

Noninvasive functional imaging techniques: positron emission tomography (PET), magnetic resonance spectroscopy (MRS), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

Ruediger E. Port

Genentech Inc., South San Francisco, CA 94080, USA

ABSTRACT In the pharmaceutical industry, there is currently increasing interest in noninvasive functional imaging techniques as potential early indicators of drug effects in patients. PET allows one to monitor absolute concentrations of radiolabeled drugs and metabolites, or of ligands to specific receptors, in tissues, and to visualize their distribution three-dimensionally. MRS is capable of monitoring metabolic conversions *in vivo* without labeling. DCE-MRI shows the distribution of small-molecular, hydrophilic weight contrast agents between blood plasma and interstitial space in tissue in real time and can be used to detect effects of antivascular or anti-angiogenic compounds.

KEY WORDS PET; *in vivo*; MRS; DCE-MRI

1 INTRODUCTION

In the pharmaceutical industry, there is currently a strong interest in applying “imaging” methods in drug development, motivated by a desire to determine drug effects in humans earlier and more precisely than by conventional clinical measures. The word “imaging”, in this context, refers to noninvasive procedures like positron emission tomography (PET), or dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) which can provide information about the distribution of drugs, the occupancy of specific receptors, or the function of vessels in target tissues. These methods may be called “noninvasive func-

tional” imaging methods, in contrast to more traditional imaging methods like X-ray scanning or computed tomography which are also noninvasive but are primarily used to obtain morphological information. Some researchers would also imply *in vivo* magnetic resonance spectroscopy (MRS) under the term “noninvasive functional imaging”, although it produces spectra rather than images, because it is another method for obtaining functional information noninvasively.

2 POSITRON EMISSION TOMOGRAPHY

PET images show the localization of radiolabeled tracers in tissues. Absolute tracer concentrations can be monitored over time and can be visualized three-dimensionally (Fig 1). If the tracer is a drug, then PET can show whether this drug gains access to a target tissue and how long it stays there at what concentrations. Local drug delivery is a major problem in the treatment of solid malignant tumors and PET is a way to study this problem in humans (Fig 1).

The interpretability of PET images is limited in that they show concentrations of the radioactive label, regardless of whether it is in the parent compound that was administered or in metabolites which are formed during the period of observation (usually about one hour). For an unambiguous interpretation of PET data, it is best to use tracers that undergo no metabolic conversion or, at most, only one metabolism step during the period of measuring.

The most widely used PET tracer is [¹⁸F] fluorodeoxyglucose (FDG) which allows one to assess the activity of glucose metabolism in tissues. FDG-PET in malignant tumors is useful for staging and prognosis, and also seems to

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Ruedi Port, MD, correspondence author.

Tel: 01-650-225-1820 Email: rport@gene.com

be a potential early indicator of therapeutic effects^[1]. FDG-PET can also help in the early diagnosis of Alzheimer's disease^[2]. PET with specific labeled ligands has been successfully applied in the development of central

nervous system (CNS) drugs by determining the occupancy of receptors, e.g. dopamine receptors, under drug treatment^[3].

