furthermore, PET/MRI may provide original functional information trough a series of procedures constituting the so called functional MRI (fMRI) and/or MR spectroscopy (MRS). [18] The obtainable data are not a NM's surrogate but an useful and original supplementary information particularly important in the analysis of neurological correlations , linked to the ability in assessing the nerve bundles, and in defining not only the structural alteration but also changes in vascular perfusion or in cell density, as possible expression of issues related to malignancy and neo-angiogenesis. Therefore, it is possible to define PET/MRI as the opening of a third eye vision in imaging, as the standard morph-structural information by MRI and the pathophysiological PET information may be enriched by functional data achievable with the same MR scanner. [19]

In this context, it could be expected that significant investment by Industries in the next years could further increase the wide spread distribution of hybrid systems although they will not completely replace the traditional ma-

chines, such as CT and MRI scanners, which will certainly remain highly diffuse, because of a wide utilization also as standalone devices. [20]

Conversely , already at the present are no more sold PET systems standalone, while is increasing the relative percentage of SPECT/CT devices respect to traditional machines for gamma emitters. It is not easy to foresee a wider diffusion of PET/MRI and eventually of SPECT/MRI scanners, which will probably find a market only if a more favourable economic condition will justify their advantages respect to the cheaper hybrid machines including CT. [21]

PET/CT with FDG

Coming back to the major protagonist in NM, i.e. PET/CT with FDG, we have to remember that FDG is a glucose analogue, which use the same transport mechanism to enter into the cell, although is differently metabolized. [22] While glucose, in its typical utilization, after the intracellular entry is rapidly converted in CO_2 producing energy, FDG after phosphorylation is trapped in the cell, remaining for a long time without further metabolic reactions. Interestingly, this is a great advantage for imaging. In fact, in this way, since transport and metabolism are closely related, there's the possibility with FDG to evaluate for hours a concentration that trace reliably the real distribution and metabolic activity of the glucose in the subject in study. This is more difficult with radiolabelled glucose , showing a too fast metabolism to allow a standardized scan in humans. [23]

Being the detection's capability of a radiotracer determined by the lesion to background ratio , it is important to remember that glucose and FDG have a physiological high concentration in the brain; therefore, because of the unfavourable ratio, FDG is not reliable in detecting cerebral metastases and a diagnostic CT or MRI brain study is requested in the neoplastic population with a high prevalence of secondary cerebral lesions. Favourable conditions in fasting subjects occur in the rest of the body, thanks to the absence of a significant physiological concentration, with exceptions due to the FDG excretion trough the kidneys, determining high concentration in the bladder, critical when evaluating, as example, a patient with a prostate cancer. [24]

The great importance of FDG in oncology is linked to the fact that, as demonstrated by Warburg, glucose concentrate more where there's an increased anaerobic glycolysis, and therefore especially in malignant tumours. Similar to glucose is the behaviour of FDG. Furthermore , in the context of a neoplastic transformation, it has been evidenced that glucose transporters expression is increased and so tumour cells have a higher glucose uptake than normal cells growing at the same rate. But it is important to remember that also benign conditions, in particular inflammatory diseases, may have an increased FDG uptake due to increased flow and metabolism, as it happens in acute disease, or to the prevalence of anaerobic glycolysis , as it may occur in chronic inflammation. [25]

It should be pointed out that probably, in presence of absolute quantitative models normalized for number of cells, of a sufficient spatial resolution and in absence of artefacts, a good discrimination between benign and malignant lesions concentrating FDG could be obtained. By the way malignant tumours showing an absent or low uptake, similar to that observed in FDG positive benign diseases, have to be considered as neoplasm with a favourable prognosis. This behaviour can be explained by many issues, as the slow growing rate and the absence of anarchic neo-angiogenesis, determining low or absent anaerobic glycolysis. Therefore, being the FDG concentration mainly determined by the dedifferentiation phenomenon, well differentiated and/or slow-growing tumours, such as well-differentiated thyroid carcinoma , neuroendocrine tumours, and prostate cancer have a low capability to concentrate FDG. In parallel, increasing the FDG's uptake with malignancy, this radiotracer can also give a prognostic information: in a population with the same histological classification, a higher FDG's uptake indicates a more malignant tumour. [26]

With respect to false positive results, it must be underlined that, if it is true that false positives are a problem in patients with cancer, determining possible mistakes in differential diagnosis, conversely FDG can become an helpful radiotracer when used in the study of some benign conditions. As example, PET-FDG is very useful in patients with fever of unknown origin (FUO); [27] moreover, FDG is extremely important in the characterization of inflammatory diseases such as osteomyelitis or in the definition of activity in chronic diseases, such as Chron's disease

and sarcoidosis: in these populations only FDG positive patients must undergo therapy. [28]

PET-FDG in oncology

In the oncologic field , PET-FDG is undoubtedly a protagonist in the diagnostic scenario. [29] To better understand its clinical role, we must focus some aspects.

