Oncologic imaging in 2002 and beyond

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The thrust of cancer care in the new millennium is implementing "risk adjusted, patient specific therapy". Cancer is not one disease, it is many, it presents a remarkably different clinical behavior and treatment response even in the same host. Modern cancer treatment planning is guided by two key principles: 1) the choice of therapy must be based on evidence rather than opinion or habit, and 2) the volume and extent of disease should be optimally assessed prior to treatment, in order to allow for the most effective patient-specific therapy.

Imaging is emerging as an important adjunct to the clinical assessment of cancer, contributing to tumor detection, characterization, staging, treatment planning and follow-up. Diagnostic imaging is widening its scope from anatomy to adding information about metabolism and function. The general forward direction of medical imaging aims toward increasing sensitivity and specificity, while decreasing invasiveness and minimizing cost. Continuing increases in computer power have fueled the progress, followed by the rapid expansion of communication technology and by the advances in molecular biology. The revolutionary advances in molecular biology and genetics are being introduced into cross-sectional imaging offering great gains to Oncology. Novel imaging paradigms are being developed to provide non-invasive assessment of tissues at the cellular and molecular levels. Imaging modalities of the future will be increasingly biology-centered. At least three modalities are poised to participate in this revolution: magnetic resonance (MR), positron-emission tomography (PET) and optical imaging. Imaging algorithms are already evolving in response to the changes in clinical treatment approaches, scientific discoveries and technological innovations.

The technologic advances that are also impacting the daily practice of oncology are PACS , teleradiology and Computer-Aided Diagnosis (CAD). PACS has empowered many leading medical centers in the United States, Western Europe and Japan (with many other countries being in transition) to become "film-less". The daily routine of "reading", flexibility in workflow, the ability to retrieve information in seconds and communicate the findings with referring physicians has dramatically changed the way we practice modern medicine. Teleradiology can provide access to sophisticated subspecialty-imaging interpretation worldwide and may help in overcoming the presently occurring shortage of radiologists in the industrialized world. Computer-Aided Diagnosis will, in the future, be an important component of modern imaging and will be essential in screening. CAD when fully developed and implemented will be able to identify normal appearing structures (as well as normal variants) making the reading by the radiologist unnecessary for a large portion of screened images. This may alleviate the staffing shortages and reduce the cost of screening. Computer-aided diagnosis will be used in reading images obtained with most techniques. While already in clinical use for mammography, it will expand to the reading of screening procedures such as virtual CT colonoscopy and lung CT.

Advances in cross-sectional imaging

The increasing computer power in cross-sectional imaging has facilitated the acquisition of 3 dimensional data, permitting high-resolution volumetric acquisition of images, thus facilitating diagnosis. Multi-row detector CT and 3D MR have also made virtual endoscopy possible and it is evolving into an increasingly accepted clinical imaging technique. This technique is presently being applied to practically every anatomic channel: colon, esophagus, stomach, small bowel, bronchial tree, blood vessels, urinary tract (including the bladder), etc. Virtual endoscopy promises to reduce the number of invasive procedures and limit conventional, invasive endoscopic procedures to targeted biopsy if the virtual studies disclose abnormalities.

Fusion of images generated from different imaging modalities, such as MR, CT and PET, is showing that the advantages of two techniques can be maximized. The advantages of PET's ability to detect metabolic abnormality are thus combined with the spatial resolution afforded by CT. PET-CT scanners are already in clinical use in multiple medical centers advancing oncologic diagnosis. Instruments providing fusion of MR and CT are currently being designed and will be of great value in diagnostic and radiation therapy planning. Scanners offering fusion of PET and MR will undoubtedly follow.

MR technology is versatile, and therefore very much in demand for functional and metabolic imaging. Functional MR has become extremely valuable in the preoperative evaluation of brain cancer guiding the surgeon away from the motor and sensory centers. Mapping of foci of specific brain activity with functional MRI by displaying images of metabolic activity data, as for instance for heat/pain sensation, motor, memory centers, etc., is becoming the basis of functionally based medicine and will have an important future role in the study of mental diseases.

Proton spectroscopic MR imaging is already used clinically in the study of brain and prostate carcinoma. Extension of MR spectroscopic techniques to breast cancer is underway in multiple centers. With this technique the spectroscopic information is superimposed as a grid on the MR image and the spectroscopy voxel can display the increased presence of Choline and NAA, supplying metabolic data from the brain tumors. This approach is particularly valuable in the differentiation of tumor recurrence from necrosis following radiation therapy. For prostate cancer, the use of different three-dimensional spectroscopic imaging data on the ratio of choline and normally occurring citrate, has resulted in improved detection, diagnosis of extra-capsular spread, assessment of tumor aggressiveness and surveillance of treatment.

PET/CT imaging

Most PET/CT studies performed today are diagnostic FDG scans. The basis of cancer detection by FDG is the increase in glucose metabolism by cancer cells. The magnitude of elevated FDG uptake and accumulation within tumors is most commonly expressed by the standardized uptake value (SUV), defined by the ratio of the activity per unit mass in the lesion, to the administered activity per unit patient mass. SUV values for FDG of >2.5 FDG have been successfully used to differentiate between benign and malignant lesions. Tumor aggressiveness may be correlated with a higher magnitude SUV. The greatest advantage of PET/CT over other imaging modalities is its' thousand to million-fold higher sensitivity over other techniques. This permits glucose metabolism and countless other biochemical reaction rates to be measured by strict application of the tracer principle. Radiotracer quantities in the nannomolar concentrations, which do not perturb the body's metabolism, may be used to perform the measurements. Since the nannomolar range is the concentration range of most receptor proteins and tumor target antigens in the body, positron-emission tomography is ideal for this type of imaging.

