GALLIUM-67 IMAGING

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Series Preface

The past five years have produced an explosion in the knowledge, techniques, and clinical application of radiology in all of its specialties. New techniques in diagnostic radiology have contributed to a quality of medical care for the patient unparalleled in the United States. Among these techniques are the development and applications in ultrasound, the development and implementation of computed tomography, and many exploratory studies using holographic techniques. The advances in nuclear medicine have allowed for a wider diversity of application of these techniques in clinical medicine and have involved not only major new developments in instrumentation, but also development of newer radiopharmaceuticals.

Advances in radiation therapy have significantly improved the cure rates for cancer. Radiation techniques in the treatment of cancer are now utilized in more than 50% of the patients with the established diagnosis of cancer.

It is the purpose of this series of monographs to bring together the various aspects of radiology and all its specialties so that the physician by continuance of his education and rigid self-discipline may maintain high standards of professional knowledge.

LUTHER W. BRADY, M.D.

Preface

The story of gallium-67 imaging is an interesting example of the role of serendipity in the progress of medicine. When Edwards and Hayes initiated their studies of gallium-67, they were primarily interested in its use as a bone-scanning agent (1). Thus, if the development of the ^{99m}Tc-labeled phosphate compounds occurred only a few years earlier (2), the original clinical studies of gallium-67 might never have been undertaken. While Edwards and Hayes must have been disappointed in the mediocre bone-localizing characteristics of their carrier-free gallium-67, they were quick to recognize the significance of the unexpected deposition of the radionuclide in tumor.

As gallium-67 began to be used clinically for tumor imaging, numerous investigators noticed that it not only localized in malignant tissue but in inflammatory lesions as well. It remained, however, for Lavender (3) and Littenberg (4) and their associates to exploit these "false positives" into an entirely new field of gallium imaging.

In spite of the fact that much of the basic clinical investigative work has been accomplished, it is still difficult for even the most dedicated practitioner to keep track of the expanding body of information on gallium imaging. New applications have been introduced, some older applications have not stood the test of time, new mechanisms of localization have been proposed, and even the determination of the energy of the major photon emissions has been in a state of flux. Changes in techniques have been introduced which have significant consequences on scan interpretation. The same pattern of distribution which is normal for the 24-hour image may be distinctly abnormal for the 72-hour image. Moreover, important information about gallium may appear in a variety of journals, many of which are not frequently read by physicians who practice nuclear medicine.

Therefore, the purpose of this book is to bring together in one concise volume the state of the art in the clinical use of gallium. While it will not be the last word on gallium, we hope it does serve as convenient primer and reference source.

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Gallium-67 Imaging

Contents

Part 1

Fundamentals

1
Mechanisms of Localization

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Many fundamental aspects of gallium-67 (^{67}Ga) transport and localization are unknown. When ^{67}Ga citrate is injected intravenously, much of the dose binds loosely to plasma protein, while some remains in soluble citrate configuration (1–3). Gallium-67 is bound primarily to transferrin and other α- and β-serum globulins. The extent of binding is dependent on numerous factors. Increase in both citrate content (above 6.6 μmol of citrate per 10 ml of serum) and carrier gallium content decreases the extent of plasma protein binding (1). Interestingly, increases in carrier gallium and citrate content have also been found to decrease localization of gallium in tumors. Iron also competes with gallium for binding sites on transferrin. Excess iron blocks ^{67}Ga binding to transferrin. If serum transferrin is saturated with iron at the time of ^{67}Ga citrate injection, tumor uptake of the radionuclide is inhibited. Paradoxically, administration of iron 24 hours after administration of ^{67}Ga citrate actually enhances tumor to background ratios (4). When ^{67}Ga citrate is administered to patients with saturated transferrin-binding sites, less localization in liver, greater renal activity, and more rapid clearance (Figure 1) occur. Scandium, administered coincidentally with ^{67}Ga citrate, also blocks protein binding of the radionuclide. However, in this case, tumor to background ratios are enhanced. Unfortunately, the doses of scandium required to enhance tumor to background ratios also cause hemolysis of human erythrocytes; therefore, this method of enhancing ^{67}Ga imaging is not clinically useful (5–7).