Diagnosis

When utilized for a first diagnosis, a high FDG uptake at level of the lesion increases the probability of malignancy, although a low or absent uptake cannot exclude a malignant tumour. [30] At the opposite, a high FDG uptake is not pathognomonic of cancer, being also encountered in some benign conditions. In other words , PET-FDG cannot be considered as unique determinant in the differential diagnosis of malignancy; although it may play a role in the overall diagnostic balance of some peculiar conditions, such as suspicion of lymphoma or as second line procedure in differentiating solitary pulmonary nodules. PET-FDG may be also used in detecting the primary tumour in presence of metastases of unknown origin. [31]

Staging

More immediately identifiable, although with some limitations, is the clinical role in staging. [32] The best example may be found in defining a lymph node involvement. Morph- structural techniques, including CT and MRI, classify a lymph node as malignant exclusively on the basis of its enlargement. [33] Therefore, many false negative results are due to metastatic lesions in the initial phase of invasion; similarly, false positive results may be associated with lymph nodes enlarged because of inflammation. In this context, PET-FDG may partially improve diagnostic accuracy. In fact , although false negative results may be seen in presence of micro-metastases, lymph nodes of normal size showing high FDG uptake are very probably malignant. At the opposite, enlarged lymph nodes without FDG's concentration are almost surely benign. Furthermore, trough a whole body analysis, PET-FDG may augment detection of distant metastases, but a the level of the brain, in which a MRI or a CT diagnostic study may individuate a higher number of lesions. [34]

Restaging

PET-FDG may be useful in restaging , having capability to detect either local recurrence and distant metastases, in all the patients in which a high uptake has been observed before the beginning of a therapeutic strategy. [35] Nevertheless , while the disappearance of a pathological concentration may reliably exclude a local relapse, false positive results may be seen due to inflammation or to a post-therapeutic active rearrangement, more frequently observed in earlier controls, within the first six months after the intervention. [36] A higher accuracy may be obtained thanks to the incremental contribution of CT or MRI, preferably with contrast media. [37]

Prognosis and connection with therapy

In general, in tumours belonging to the same histologic class, a higher FDG's uptake is associated with a worst prognosis. [38] Similarly, in follow up of patients with well differentiated tumours, the appearance of a FDG's uptake individuate undifferentiated lesions, and therefore a malignant transformation. [39] As further advantage in follow up, PET-FDG may better evaluate tumour response respect to CT or MRI, being the glucose variation an earlier marker of response respect to changes in size of the lesion. [40]

PET-FDG before therapy

For all the reasons above, oncologic applications of PET-FDG are extremely useful in a large number of patients with cancer. Although a lower interest is observed in differential diagnosis, but in a limited number of patients, as those with diagnosed solitary pulmonary nodule PET-FDG may be indicated before therapy for its contribution in staging and in prognostic stratification, which can determine changes in therapeutic strategies. Furthermore, if PET-FDG is considered as possible tool to be used in follow

up, a pre-therapeutic scan is mandatory as reference for the post-therapeutic evaluation. [41]

Very important is also the role of FDG-PET in guiding a biopsy, to activate a more or less aggressive therapeutic approach on the basis of intensity and extension of the FDG's uptake, in defining the target for radiotherapy.