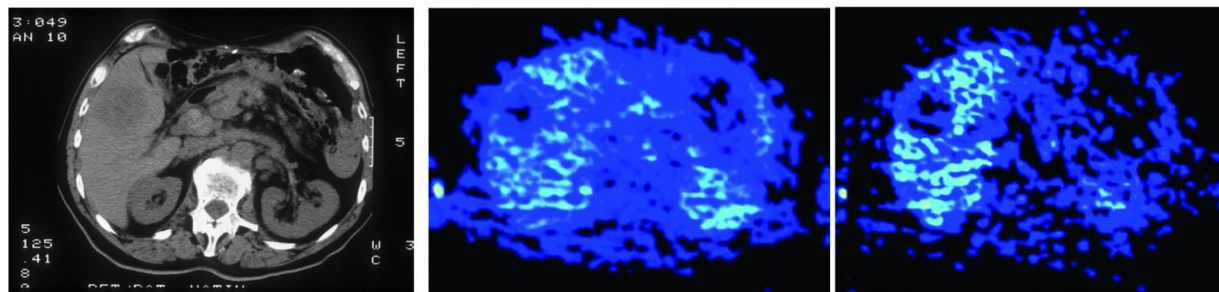


Fig 1 Male patient, 76 years, liver metastasis of a colon carcinoma

Top: CT image showing a hypodense area (metastasis) in the ventral part of the right liver lobe. Middle: PET image obtained 1—2 min after the injection of ^{15}O -labeled water. Bottom: PET image obtained 20—30 min after the beginning of a 12-min infusion of ^{18}F -labeled fluorouracil. Much less radioactivity from labeled water as well as the drug is seen in the metastasis, as compared to normal liver tissue. (Images courtesy of L.G. Strauss.)

Because of the short half-life of most of the radioisotopes used in PET (two hours for ^{18}F), these isotopes are typically generated on the day of the PET examination and are used for automated radiosynthesis of the desired tracer immediately thereafter.

3 MAGNETIC RESONANCE SPECTROSCOPY

MRS *in vivo* allows one to monitor relative concentrations of compounds of interest in tissues over time. No radioactive labeling is required. Parent compounds and metabolites can be followed separately in the same experiment^[4] (Fig 2).

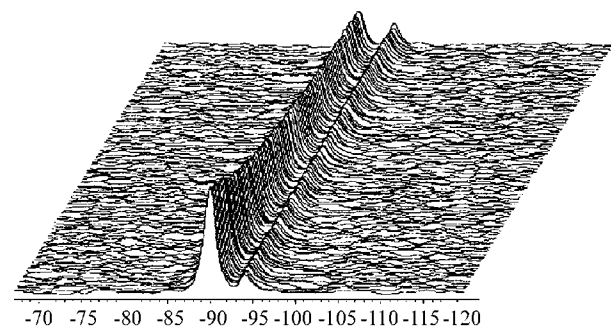


Fig 2 ACI rat, subcutaneous Morris hepatoma 3924A

^1H MR spectra of tumor obtained 105—326 min after the intratumoral injection of 30 mol floxuridine (2.5% of DL_{50}). Temporal resolution: 4.5 min. x-axis represents difference in resonance frequency from standard (trifluoroacetic acid). The areas under the resonance peaks are proportional to the amounts of floxuridine (—90 ppm) and its primary metabolite, 5-fluorouracil (—94 ppm) in tumor. The local elimination of the parent drug and the formation of the metabolite 5-fluorouracil were noninvasively monitored for six hours after the injection. The experiment could be repeated in the same animal if desired. (From reference^[4], with kind permission of Springer Science and Business Media.)

Sensitivity and specificity is best with compounds containing fluorine. Concentrations in tissue have to be 100 mol/L or higher to be detectable so that, for drug monitoring, there is often a sensitivity problem unless the drug is administered in gram doses, like 5-fluorouracil. Sensitivity is much less of a problem when measuring at the site of an interstitial injection (Figs 2, 3).

Endogenous compounds which are present in high concentrations, such as choline, N-acetylaspartate, lactate and citrate, can also be monitored, for example to support diagnosis and therapy monitoring in malignant tumors^[6].

4 DYNAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) uses signals from water protons. The chemical information available in MRS to discriminate parent drugs and metabolites is traded for spatial information in MRI. The result are images showing the distribution of water in the body. Again, no radiolabeling is required. There is no sensitivity problem because of the high natural concentration of water in tissues (68 mol/L). Spatial resolution is higher than with PET. Measurements can be made such that signal intensity is increased in the presence of a contrast agent, usually a heavy metal chelate like gadolinium diethylene triamine pentaacetic acid (Gd-DTPA, gadopentetate). DCE-MRI implies the repeated acquisition of images at regular intervals during and after the administration of a contrast agent, for example every five seconds for five minutes.

These images then allow one to literally watch the distribution of the contrast agent in and out of target tissues, like malignant tumors. Gd-DTPA is highly polar and does not cross cell membranes; it is not bound to tissue components. Its kinetics in tissue reflect the distribution be-

tween blood plasma and the interstitial space which depends on blood flow, and on the density and permeability of capillaries. Thus, monitoring Gd-DTPA kinetics in tissue can give information on drug effects on vessel function in target tissues^[7] (Fig 4).