Approximately 15–25% of ^{67}Ga is excreted by the kidneys within the first 24 hours after intravenous injection. Clearance of radioactivity from the body after the first 24 hours is usually slow. The remaining ^{67}Ga is distributed in the plasma and body tissues and retained for several weeks; its biologic half-life is approximately 25 days (8,9). After 24 hours, the major route of excretion is the colon.

Swartzendruber et al. (10), by use of ultracentrifugation, originally determined that the intracellular localization of ^{67}Ga occurred in lysosomes or lysosome-like granules of the cell. Aulbert and associates (11) confirmed

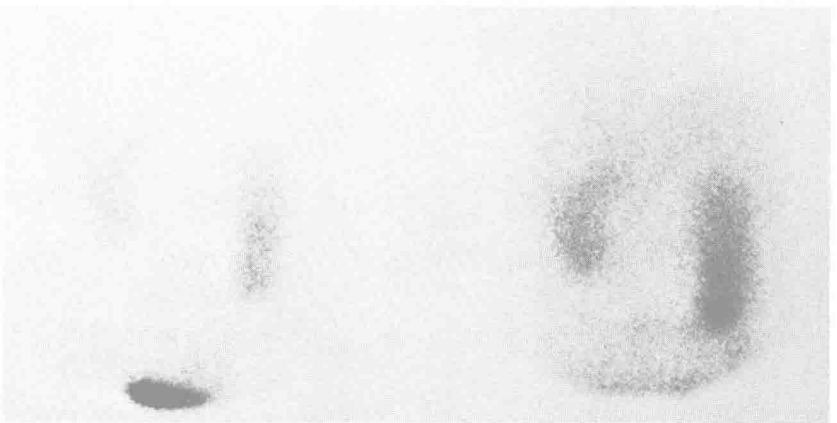

Figure 1. Scan performed 48 hours after ^{67}Ga injection in patient with hemochromatosis. No hepatic, splenic, or bone activity is observed. Only kidney and some bowel activity are detectable. This abnormal pattern of ^{67}Ga localization in patients with hemochromatosis supports the concept that ^{67}Ga acts in certain respects as an iron analog.

lysosomal localization of ^{67}Ga in the liver. Subsequent ultracentrifugation studies (12) demonstrated that normal tissues, such as the liver, localized ^{67}Ga in the lysosomal fraction. Animal hepatomas and lymphosarcomas, however, localized ^{67}Ga not only in lysosomes but also in smaller cellular particles that are associated with the endoplasmic reticulum and in small, electron-dense, single-membrane granules. Ito and colleagues (13) showed a somewhat different pattern of intracellular localization. They found significant quantities of ^{67}Ga in soluble fractions and bound to nuclear, mitochondrial, and microsomal cell components. They also demonstrated preferential localization in viable, as compared to nonviable, tumor tissue. Clausen et al. (14) found ^{67}Ga localized primarily in the nuclear fraction of tumor tissue, while Anghileri (15) demonstrated ^{67}Ga binding to intracellular lipoproteins, nucleoproteins, phospholipids, and nucleic acids. The localization of ^{67}Ga has been likened to the localization of calcium and magnesium, with the speculation that ^{67}Ga displaces these ions from their intracellular divalent cation-binding sites (16,17). There is controversy over the relationship of ^{67}Ga accumulation, lesion growth rate, and metabolic activity. Some lesions clearly show a correlation between growth rate and ^{67}Ga uptake, whereas others do not (18–22). Considering the confusing array of observations, it is not surprising that few investigators agree on a single concept to explain the mechanism of ^{67}Ga localization.

