OMICS Journal of Radiology
ISSN: 2167-7964

Djekidel, OMICS J Radiology 2013, 2:3
DOI: 10.4172/2167-7964.1000116

Short Commentary Open Access

The Metabolic Signature of Tumors as an Imaging Biomarker in Staging, Restaging and Therapy Response on FDG PET

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The use of ^{18}F FDG PET has been ever growing over the past decade. CMS reimbursements have followed an increase in the evidence of its utility and superior sensitivity to other morphological exams. This has been greatly aided by the National Oncologic PET Registry (NOPR), which allowed us to evaluate its impact on clinical management. Beyond the static notion of staging [1,2], FDG PET was shown in an NOPR report to change predicted clinical management in 33% of cases [3], not an insignificant number of patients whose therapeutic interventions would have been impacted, as well as an influence on cost saving and morbidity sparing strategies in cases where surgery was no longer an option. This effect was mostly due to a change in staging, by either down staging or upstaging patients. However, other clinical management tools can be extracted from medical imaging and guide the selection of the initial therapeutic approach as well as subsequent treatment modulation. Additional initial staging and restaging FDG PET indications are appropriately being added to the clinical arsenal physicians can use. Imaging in general and FDG PET more specifically could have a great value as an imaging biomarker. For example, the initial therapeutic approach could be impacted by the cancer specific Metabolic Signature (MS) of tumors beyond the notion of simple staging. Tumors of apparent similar histology and staging but different MS as defined by a quantitative FDG measure (SUV, total lesion glycolysis or other) may have a different prognosis and may require a different clinical management. FDG has been shown to correlate with Ki67 a marker of tumor proliferation and tumor aggressiveness [4-6]. The value of FDG PET imaging in this instance is that it can assess this parameter not only in the biopsied lesion but may give us some insight on the global and specific tumor burden of individual lesions within the same patient. It should be noted that tumors have been shown to often exhibit heterogeneity of at least molecular expression but also grade, proliferation and differentiation between the primary lesion and its metastasis. We have also described an aspect of this paradigm in an esophageal cancer patient where the HER2 molecular expression was absent in a metastatic liver lesion that responded to treatment but was present in the primary tumor that did not respond [7]. We can see this concept extrapolated to many tumors and readout sessions whether in the initial staging or follow-up phases of treatment. Another frequent occurrence with PET imaging nowadays is the flare up of granulomatous disease seen in the post-chemotherapy phase. We see this on a regular basis in nodal stations, the lungs and even the bone marrow and should not be misread as progression [8]. Although this can be seen with any cancer, it is especially true in lymphoma patients where these findings may be more problematic to interpret.

The metabolic signature of tumors can also add some insight into the decision of whether low-grade follicular lymphoma patients should be treated. The current paradigm is not to treat low volume or asymptomatic patients. However if the MS of an individual patient was high, could that be evidence enough of a possible therapeutic benefit. Or if an upward change in MS is noted on serial surveillance FDG PET scans, would that be evidence enough of a transformation and therefore encourage re-biopsy and treatment.

The MS of tumors could be used as an imaging biomarker (-although expensive at times when not already performed as part of routine clinical care-) in guiding therapeutic decisions. Discordance of response to a chemotherapeutic agent by different lesions within the same patient should prompt re evaluation of the possibility of lesion heterogeneity and a combination agent could be used after tissue sampling confirmation [7-9]. Discordance can be seen between imaging modalities. For example morphologic modalities are not accurate enough in the initial staging and restaging of bony lesions. FDG PET fulfills this role pretty well, albeit some limitations. On the other hand discordance can also be seen between functional imaging modalities. What should a clinician do with an improvement of the MS of lesions on an FDG PET while they are increased on a Fluoride PET? In cancers where FDG performs well, it would be reasonable to assume the tumor has responded. The promotion in recent reports of combo injections of FDG and Fluoride would not allow for this distinction to be made and does not seem like a reasonable clinical approach [10-13].

Another frequent occurrence is that the current clinical paradigm uses empirical strategies in selecting patients for chemotherapy, although occasionally supported by data and possibly molecular expression profiles. Nonetheless, imaging being performed today (morphologic or functional) provides only a static picture clinically. Some information may be lost and its utility, as a biomarker being able to guide therapeutic choices of cytostatic or cytocidal drug selection should be explored further [14].

Additionally, the usefulness of the MS in being able to detect an escape phenomenon of a biological drug while on therapy would be beneficial in improving early detection and possibly switching agents, therefore improving survival. The MS could also differentiate intra-patient heterogeneity of lesions between malignant and benign foci [8,15,16].

Furthermore we have noted that the MS of tumors could be relevant in disease processes where anatomic imaging can be challenging to interpret such as in intimal sarcomas [15], where contrast enhanced CT may have a limited value in differentiating tumor thrombus from vascular thrombus. In these instances FDG can have a high impact on survival in a disease process where diagnosis is usually made postmortem for this exact aforementioned reason.

We have already seen a move towards the development and inclusion of functional therapy response assessment criteria in clinical practice and clinical trials including EORTC PET, IWG+PET and most

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Received January 07, 2013; **Accepted** April 16, 2013; **Published** April 22, 2013

Citation: Djekidel M (2013) The Metabolic Signature of Tumors as an Imaging Biomarker in Staging, Restaging and Therapy Response on FDG PET. OMICS J Radiology 2: 116 doi:10.4172/2167-7964.1000116

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recently PERCIST as well as other dynamic imaging techniques [17-31]. Using quantitative MS/SUV measurements is attractive because discordant measurements between different readers are unlikely. The variability usually stems more from technical factors related to acquisition parameters, different cameras, image reconstruction algorithms, FDG dose, and glucose. These difficulties can be easily overcome in a single institution daily clinical paradigm where the same standard is used, but proves to be difficult in clinical trials where multicenter studies are performed. More robust methods are needed not only for clinical trials but especially daily clinical practice as these modalities are nowadays used to assess clinical response based on some data coupled with INDIVIDUAL expertise from the imaging or oncology expert. This does not favor widespread consistency. We believe that guidelines using a combination of morphological, functional, staging and other MS criteria are difficult to develop and use, however they offer the highest value. These more complex systems can be used and could be helpful in initial staging, restaging, chemotherapy selection (cytocidal or cytostatic), response assessment, response modulation, and lesion characterization. The NOPR coverage with evidence development as well as other settings may be the optimal avenues for the exploration of more sophisticated imaging assessment tools. The use of more advanced functional or anatomical imaging techniques requires expertise, training and data.

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