Predicting Therapy Outcome with Quantitative PET: What Is Needed and What Can Be Done?

Ludwig G. Strauss Antonia Dimitrakopoulou-Strauss

German Cancer Research Center, Heidelberg, Germany

One major aim of using morphological and/or functional methods is to predict therapy outcome at a very early phase of treatment, even before treatment. Several studies demonstrated the value of positron emission tomography (PET) in different cancer types for predicting therapy outcome. However, we should remember Niels Bohr, who said that ‘prediction is very difficult, especially if it’s about the future’. This statement refers to the difficulties using a forecasting model out of sample. A model may be found easily that fits all the existing data very well, however, it remains open if this model will indeed work well with prospective data, as well.

Several approaches have been used to gain predictive information in patients with esophageal cancer. The use of the keywords ‘esophageal cancer, FDG, prediction’ in PubMed reveals 22 publications. One of the first publications, Weber et al. [1], reports very promising results using a cut off value of 35% change in SUV as a criterion to distinguish responding and non responding tumors to chemotherapy. However, this publication initiated a discussion about the results. The authors used just simple filtered backprojection to generate the images, which provides a limited image quality as compared to iterative reconstruction techniques. Furthermore, just simple circular regions of interest (ROIs) were used for quantification purposes, which cannot fit the demands of an irregular tumor. Several other studies were performed in esophageal cancer with retrospective and prospective analysis using thresholds for the change in fluorodeoxyglucose (FDG) from 20 to 35% with different results. Gilham et al. [2] investigated the change in FDG uptake during induction chemoradiation and was unable to show an advantage of the change in standardized uptake value (SUV).

The article by Klaeser et al. [3] reports the results of a multi-center trial in patients with esophageal cancer and the assessment of response using PET. Overall, 45 patients were included into the study, receiving treatment with cisplatin

(75 mg/m²) and docetaxel (75 mg/m²). The median percentage change in FDG uptake, as measured with the maximum SUV, was –53% for responders and –31% for non-responders. However, the sensitivity and specificity for predicting non-response to therapy was only 68% and 52% using a cut-off level of –40%. The use of this cut-off level was also not helpful to achieve statistical significance regarding overall survival. This study is very important, because the value of PET SUV is prospectively tested regarding the predictive value of global FDG uptake measurements. The results clearly demonstrate that changes in FDG uptake measurements alone cannot be used to exclude patients from the ongoing treatment.

FDG is closely related to molecular biological parameters, so why is PET with FDG not helpful to assess changes in tumor biology? Interestingly, a few authors tried to link PET FDG results with molecular biological data. Choi et al. [4] performed PET FDG studies in patients with esophageal squamous cell carcinoma and compared the PET results with molecular biological data. The authors report that the number of FDG positive lymph nodes, intratumoral microvessel density, and VEGF-A expression are prognostic predictors. However, the maximum SUV of the tumor itself was not predictive for survival. The data point to one important aspect which is frequently not considered in most of the PET studies regarding therapy prediction: SUV gives only limited information about molecular biological parameters. SUV is a global measure of FDG uptake. Based on the kinetics of FDG, this includes FDG in the fractional blood volume of the tumor, transported but not metabolized FDG in the tumor cells, as well as phosphorylated FDG in the cells. More detailed information about the FDG kinetics can be obtained by applying compartment and non compartment analysis to dynamic PET (dPET) data. dPET requires the acquisition of PET data over the target region for about one hour. Thus, the distribution of the tracer in space and time can be quantitatively assessed. It

was shown for the differentiation of colorectal tumors from normal colon tissue that the impact was highest for the fractal dimension, followed by SUV, FDG influx, and k_3 (reflects the phosphorylated fraction of FDG) [5]. The highest classification accuracy was achieved with a combination of all kinetic parameters with an accuracy of 97.3%. The results demonstrate that one parameter is not accurate enough for tumor classification.

Similar results are already reported for therapy management of other tumor types. PET FDG follow up studies in patients with metastatic colorectal tumors demonstrated that the use of the SUV as well as the change of SUV alone resulted in correct classification rates regarding response between 62 and 69% [5]. However, combining the kinetic data from the initial PET examination and a follow up study after the third cycle a correlation coefficient of 0.85 was achieved concerning individual survival. Thus, quantitative dPET studies may be used in these patients to predict survival individually. Unfortunately, there are no real dPET study results available for esophageal cancer. However, recently a first report about dPET in 14 patients was presented at the 2009 meeting of the

Society of Nuclear Medicine by von Gall et al [6]. Again, SUV alone as well as the changes in SUV were not helpful to accurately identify response to treatment. The authors applied a linear discriminant analysis to their kinetic results and noted a 100% discrimination of responders and non-responders using k_3 , VB (fractional blood volume, vessel density), and FD (fractal dimension) [6]. However, more data are needed to assess the impact of dPET for therapy management.

The paper from Klaeser et al. is important to guide the ongoing research regarding the applications of PET in a new direction. If patients receive radioactivity during a PET/CT examination, we have the obligation to gain a maximum amount of information from this examination. Therefore, dPET studies, either as 60-min acquisitions or using shortened acquisition protocols, will find increasing use in future to assess the parameters of the FDG kinetics quantitatively. Technical improvements like larger axial field of view, faster computers, more sophisticated data evaluation software, etc. will facilitate the use of dPET and dPET/CT. Thus, it is likely that quantitative PET examinations can contribute significantly to therapy management in the future.

References

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