Predicting outcome by images?

Dirk De Ruysscher

Author's affiliation: University Hospitals Leuven/ KU Leuven, Belgium

Corresponding author:

Dirk De Ruysscher, MD, PhD

Department of Radiation Oncology
University Hospitals Leuven/ KU Leuven
Herestraat 49
3000 Leuven
Belgium

dirk.deruysscher@uzleuven.be

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Summary

Features from CT, MRI and PET scans are related to survival of NSCLC patients. Individualized image-based tissue characterization allows a whole body view of all tumor deposits and organs at risk. The time is ripe to embark huge international studies aiming to validate and implement this technology in clinical practice.
In this issue of *Clinical Cancer Research*, Win and colleagues (1) present data that suggest that tumor characteristics, and more specifically textural heterogeneity on a CT scan predict survival in patients with non-small cell lung cancer (NSCLC).

The idea to characterize tissues on the basis of imaging is obviously not new. Already in the early 1980’s, attempts were reported aiming at characterizing tissues and tumors to predict response to treatment. The concept is indeed very attractive: with one image, it would be possible to know the prognosis of patients and to predict what the best therapy would be, taking into account the features of the tumor and healthy tissues at risk. Heterogeneity within a tumor or between the primary tumor and its metastases could be defined. Changes over time would be easy to investigate.

However, it became clear that bringing this idea into clinical practice is difficult. Even a seemingly trivial exercise as delineating a tumor mass proved to be difficult to standardize (3). Inter-and intra-observer differences of up to 300 % have been reported when no strict standardized protocols were used. A 10-30 % variability is probably the best what can be achieved with manual tools. It should be emphasized that even these far from optimal results only can be achieved when strictly standardized and validated technical protocols are applied. More recently, national and international organisations have published thorough guidelines for standardization e.g. for CT and PET scans. Thanks to the dramatic improvement in image quality and the availability of fast computers, automated segmentation algorithms have been developed. For CT scans, the selection of ranges of Hounsfield units (which represent the linear attenuation coefficient of the X-ray beam by the tissue) has been used to define tissue types. Calculation of the gradient of an image can reveal the borders between tissue types. The development of 4D-CT scans that allow to take into account blurring artifacts due to motion have further improved the accuracy for tissue characterization. It is likely that dual energy CT and in the near future spectral CT will further boost tissue characterization.

In the same time era, PET scan technology has moved towards 4D acquisitions and highly standardized procedures as well. PET scans nevertheless suffer from a lower resolution than CT scans and the information is highly dependent on the tracer that is used. Nevertheless, an aspecific but biologically sound tracer such as $^{18}$F-
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Deoxyglucose (FDG) has shown not only to be prognostic for survival in many, though not all, series, it also enables to determine the areas within a single tumor that show differences in sensitivity for radiotherapy (3). Obviously, recent results with PET-labelled drugs such as $^{11}$C-docetaxel (4) and $^{11}$C-erlotinib (5), a technology that is useful for many interesting small molecules (6) will further enhance the use of PET scans for tumor characterization.

These technical developments have lead many research groups to look in more detail to the image characteristics of tumors themselves. In general, texture on CT was quantified as mean grey-level intensity, entropy and uniformity (7). A relationship between texture features in NSCLC on non-contrast-enhanced CT and tumor metabolism and stage was reported (8). In metastatic renal cell carcinoma treated with sunitinib, cedirinib, pazopanib or regorafenib, CT texture analysis reflecting tumor heterogeneity was an independent factor associated with time to progression showing its potential as a predictive imaging biomarker of response (9).

Fine-texture features are associated with poorer 5-year overall survival rate in patients with primary colorectal cancer (10). Entropy, uniformity, kurtosis, skewness, and standard deviation of the pixel distribution histogram were derived from CT images each parameter was independent from the stage predictor of overall survival rate.

Qualitative imaging parameters on CT and MRI scans have been used to predict mRNA abundance variation e.g. in brain tumors (11).

The study of Win et al. (1) adds further evidence that textural heterogeneity of the tumor indeed is correlated with survival of NSCLC patients. These investigators build a model for survival in a training set of 56 patients and validated the model in an independent validation cohort consisting of 66 individuals. Textural heterogeneity were prognostic for survival in univariate analysis, whether based on CT or on FDG-PET scans as well as DCE (diffusion-enhanced)-CT measured permeability and stage. The maximal uptake of FDG was not related to survival. In a multivariate analysis, permeability ($p<0.001$) was the most important survival predictor, followed by stage ($p=0.001$) and CT textural heterogeneity ($p=0.021$).
It is conceivable that the coming years, we will witness a growing body of evidence that multi-dimensional parameters derived from different imaging modalities will be able to characterize tumors. The input may be plain scans, functional imaging such as perfusion parameters and molecular imaging. CT, MRI and PET will surely be complementary. In view of the remarkable heterogeneity between patients, tumors and metastases and the changes of the tumor and its micro-environment over time, imaging will probably become an essential component for therapy selection together with other parameters such as clinical data and molecular signatures from tumor cells or DNA from circulating lymphocytes. It remains to be seen which features are specific for a given tumor or treatment and which are more generic. The latter would obviously simplify research very much. The ultimate aim of this research should be to create a framework for individualized image-based tissue characterization for prognostic and predictive use (figure 1). This should include not only tumor characterization, but also take into account the tissues and organs at risk for side effects. Only then, a truly individualized therapeutic ratio can be determined.

Individualized image-based tissue characterization will be of importance for systemic and local therapy and may even be of interest for screening and staging, e.g. for the determination of small nodules. However, a huge international effort is needed to accomplish this goal. Standardization, large databases and decision-support systems are key, as well as prospective validation of the findings in randomized clinical trials (12).

Current knowhow allows this to happen at present. It is the research community, the funding agencies and companies working together that will be able to address the challenges and tackle them. At the very end, patients and all stakeholders will benefit from this paradigm.
**Figure 1.** Schematic overview of individual image-based tissue characterization and its possible prognostic and predictive use.
References


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Selection of local therapy
Determination of best radiation dose:
escalation or deescalation
Selective avoidance of most susceptible parts of healthy organs

Selection of systemic treatment
Most appropriate drugs, dose and sequence

Tumor cells:
e.g., genetic instability, mutation status, resistance

Microenvironment:
e.g., hypoxia

Malignant potential:
e.g., undetermined pulmonary nodules
At screening or staging

e.g., ventilation and perfusion heterogeneity

Individual image-based tissue characterization:
Possible prognostic and predictive use

Image analysis

Normal tissues (e.g., lungs, heart)
Predicting outcome by images?
Dirk De Ruyscher

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