As example , using the semi-quantitative method called SUV (inaccurate and improper technique for a rigorous diagnosis, but certainly useful to establish the grade of uptake and in evaluating the same subject in follow up), it may result that a patient with a lymphoma with a high SUV has to be treated with a more aggressive therapy than a patient who has a lymphoma with a lower value, treatable with a less toxic approach. [42]

It has also been already mentioned the importance of PET-FDG in the biological definition of the target in radiotherapy either for the better definition of the viable malignant component respect to necrosis and fibrosis, and/or for the improved diagnostic accuracy, which allows to exclude, as example, a lymph node involvement in enlarged lymph nodes w/o uptake. Furthermore, PET-FDG may help to follow the effectiveness of radiotherapy on the tumour itself during the treatment. [43]

PET-FDG in follow up

As previously anticipated, in patients with a neoplasm showing a low probability of uptake, PET-FDG can be useful in follow-up only when a prognostic worsening is suspected. [44] For example, in patients who underwent a total thyroidectomy for a well differentiated carcinoma, PET-FDG has to be performed in cases in which an increased value of thyroglobulin is not accompanied by the evidence of radioiodine-concentrating lesions. In these subjects, PET-FDG may detect the presence of dedifferentiated metastases concentrating FDG but not iodine. [45]

PET-FDG and the NOPR study

The NOPR study (National Oncology PET Registry) has clearly demonstrated that in the majority of patients with a high clinical probability of oncologic diseases, [46] there is a high chance of finding utility from PET-FDG. In fact, this procedure may be useful, more than for the possibility of a differential diagnosis, to better perform a staging and to allow a more correct prognostic stratification of the patient; as consequence, it may be reduced the number of individuals operated in presence of metastases or, on the contrary, surgical opportunities may be provided to subjects in which a re-evaluation of the stage is obtained , as example defining negatives lymph nodes erroneously considered neoplastic by CT.

The NOPR study has also demonstrated the importance of a basal scan in patients which will probably perform PET-FDG in follow up, and the possible role of a pre-therapeutic scan in defining therapeutic strategies on the basis of intensity and extent of the FDG's uptake.

On the basis of these premises, in patients highly suspicious for cancer, a new terminology has been proposed , which express major changes respect to a standard approach. [47]

In particular, diagnosis and staging, traditionally individuated as separated steps, are considered together in the term "initial pre-intervention strategies". In this context, PET-FDG may acquire relevance more than for the possibility to perform a differential diagnosis, for its contribution in staging, prognostic stratification and definition of therapeutic plans. Similarly, the term "subsequent treatment strategies" include together "treatment monitoring and restaging/detection of recurrence". [48]

Adopting this new paradigm, PET/CT with FDG could acquire a fundamental importance in the most cancers, with some notable exceptions such as in prostate cancer, breast cancer and melanoma. These exclusions are justified for prostate, by the low sensitivity of FDG in this neoplasm; respect to breast cancer and melanoma, a different choice has to be adopted in patients early diagnosed, being Mammography/Echography/FNAB, and sentinel node techniques , more cost/effectives and accurate respect to PET-FDG. In prostate cancer different approaches , including MRI and eventually radiotracers beyond FDG have to be preferred.

RECIST versus PERCIST

In the definition of a therapeutic efficacy in oncology, the system currently used, the so-called RECIST, even in its most advanced edition

RECIST-1 is affected by many limitations, being unable to provide a rapid response about effectiveness. [49] The core approach of RECIST, which uses CT, is to evaluate a therapeutic efficacy on the basis of the reduction in size of the most relevant tumour lesions, from the time of diagnosis to the time chosen for a post-therapeutic monitoring. It is clear that these changes occur generally in a long time. Furthermore in some tumours as GIST, the therapeutic efficacy isn't evidenced by a reduction of the mass, but by the increase of the necrotic component , which is accompanied by an almost unchanged size of the lesion. A further problem for RECIST is present in patients undergoing biological therapies, and more in general submitted to the so called target therapies, in which a therapeutic efficacy is frequently independent of the volume reduction, stopping the malignant evolution of the mass itself. [50]

In these conditions, i.e. in tumours as GIST and when biological therapies are used, and more in general in the large majority of tumours also when using a traditional chemo and/or radiotherapy, FDG may indicate a therapeutic response earlier than CT.

