Medical Uses of Monochromatic X-rays

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BACKGROUND:

At a time in which medical costs are straining the economic welfare of our country, do we need another new technology to diagnose and treat diseases? To answer that question we must explore any shortcomings of our present system and assess the benefits that we might hope to derive from the costs of another layer of expensive technology. If our longevity and quality of life can be significantly altered by development of monochromatic x-rays, then by all means we must pursue this holy grail.

ARE MONOCHROMATIC X-RAYS USEFUL?

Present day diagnostic x-ray systems suffer from many ills. Among these are: (1) the delivery of relatively high radiation doses; (2) limited resolution; and (3) less than optimal sensitivity and specificity secondary to the acceptance of scattered radiation, a suboptimal radiation spectrum and the failure to effectively use energy discriminant information.

Boone and Siebert have developed a method for calculating a Figure of Merit (FOM) designed to establish whether or not monochromatic x-rays (MXR's) are an improvement over standard x-ray beams [1]."It embodies parameters related to image quality in the numerator and radiation integral dose to the patient in the denominator. In this manner, maximizing image quality and minimizing radiation dose amount to maximizing the FOM." Their work in the area of angiography concludes that "monochromatic x-ray beams are capable of delivering the same image quality at about half the radiation dose to the patient compared to conventional x-ray tubes". In other areas and using other techniques, we can improve significantly even on the FOM seen in angiography, as the figures used in that procedure are those obtainable using standard image intensifiers and digital subtraction techniques.

If we were able to produce tunable MXR's we could reduce radiation dose to a patient for many reasons: (1) Softer x-rays would be absent from the beam thereby lowering entry dose ; (2) Higher energy photons would also be eliminated reducing the amount of scatter seen by the detector; (3) Enhancements to imaging would be gained by using phase contrast imaging; (4) Scatter reduction would be appreciable using time of flight imaging; (5) Selection of the MXR energy most suited to the tissues being studied takes advantage of energy discriminant information; and (6) Inherent differences in the linear attenuation of some tissues can be used more effectively. By combining tunable MXR's with rapid gating of detectors to accomplish direct "3-D" digital acquisition and computer generated "2-D" reconstructions and image screening, we could be light years ahead of our present inadequate system. But first we must produce a usable beam.

VANDERBILT'S APPROACH TO THE PRODUCTION OF MONOCHROMATIC X-RAYS:

Why Use the Free Electron Laser?

The FEL is unique in that it is **simultaneously** a dual source of electrons and photons . Both its high brightness electron beam and its high intensity infrared (IR) output are delivered in picosecond pulses. Since the electrons are mostly at the same energy and the IR photons are mostly at the same frequency, X-rays produced by Thompson scattering (when one redirects the IR and e-beams into a head-on collision) will mostly be at the same energy [2]. Since the FEL is tunable, the X-rays will be tunable. Additionally, since the IR and e-beam interaction zone is small (50 microns), the "source" of the x-rays is for all intents and purposes, a point source radiating into a forward-directed cone of radiation. This creates an ideal geometry for imaging (i.e.- a circular beam covering 10 cm or more at 10 meters distance). Fluxes generated (10^8 x-ray photons/mm^2 /second) are equivalent to those available from standard diagnostic x-ray tubes [3,4]. Therefore, the FEL can deliver tunable, near-monochromatic x-rays in picosecond pulses with high flux and in an ideal geometry for imaging. Why use anything else?

WHAT ARE SOME OF THE ANTICIPATED DIAGNOSTIC USES?

Sorting out tissues by attenuation:

Among the anticipated uses for MXR's is the diagnostic evaluation of the breast for malignancies. If use of the MXR's created a benefit of only a twofold improvement in the FOM, one could halve the radiation dose delivered in one of the most common x-ray examinations performed today. However, there is an additional advantage to be gained, in that the interaction of X-rays with matter in the mid-teen keV range tends to favor photoelectric scattering rather than Compton scattering. Because of this, there is a "trough" for reduction in radiation dosage in the 14-18 keV region, allowing further reduction in dose from 6 to 50 times.

Furthermore, if we are to derive maximal benefit from use of MXR's, we must learn more about how these x-rays interact with the "target". To that end, specimens of breast tissues were studied at the Brookhaven National Laboratories, National Synchrotron Light Source (NSLS) using MXR's from 14 to 18 keV. Prior work by Johns and Yaffe between 20 and 100 keV had shown that cancerous tissues absorbed MXR's more "avidly" than do normal tissues at energies below 30 keV [5]. Our work confirmed and extended their findings by showing that cancers tend to exhibit a higher effective Z at energies lower than 20 keV, and that they absorb approximately 11% more MXR's than do normal tissues through the 14-18 keV range [6]. Unfortunately, this fact alone would not assure visualization of tumors using standard "2-D" imaging by plain film mammography. However, direct digital acquisition of data with motion of patient and detector (given our beam must remain stationary) allows for "3-D" imaging and the ability to study the breast (or any organ) slice by slice without superimposition of confusing shadows. Computers can offer assistance by searching voxel by voxel (voxel = a picture element (pi**xel**) with a finite depth (**vo**lume)) for tissues exhibiting a high attenuation and flagging these for further perusal by the radiologist. Computers can also search for minute calcifications, stellate tissue aberrations, and asymmetry of the breasts assisting enormously in every day screening.
This same methodology can be applied to any organ system in the body (e.g.- lung, liver, brain, etc.) to diagnose aberrant high attenuation tissues within relatively homogenous organs or to permit precise three-dimensional localization of tumors for procedures such as stereotactic brain surgery.

