REVIEW ARTICLE

Molecular Imaging: Implications for Oral Cancer

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Abstract

Cancer is a scourge that affects millions of the world population. The incidence of oral cancer is alarmingly high in the Indian subcontinent. What is more appalling is the low survival rate of these patients. Various efforts are being made to bring about early diagnosis, accurate staging and aggressive treatment. Molecular imaging is one step in this direction.

Today, imaging plays a role not just in detecting what is radiopaque and what is radiolucent, but also plays a very active role in detecting disease down to the level of a single cell. The field of molecular imaging has been defined as 'the visualization, characterization, and measurement of biologic processes at molecular and cellular levels in humans and other living systems'. The amalgamation of advanced imaging techniques such as Positron Emission Tomography and Single Photon Emission Computed Tomography with Computed Tomography, the use of newer contrast agents, incorporation of nanoparticles all have brought about these revolutionary changes in imaging.

The purpose of this article is to describe the various techniques used in molecular imaging specifically highlighting their application in head and neck cancer.

Keywords: Molecular imaging, head and neck cancer, imaging.

INTRODUCTION

Cancer is one disease that continues to baffle physicians and scientists alike. It is predicted that 15 million new cases of cancer will occur worldwide by 2020.[1] In south Asia, the incidence of oral cancer is about 12.7 per 100,000 population among men and 8.3 per 100,000 population among women.[2] In India, oral caner accounts for 50 to 70% of total cancer mortality.[3]

India has the highest incidence of oral cancer in the world. Cancer registries have confirmed a high incidence of oral cancer and case control and cohort studies have established that the high incidence is due to widespread habits of tobacco chewing and smoking. The proportion of advanced cases is significantly high and these patients have a dismal survival despite aggressive therapy.[4]

Imaging plays an integral part of cancer patient management and is used to detect, characterize, stage, assess post-therapeutic response and determine recurrence.

Imaging technologies may be classified as being structural or functional. Structural imaging using CT, MRI, and ultrasound allows assessment of morphological features of normal tissues and organs of the body and of malignant lesions in these structures.

In contrast to this, the new buzzword in the field of imageology since the mid 1990s is molecular or functional imaging. It has been defined by the Society of Nuclear Medicine as 'the visualization, characterization, and measurement of biologic processes at molecular and cellular levels in humans and other living systems'.[5] Molecular imaging uses several techniques in association with CT, MRI, PET and SPECT.

The advantages offered by molecular imaging over structural imaging are numerous. Gross macroscopic changes in cancer detected by structural images lag behind alteration at a molecular level. Thus, molecular imaging allows one to detect neoplastic changes earlier. Macroscopic changes, such as enlargement of lymph nodes, tend to be nonspecific. Presence or absence of malignancy can only be detected by molecular imaging. Molecular imaging also provides information about the physiological, biological and molecular processes in tumors, which are impossible with structural imaging.

The purpose of this article is to describe briefly the various techniques used in molecular imaging with emphasis on head and neck cancer.

TECHNIQUES IN MOLECULAR IMAGING

Superparamagnetic Iron Oxide Nanoparticle based Detection

Biodegradable nanoparticles composed of an iron oxide core and coated with dextran are injected intravenously. These are taken up by the reticuloendothelial system and degraded by macrophages in lymph nodes. Metastatic nodes, which

have no macrophages, are not able to degrade the nanoparticles. On subsequent MRI, these nodes have higher signal intensity than normal nodes.[5]

Anzai et al evaluated 29 patients with metastatic nodes with a biodegradable nanoparticle (ferumoxtran-10) enhanced MRI. They found that postcontrast nodal staging was more accurate than precontrast staging.[6] Results of a study[7] of head and neck cancer showed higher diagnostic performance at MR imaging performed with ferumoxtran-10 than at MR imaging performed without it.

Imaging Cancer Metabolism

Normal cells metabolize glucose by oxidative phosphorylation, whereas cancer cells do so by glycolysis. This phenomenon is known as the Warburg effect.[8] This utilization peaks during hypoxic conditions, as occurs often in cancers. F-18 is incorporated with deoxyglucose [2 (F-18) fluoro-2deoxyglucose or FDG] and injected intravenously. This is readily taken up by cancer cells, which express glucose transporters (GLUT-1) in higher concentration. Following the glycolytic pathway, FDG is metabolized to 2-deoxyglucose 6-phosphate, which cannot be catabolized further and becomes trapped within the cell. PET imaging then carried out depicts areas of deposition of FDG denoting hypoxic areas in a cancer. The main disadvantage of FGD-PET is its high uptake in other tissues, including inflammatory tissue.[5]

Several studies[8,9] have shown that FDG-PET is useful in diagnosing, staging and monitoring response in head neck cancer, since these have an accelerated glucose metabolism also have higher number of GLUT-1 transporters.