For these reasons, PET-FDG may be already suggested as first line diagnostic method to identify patients undergoing biological therapies, having capability to reliably separate responders versus non responders. In this way, a huge gain for the health system may be obtained , individually identifying patients who can benefit from a high-cost treatment. [51]

The better capability to earlier individuate responders respect to CT may play a major role also in monitoring tumour response in the large majority of patients with cancer submitted to chemo or radiotherapy. In this way, trough an evaluation performed few days or weeks after the intervention, the decision to continue or not a therapeutic strategy may be better and earlier defined with enormous advantages for the patient, also in terms of a reduction in toxicity. Unfortunately, PET-FDG is not a perfect method in evaluating tumour response: if it is true that we can reliably and rapidly discriminate responders from non-responders, it is also true that it is not always possible to understand whether there will be a full therapeutic efficacy. In other words, an early decrease of the FDG's uptake cannot predict certainly a complete therapeutic response, in particular in polyclonal neoplasm in which a clone could continue to grow despite the radiotracer's reduction seen at the first evaluation. [52]

Nevertheless, for its advantages respect to radiological methods, which are however more standardized and continue to be more widely utilized, PET-FDG is now slowly entering in protocols, having already acquired a primary role in some tumours.

Currently, a routine worldwide application is already present in lymphomas, in which PET-FDG is also utilized as interim procedure to define the correct therapeutic strategy in individual patients. It has to be pointed out that the favourable situation in lymphoma is either due to the type of neoplasm and to a very close and interactive international collaboration between some of the major experts in the field, which allowed the definition of well organized and standardized protocols, fully shared by all the participants to the multicenter trials. Therefore, reliable data have been acquired in a large population, using identical procedures and therapeutic strategies. Interesting results begin to appear in myeloma, while it is more difficult to obtain homogeneous data in solid tumours.

To facilitate a diffusion of PET-FDG in the evaluation of solid tumour response, R. Wahl has proposed the PET Response Criteria in Solid Tumors (PERCIST), as alternative to RECIST; this method is based on a semi-quantitative analysis of the variation in FDG's uptake calculated in the most relevant lesions present in solid tumours. Relatively to the quantitative system applied, the chosen method has been the standardized uptake value (SUV). This method, although partially inaccurate, still remains the most easily and rationally usable in a strategy of standardization. Obviously it would be ideal to have absolutely quantitative methods, but these approaches are still far from the clinic. It has however to be pointed out that, although its limitations, the SUV measurement allows a lower intra and inter-observer variability respect to the RECIST method, more affected by a subjective evaluation. Nevertheless , although its advantages respect to the alternative radiological method, PERCIST is not yet widely adopted in defining tumour response in patients with solid neoplasm. For a wider diffusion, based on validated extensive data, well organized and standardized multicenter trials, as for lymphoma, are mandatory to demonstrate an evidence based efficacy.

In this way, the already perceived impression of its superiority respect to RECIST in earlier distinguish responders from non responders, could support a wider and more consolidated diffusion in many neoplasms. [53]

As previously mentioned, when using PERCIST , it must be realized a series of successive controls because an early response is not synonymous of a total response; therefore a more extensive clinical research has to acquire many other data to better define the most effective and rationale utilization. At present interesting data start to be published on the application of PET-FDG in the evaluation of therapies in tumours, such as those of breast, lung, colorectal and oesophagus. It is hoped that further data will rapidly give to oncologists a relevant tool able to more reliably and earlier define therapeutic strategies, changing drugs when it is realized a lack of effectiveness.

PET beyond FDG

Together with a further clinical research on PET-FDG, with the aim to optimize its contribution in this specific field, interesting perspectives are associated with other radiotracers beyond FDG. In defining tumour response a strong rationale justifies a wider application of radio-labelled nucleosides as Fluoro-thymidine, tracing DNA's multiplication. In this way, also because there are no false positive results in inflammation, a more rigorous and univocal semi-quantitative evaluation of the therapeutic response compared to FDG could be obtained. Interesting perspectives , mainly in better defining response to radiotherapy , could be connected with radiotracers of hypoxia. But many other radiotracers could have a primary role in the near future , as those tracing neo-angiogenesis, creating opportunities in optimizing new targeted therapies, in the scenario of a tailored medicine. [54]

This is a long, but promising and exciting process, in which it is fundamental, on one hand, to develop research and on the other, better define clinical applications, methodological standardization, quantitative analysis and so on.

In this context , an essential issue is the strong and interactive relationship between the molecular imager and his/her referents , the clinicians.

It is already time for them to understand that the diagnostic information is no more sufficient alone, being more effective, for the whole understanding of the patient and of his disease, to think giving more importance to the pathophysiological than to morphostructural information in a future scenario which will be probably dominated by hybrid machines.

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