Time of flight imaging:

As x-rays traverse tissues they are, of course, scattered to some extent. These scattered x-rays offer little useful information for imaging purposes and comprise 65-95% of the detected intensity in standard radiography. If we were able to utilize only the unscattered portion of the beam (i.e. the photons which pass through the tissues unscathed, called "ballistic photons"), we could improve conspicuity of lesions another 6 to 9 times due to improvement in the signal/noise ratio. In an imaging setting, ballistic photons may be expected to exit the tissues within 10 to 100 picoseconds. Scattered photons, on the other hand, exit in a nanosecond time regime. Rapid gating of an imaging chain with a multichannel plate and CCD to accumulate only ballistic photons has already been accomplished using x-rays from a laser-produced plasma [7].

Phase contrast imaging:

The x-ray absorption coefficients of light elements are very small, yet if one uses an x-ray interferometer and some "3-D" imaging techniques, phase shifts in the x-ray beam traversing the tissues can be elicited by light elements which are large enough to be detected. This technique is approximately 100 times more sensitive to the presence of these light element than absorption contrast imaging [8]. Since x-ray interferometers to date have been made from large and highly perfect single-crystal blocks, they have been quite small [9,10,11]. This lends itself to performance of X-ray microscopy and computed tomography only of small specimens. Whether or not this can be scaled up to a large enough size to allow imaging of large body appendages or the whole body remains to be seen. However, the ability to image tumors directly without the injection of contrast agents holds great promise and warrants the pursuit of larger interferometers.

Subtraction Imaging in Angiography:

Dual energy digital subtraction imaging has had some limited success in the study of vascular anatomy using contrast injections and filtered standard beams. As Boone and Seibert have noted a change to MXR's will allow a reduction in radiation dose and by imaging just above and just below the k-edge of iodine a reduction in the amounts of contrast needed for a study.

Other applications:

Veterinary use, X-ray microscopy and holography are other potential uses for these MXR's, but will not be discussed here.

THERAPEUTIC USES ANTICIPATED:

The union of chemotherapy and radiotherapy in order to deliver "more bang for the buck" to tumors is within the reach of MXR's and new experimental drugs. One can deliver multiple small doses of a drug over a time period of days or weeks. And if the material accumulates incrementally within a malignancy, one has a clear-cut method for delivering metals

into a tumor. By substituting metallic ions into the drug's molecular labyrinth and selecting a metal with a k-edge near that of the MXR's deliverable, one can stimulate the production of focal concentrated radiation damage in a tumor by knocking k-shell electrons loose from the drug by resonance with the MXR's.

Several drugs are under investigation including metalloporphyrins (By J. Nelson, M.D. at the University of Washington, Seattle) , IUDR and BUDR (iodinated and brominated deoxyuridines) and monoclonal antibodies in other laboratories. Localization of which site needs to be irradiated with MXR's can be accomplished by magnetic resonance imaging, if a small percentage (5-10%) of the metal substitute is replaced by a metal with a magnetic moment making the site of drug accumulation discoverable in the MR scans. This combination of drug with radiation can be a particularly useful mode of therapy in brain tumors. Localized lesions are amenable to excision and stereotactic attack, but infiltrating tumors that have worked their way in among adjacent cells cannot be approached any other way surgically. Chemoradiotherapy offers a reasonable alternative for treatment here , as the metal containing drug will accumulate only in the cancerous cells and not the normal tissues.

FUTURE NEEDS:

Compact FEL's will be needed if these devices are to be used in a hospital setting. The current devices are large, temperamental, and expensive. A single use machine could easily be fabricated for the production of MXR's alone. If one were to add hard x-ray optics to a compact FEL, we would expand the utility of MXR's tremendously [12].

Quantum efficient, fast detectors with high resolution are currently under development [13]. These will assist in the reduction of radiation dose to the patient. However, we may come to a point whereby the radiation dose is limited by quantum mottle. We may be unable to define the edges of anatomic structures if we too severely limit the number of photons available to the detector.

SUMMARY:

If we take advantage of time of flight imaging, phase imaging, energy discrimanant information, inherent absorption differences of tissues, fast gated digital detectors, computer enhancements and reconstruction of data , and new chemoradiotherapeutic agents, monochromatic x-rays will have a shining future in medicine.

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