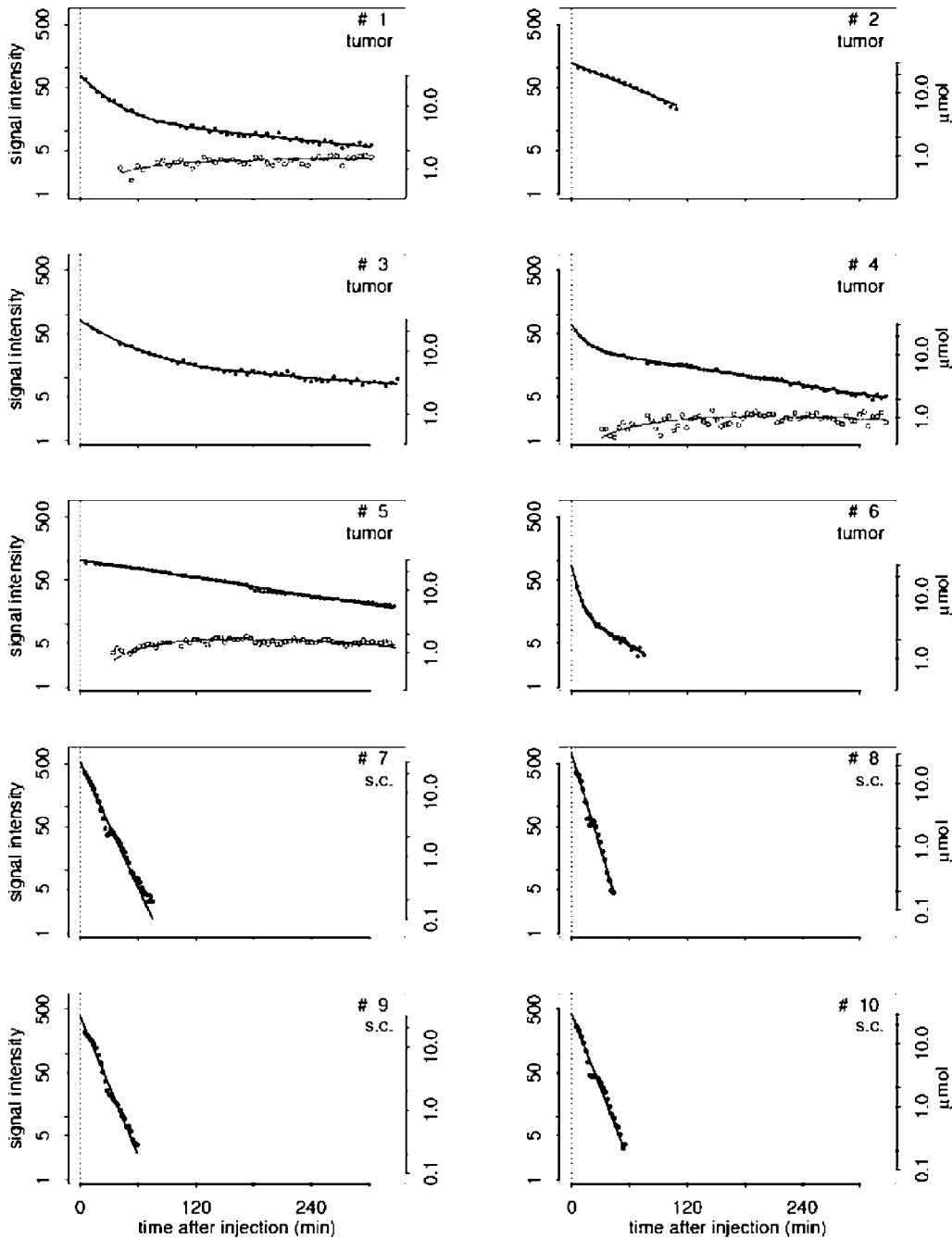


Fig 3 ACI rats, Morris hepatoma 3924A, located subcutaneously

Bolus injection of 30 mol floxuridine either intratumorally (Morris hepatoma 3924A, #1–6) or subcutaneously (#7–10). ¹H MR signal intensities measured *in vivo* at the injection site versus time after administration. Filled circles; floxuridine; open circles; 5-fluorouracil (metabolite). Right y-scale, amount of parent drug remaining at the injection site. The local pharmacokinetics of the parent drug and its primary metabolite were noninvasively monitored for up to five hours. Local disposition of floxuridine is rapid in subcutaneous tissue with half-life of 6–9 min whereas in tumors, there is always a slow component of disposition with half-life varying from 1/2 to 5 hours. (From reference^[5], with kind permission of Springer Science and Business Media.)