Tumor uptake by FDG, and the resultant value of the test, is cancer site specific. The FDG radiotracer is not well suited for the detection of all cancers; e.g. prostate cancer, especially when the cancer is low-grade. Several alternative tracers are currently under clinical investigation and new ones, with a promising potential for tumor biology, are under development. ^{11}C-methionine, a tracer, which has been used to differentiate tumor from normal tissue on account of elevated protein synthesis is a candidate for this application. The rapid (10 minute) uptake and plateau of ^{11}C-methionine within prostate cancers, allows whole body PET/CT imaging (with decay correction), in spite of the short 20-minute half-life of ^{11}C methionine, with minimal interference from the bladder. The use of ^{18}F-fluorodihydrotestosterone has recently been studied in patients with metastatic prostate cancer in search for a non-invasive method to quantify androgen receptors (AR) by PET. The mismatch in positive findings between FDG and ^{18}F-FDHT suggests the presence of variations in androgen dependence of the different sites, but histologic confirmation of this finding has not yet been obtained.

PET/CT can also be used as an adjunct to CT and MRI in measuring treatment response. The ability to discern viable from necrotic tissue has been an important application of PET. However, the difficulty of separating viable tumor post therapy from inflammation has reduced the reliability of FDG as a quantitative index of response. Most analyses consist of an assessment of the change in SUV. As SUV is a concentration measure, a reduction in tumor volume can result in improved tumor perfusion, which would be manifested in an increase in the SUV. To circumvent this paradox where an increase in FDG could be a consequence of either tumor progression or response, we have introduced the concept of total lesion glycolysis, which combines SUV with the volume of FDG elevation. This semi-quantitative value is a practical and empirical method with which to test the hypothesis of the utility of FDG in the assessment of treatment response. The optimal choice of radiotracers for tumor diagnosis and follow-up depends on the organ site. The concept of using PET with multiple radiotracers, which answer different questions, is likely to become an important thrust in the future of nuclear medicine.

Molecular imaging

Molecular imaging can be defined as the *in vivo* depiction and measurement of metabolic processes at the cellular and molecular level. This differs from classical diagnostic imaging that focuses on anatomical abnormalities. The development of basic molecular biological assay techniques is providing more tools for the better understanding and treatment of disease processes at a basic level. The development of transgenic and knockout animal models of human diseases, allows the systematic approach to the study of the genetic and molecular basis of cancer in a reproducible animal model system. Associated with these developments, the newly introduced reporter gene systems, have allowed the non-invasive imaging of fundamental biological processes, such as gene transcription.

Utilizing the experience gained from the application of cellular and sequence specific DNA probes for florescent microscopy of tissue sections, new approaches have been developed for the *in vivo* study of these processes. This has resulted in new techniques, using reporter constructs and molecular probes, which allow the measurement and monitoring of transcriptional activity (both activation and suppression) of endogenous genes in host tissue.

These developments are providing exciting opportunities to assess specific signal transduction pathways targeted by specific anti-tumor drugs. This should lead to individual patient-specific drug therapy. Imaging would be the guide for the optimal drug regimen and dose. It would be monitoring the therapeutic impact of the selected drug regimen by measuring the drug's effect on specific protein-protein interactions. From this research, new "end points" for monitoring drug response may emerge. Clinicians would benefit from new quantitative methods for the identification of "partial response" and "complete response" reflecting changes in the metabolism and biology of the tumor. Purely anatomical descriptors, such as caliper diameter measuring tumor size will become obsolete.

Imaging reporter constructs to monitor gene therapy is another approach of molecular imaging. It is now possible to monitor the distribution, concentration and persistence of viral vectors and the level of therapeutic transgene expression by this non-invasive imaging technique.

Further developments of imaging probes include radiolabeled substrates, targeted contrast agents and ligands, which allow the non-invasive elucidation of specific cell cycle systems and signal transduction pathways, which are altered in cancer. With the further development of molecular imaging techniques, it is anticipated that we will be able to visualize the actual molecular signatures of cancer in patients. It should be possible within the next decade to visualize and determine which genes are being expressed in specific cancers and translate this information directly into better clinical management of an individual patient.

At present, all the *in vivo* research in molecular imaging is being conducted on animals, mostly on mice and rats. New animal imaging instruments: Micro-PET, micro-CT and small animal MR have facilitated this research. These noninvasive approaches of obtaining measurable information in a sequential mode have produced significant advances, as has the development of suitable receptors integrating and following reporter gene manifestations.

Genetic imaging

Genetic imaging is assuming increased importance. To be able to participate in genetic medicine, the information must be imaged at the molecular level. The directions of genetic imaging are:

a) Gene expression using intracellular or extracellular reporter genes. An accepted technique in animal genetic imaging employs reporter genes such as Lucifer's (the firefly gene responsible for making it glow in the dark).

b) Screening of populations at known risk (either specific gene identification or family disease history) in order to discover the earliest phase of disease.

c) Providing guidance for and follow-up of gene therapy. Image-guided gene therapy, whether introducing good genes carried by adeno or retroviruses or with stem cells carrying the good gene, is making slow advances. All present imaging techniques will be used to guide the micro-catheters or needles to the desired target. Although progress is painfully slow there have been successes.

Suggested reading

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