LOCALIZATION IN NORMAL TISSUES

We have recently demonstrated that ^{67}Ga in human colostrum is bound primarily to lactoferrin (23). Lactoferrin is a protein with a molecular weight of approximately 80,000 and is somewhat similar in configuraation to transferrin. It binds both iron and gallium more avidly than transferrin and is therefore capable of attracting ^{67}Ga from transferrin. The migration of ^{67}Ga from transferrin to lactoferrin occurs most efficiently in an acid environment since ^{67}Ga binding to transferrin is inhibited below pH 7 while binding to lactoferrin is not inhibited above pH 3 to 4. Lactoferrin is present in high concentration in many of the normal tissues and secretions in which gallium localizes including lacrimal glands, tears, salivary glands, nasopharynx, spleen, bone marrow and gut. Lactoferrin is also a major protein constituent of neutrophilic leukocytes (24). Both lactoferrin and transferrin are metabolized in the liver. The combination of migration of ^{67}Ga from plasma proteins, principally transferrin, to tissue and secretory proteins such as lactoferrin as well as the normal metabolic accumulation and destruction of both transferrin and lactoferrin in the liver provides a convenient explanation of the normal pattern of ^{67}Ga localization.

LOCALIZATION IN INFLAMMATORY LESIONS

Gallium-67 localization in inflammatory disease is mediated in some way through the action of the neutrophilic leukocytes. ^{67}Ga uptake in abscesses is suppressed in severe leukopenia (25). It is unknown whether ^{67}Ga binds to leukocytes which subsequently migrate to the inflammatory lesion or the ^{67}Ga binds to leukocytes which have already localized in the lesion. Both mechanisms are possible. ^{67}Ga accumulation in such sites is enhanced by increased blood

supply and the "leaky" capillary endothelium usually associated with both abscesses and tumors. Tsan and associates have shown that ^{67}Ga may also be taken up directly by many microorganisms. (26)

A number of possible explanations of the precise mechanism of ^{67}Ga localization exist. The ^{67}Ga-transferrin molecule may bind to the surface of both leukocytes and bacteria (transferrin is known to bind to cell surfaces) (27). Alternatively, ^{67}Ga either bound to transferrin or in the ionic state may pass into the cell and be protein-bound to intracellular proteins such as lactoferrin. Finally, ^{67}Ga may become incorporated into the leukocyte or bacteria as part of a metabolic enzyme system. The presence of lactoferrin in high concentration in neutrophilic leukocytes and the presence of this protein in abscess fluid suggests that it plays some role in the process.

LOCALIZATION IN TUMOR

Ito et al. (13) and Winchell and coworkers (28,29) postulate that ^{67}Ga is taken up in tumors as a result of binding to intracellur tumor proteins which compete successfully with transferrin for ^{67}Ga. Clausen and coworkers (14) showed that one-third of intracellular tumor ^{67}Ga is bound to ferritin. Ferritin is present in high concentration in certain malignancies such as Hodgkins disease as well as normal liver, spleen, gastrointestinal mucosa and bone marrow. Hayes and associates have found ^{67}Ga bound to 45,000 molecular weight glycoprotein in tumors (30).

Lactoferrin is also present in increased concentration in some tumors (32) although it has not been shown to bind ^{67}Ga within tumor. The exact mechanism by which ^{67}Ga enters the tumor cell to become associated with tumor proteins is unknown. It may diffuse in directly in ionic form, become attached to the cell surface in the form of ^{67}Ga-transferrin or ^{67}Ga-lactoferrin or be carried into the tumor region associated with inflammatory cellular elements.

GENERAL CONCLUSIONS

Most of the currently popular proposed mechanisms of ^{67}Ga localization assume that ^{67}Ga acts in part as an iron analog. It binds to iron binding proteins although it is incapable of becoming incorporated into the heme molecule, perhaps because of its inability to undergo reduction and subsequent reoxidation reactions within the body. Transferrin appears to act primarily as a carrier protein for ^{67}Ga, transporting it from the site of injection to the site of cellular localization. Greater knowledge about specific tissue proteins which are capable of ^{67}Ga binding may lead to improved radiopharmaceuticals for both tumor and abscess localization. Such proteins may be responsible for the localization of other cations as well.

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