Malignant tumors with rapid Gd-DTPA exchange between blood plasma and the interstitial space seem to be more responsive to chemotherapy than those with slow exchange.

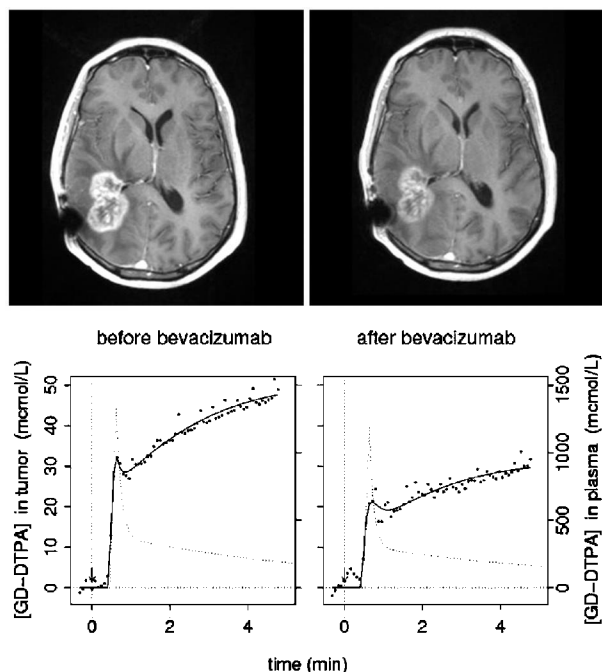


Fig 4 Recurrent glioblastoma

Top: Contrast-enhanced static MR images, 24 hours before and after the first dose of the antiangiogenic antibody drug bevacizumab. Bottom: Dynamic contrast-enhanced MRI, contrast agent concentration in tumor versus time. Arrow: time of bolus injection of contrast agent. Each point represents one dynamic measurement. Dotted curve and right y-scale: Contrast agent concentration in blood plasma versus time, model fit. -Contrast agent leakage into tumor is greatly reduced by drug treatment, possibly by reducing pathological permeability of tumor capillaries. (L. Xu, D. P. Barboriak and R. E. Port, unpublished data.)

5 CONCLUSION

PET, MRS *in vivo*, and DCE-MRI can provide in-

formation about distribution, metabolism and binding processes in tissues in a noninvasive way. Measurements can be made before and after drug treatment in order to detect drug effects. PET can determine absolute concentrations of a radiolabel with high sensitivity, MRS *in vivo* can monitor metabolic processes without radiolabeling but with lower sensitivity, and DCE-MRI can show the distribution of non-radioactive contrast agents in tissues with high temporal resolution. All of these methods hold great promise as potentially powerful tools for drug development as well as for more basic research looking at mechanisms of drug effects at the tissue level.

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非损伤性功能成像技术: 正电子发射断层扫描术、磁共振波谱分析和动态对比增强磁共振影像学

Ruediger E. Port

Genentech Inc., South San Francisco, CA 94080, USA

摘要 当前在医药工业中越来越关注将非损伤性功能成像技术作为潜在的病人体内药物作用早期检测技术。正电子发射断层扫描术可监测组织中放射标记的药物和其代谢物的绝对浓度,或者是特殊受体的配体浓度,且可以三维直观地显示它们在体内的分布。磁共振波谱分析可监测体内未标记药物的代

谢转化。动态对比增强磁共振影像学可显示小分子、亲水的造影剂在血浆与组织细胞间隙间的即时分布,并可以用来检测抗血管或血管生成的化合物的作用。

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