Presented at: Haga Workshop on Synchrotron Radiation
Haga, Japan
August 9-10, 1997

BNL- 64697
CONF-970891--

Synchrotron Radiation Applications in Medical Research

W. Thomlinson

National Synchrotron Light Source
Brookhaven National Laboratory
Upton, NY 11973-5000

August 1997

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Upton, NY 11973

Work performed under the auspices of the U.S. Department of Energy,
under contract DE-AC02-76CH00016

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National Synchrotron Light Source, Brookhaven National Laboratory, Upton, NY 11973

SUMMARY. Over the past two decades there has been a phenomenal growth in the number of dedicated synchrotron radiation facilities and a corresponding growth in the number of applications in both basic and applied sciences. The high flux and brightness, tunable beams, time structure and polarization of synchrotron radiation provide an ideal x-ray source for many applications in the medical sciences. There is a dual aspect to the field of medical applications of synchrotron radiation. First there are the important in-vitro programs such as structural biology, x-ray microscopy, and radiation cell biology. Second there are the programs that are ultimately targeted at in-vivo applications. The present status of synchrotron coronary angiography, bronchography, multiple energy computed tomography, mammography and radiation therapy programs at laboratories around the world is reviewed.

KEY WORDS: synchrotron, medical applications, angiography, mammography, radiation therapy

INTRODUCTION

In order to understand the role of the synchrotron in medicine it is necessary to be aware of competing technologies that are presently utilized as well as their potential. The medical community already utilizes many advanced imaging and therapy modalities, and the technologies are always advancing in areas such as digital mammography and angiography, nuclear medicine, ultrasound, MRI and radiotherapy. These are the modalities with which synchrotron based applications must successfully compete. The discussions in this paper will be limited to those areas where the fields of medicine and synchrotron radiation science have joined to create new tools for medical research, diagnosis, and treatment.

Figure 1 is a representation of the many fields of medicine presently being studied. The accompanying Table I is a summary of the status of each program, indicating where they have progressed to the human and animal research stages. The sections below will concentrate on those applications which involve in-vivo research or which are directly associated with such programs. Details of in-vivo and in-vitro biomedical research at synchrotron facilities have been presented elsewhere [1,2].

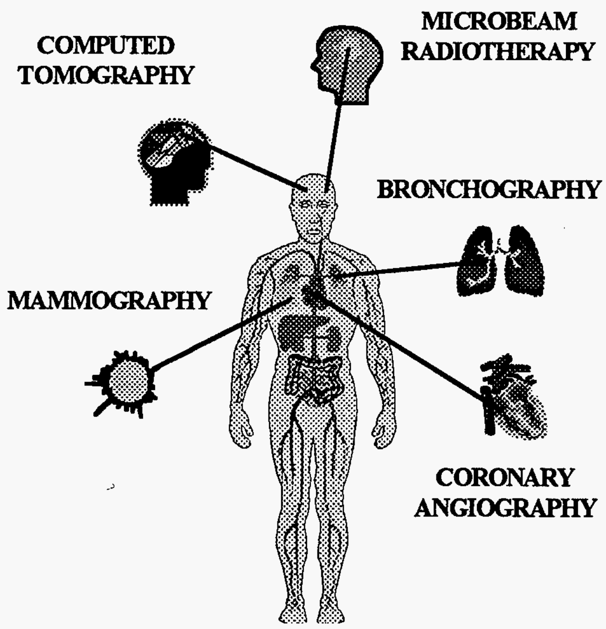

Fig. 1. The medical research areas presently active at synchrotron facilities

Table 1. Synchrotron based medical research programs

	TYPE OF IMAGE OR THERAPY	PRIMARY ANATOMY	RESEARCH STATUS
Angiography	Projection Image	Coronary Arteries	Human Studies
Bronchography	Projection Image	Lungs	Human Studies
Computed Tomography	CT Image	Head and Neck	Animal Models
Mammography	Projection Image	Breast Tumors	In-Vitro Tissues
Radiotherapy	Microbeam Therapy	Brain Tumors	Animal Models

Unique Properties of Synchrotron Radiation

The properties of synchrotron beams which make them applicable to medical research are their extremely high intensity and broad-band energy spectrum. Several orders of magnitude more flux and the smooth, continuous spectrum of the synchrotron contrast with the sharply peaked characteristic emission peaks from a tube. Basically, the high intensity and tunability allow monochromatic beams to be generated at virtually any energy. The standard problem of beam hardening in both medical imaging and therapy is eliminated by the monochromatic beams since the energy spectrum does not change with passage through tissue, only the intensity changes. The tunable spectrum allows enhancement of images and therapeutic dose by selection of the most effective energy for a given procedure. Benefits to the patients come from more effective dose delivery in therapeutic modalities and less dose with greater image quality in imaging procedures.