Cell Proliferation Imaging

It consists of assessment of uptake and metabolism of nucleosides used in nucleic acid synthesis. The most widely used tracer is 3'-deoxy-3'-F-18-fluorothymidine (FLT). It enters cells through carrier mediated diffusion. If thymidine kinase phosphorylates FLT to fluorothymidine phosphate, this gets trapped within the cells as it cannot be further metabolized. This accumulation can then be detected by PET. Detection of bone metastasis is difficult because of the high uptake by proliferating marrow cells. In general, the sensitivity of detecting tumors by FLT is comparable to that with FDG. However, unlike FDG, FLT can discriminate between tumor and inflammatory cells.[10]

Troost et al found that in head and neck cancer patients, ^{18}F-FLT PET showed uptake in metastatic as well as in nonmetastatic reactive lymph nodes, the latter due to reactive B-lymphocyte proliferation. They concluded that because of the low specificity, ^{18}F-FLT PET is not suitable for assessment of pretreatment lymph node status.[11]

During the course of therapy, the reduction in the proliferative activity of the primary tumor can be accurately imaged by ^{18}F-FLT. The changes in the ^{18}F-FLT PET signal during therapy in patients with squamous cell carcinomas of the head and neck treated with radiotherapy alone or with concomitant chemotherapy are being assessed.[12]

Oxygenation Imaging

Increased cellularity of tumors triggers hypoxia, which in turn triggers angiogenesis and is associated with tumor progression, likelihood of metastatic tumor spread and poor clinical outcome.

Several techniques have been devised to visualize hypoxic regions in tumors. ^{18}F-fluoromisonidazole (FMISO) is a lipophilic compound that binds to intracellular proteins in live cells with active mitochondria when oxygen concentration is below 20 mm of Hg. Rajendran et al showed that pretherapy FMISO uptake shows a strong trend to be an independent prognostic measure in head and neck cancer.[13]

^{64}Cu (II) diacetyl-bis (N4-methyl thiosemicarbazone) (Cu-ATSM) is another compound used to image hypoxia. In hypoxic cells, the redox state of the Cu atom changes and ^{64}Cu becomes trapped in the mitochondria after dissociation of the Cu-ATSM complex.

2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide (EF5) labeled with ^{18}F-fluorine is another newly developed PET tracer that has been used as a hypoxia marker. Komer et al[14] found the potential of ^{18}F-EF5 to detect hypoxia in head and neck cancer is encouraging. Further development of ^{18}F-EF5 for eventual targeting of antihypoxia therapies is warranted.

50 to 60% of tumors contain hypoxic regions with a partial pressure of oxygen (pO_2) $\leq$ 5 mm of Hg. Positive accumulation of these agents is proportional to the extent of hypoxia in the pO_2 range of a few mm of Hg. Although the extent of hypoxia does not correlate with tumor size, oxygenation imaging can be used as a predictor of survival, and can help direct treatment of head and neck cancers since it is known that hypoxic cells are more radioresistant and possibly more chemoresistant than normoxic cells.[15]

Angiogenesis Imaging

Vascular endothelial growth factor (VEGF) is a leading factor in tumor angiogenesis. It induces the proliferation, differentiation and migration of vascular endothelial cells, increases capillary permeability and enhances endothelial cell survival by preventing apoptosis. VEGF can be radiolabelled and studied by MRI, SPECT, PET or ultrasound. Kyzas et al in a meta-analysis showed that VEGF protein overexpression, as detected with immunohistochemistry, is associated with worse overall survival in patients with head and neck cancer.[16]

Another compound that is significantly upregulated in tumor vasculature but not in quiescent endothelium is integrin $\alpha_v\beta_3$. It binds to arginine-glycine-aspartic acid (RGD) containing compounds. F-18 labelled RGD compounds allow for visualization of $\alpha_v\beta_3$ expression in the body using PET.[17] Beer et al[18] concluded that $\alpha_v\beta_3$ expression is promising as a marker of angiogenesis in head and neck cancer and that [^{18}F]Galacto-RGD PET might be used as a surrogate variable of angiogenic activity. However, they also cautioned that contradictory reports about the role of $\alpha_v\beta_3$ exist as well and that the ultimate meaning of $\alpha_v\beta_3$ expression in the context of angiogenesis was very complex.

MR Spectroscopy

It allows one to quantitatively assess the amount, type and location of various small molecules within a tissue or organ of interest. Proton (^{1}H) MR Spectroscopy (MRS) assesses the spatial distribution of tissue metabolites such as creatine, choline, amino acids, nucleotides, lactate and lipids.

Typical spectral patterns associated with head neck cancer include an increase in total choline signal relative to creatine, often coupled with lactate. Choline levels are raised due to increased cell membrane synthesis, and lactate levels due to increased metabolism through the glycolytic pathway.[19]

Application of Molecular Imaging to Head and Neck Cancer

Accurate staging: Imaging using iron oxide nanoparticles and FDG-PET can aid in accurate staging by detecting micrometastasis to the regional lymph nodes.

Treatment planning: FDG-PET helps define the tumor volume; oxygenation imaging with FMISO-PET and other agents helps in planning intensity-modulated radiation therapy (IMRT); angiogenesis imaging aids in planning antiangiogenic therapy.

Assessment of tumor response: Serial FDG-PET before and after treatment for cancer helps predict the prognostic response as patients who have lower uptake values have a longer survival; FLT-PET can provide an early detection of therapeutic response; FMISO-PET can be used to monitor chemoradiation therapy, with early resolution of FMISO uptake being associated with excellent locoregional control; Cu-ATSM retention has been shown to be associated with poor prognosis after radiotherapy; changes in MRS have been found to be different among complete responders to incomplete responders, thus enabling prediction of treatment outcome.

CONCLUSION

Even with years of research behind us, the prognosis of oral cancer remains poor. The onus lies on oral physicians to detect disease in the early phases, provide an accurate staging in order to bring about an improvement in the prognosis of oral cancer.

It is expected that the fruits of today's molecular imaging research will have a direct effect on patient care within the next 5 to 15 years. Thus it becomes imperative that oral physicians keep abreast of latest advances in this field. This knowledge will ultimately be translated into better patient care.

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