The advantages of the synchrotrons and their powerful beams come with some distinct disadvantages for medical applications. The planar beam is a distinct disadvantage when one tries to create a large two-dimensional image. The real problem comes when considering the application of synchrotrons to clinical diagnostic programs for humans or even large scale research programs involving human subjects. At present, and in the foreseeable future, there is little access to the synchrotron beams for medical purposes, due both to lack of development of such programs and the very high cost of both facilities and research beamlines. Assuming that technical matters can be solved, it will be imperative to develop compact sources which will be cost effective for hospitals, research centers, or medical centers. Without such development, the medical applications will be limited to a few well defined research programs and will not greatly influence the clinical technologies.

Synchrotron Sources

Each synchrotron source has unique characteristics so it is necessary to make decisions regarding the medical programs which can be effectively pursued. The most important parameter is usually the flux available in the energy range required by the application. A careful analysis of the source and programmatic needs must be made. Not all storage rings or magnetic devices provide the necessary beam for all applications. Experience has shown that new advanced medical technologies can only be developed in a timely fashion if the experimental facility is dedicated to the program and sufficient beam time is available. Although a dedicated clinical facility called SMERF was constructed at NSLS [3], it shares beam time with many other medical and non-medical programs. Due partly to the long development time necessitated by lack of beam time, the angiography project is now on hold with no new studies planned at this time. It is fortunate that at both the ESRF [4] and ELETTRA [5] dedicated beamlines have been built for medical research. At HASYLAB, the angiography beamline has been dedicated for an extended period of time to carry out a large trial of the technology [6]. When medical programs are started at new or existing facilities, it is imperative that the need for dedicated operations is considered.

Multiple-energy Computed Tomography

Monochromatic synchrotron x-rays have two distinct advantages over the radiation obtained from x-ray tubes for radiology in general and for computed tomography (CT) in particular. The monochromatic x-rays do not beam harden. Beam hardening is particularly troublesome for image reconstruction of CT images. Second, the tunability of the spectrum allows both dual-photon absorptiometry (DPA) and K-edge subtraction (KES) imaging. Multiple Energy Computed Tomography (MECT) was first developed at Brookhaven National Laboratory to utilize synchrotron radiation beams for DPA and KES [7]. That program has advanced to the stage of imaging small mammals, but its long range goal is to image the human head and neck. Another long term goal is to do high resolution in-situ imaging for patient orientation and positioning for subsequent radiotherapy treatment. A new human studies CT program is just starting experimentation at the ESRF [4]. In addition, developments in Japan are focusing on the fundamental technology of synchrotron computed tomography; for example, phase-contrast x-ray computed tomograhy [8].

The synchrotron geometry is ideal for doing CT of the brain, since beams are naturally collimated in the vertical direction and are fan shaped in the horizontal plane. In addition, the highly collimated beams allow the detector to be placed far behind the patient, thus reducing the problem of subject to detector scatter. The CT configuration is that of a fixed, horizontal fan beam and a subject seated in a rotating chair. The KES studies will image the brain, large blood vessels of the head and neck, and arteriovenous malformations. DPA will obtain images that map the low Z and intermediate Z elements. Progress to human studies will eventually occur at NSLS and ESRF.

Mammography

It has been suggested that the use of the synchrotron source for mammography with its monochromatic, highly collimated, tunable radiation could increase the signal to noise and increase the contrast resolution in the images, possibly at lower dose to the patient. Burattini, et al [9], recently reported their work using synchrotron radiation and conclude that the monochromatic images have higher contrast, better resolution, and similar or less radiation dose. A dedicated mammography beamline is being constructed at the ELETTRA facility in Trieste, Italy [5].

Experiments have been done at the NSLS by Dr. R. Eugene Johnston from the University of North Carolina and his collaborators using monoenergetic x-rays to explore the potential of monoenergetic photons for mammographic imaging [10]. The experiments done on the X27 beamline have shown that superior image contrast can be obtained relative to the conventional film-screen techniques. Images of various mammographic phantoms and real tissue have been carried out in the energy range 16 to 24 keV. In these early experiments, it was clear that improved contrast at equivalent or less dose is obtained. Scoring of the phantom images according to American College of Radiology criteria shows improvement over the conventional systems, with similar or less mean glandular dose. The early work at the NSLS has utilized available image plate and conventional mammographic film detectors. It is planned to study digital detectors and new imaging optical configurations. The elimination of scatter is expected to produce images with higher contrast than conventional imaging systems. Complimentary experiments studying diffraction and image quality are underway at Daresbury Laboratory [11].

Recently, a new radiographic imaging modality called Diffraction Enhanced Imaging (DEI) has been developed by D. Chapman and co-workers at the NSLS [12,13]. This new modality uses an x-ray analyzer crystal (Bragg or Laue geometry) as a scatter rejection optic that diffracts the beam which is transmitted through the object being imaged. Experiments performed with this scatter rejection optic revealed tah the system is sensitive to refractive ndex effects within the object in addition to the x-ray absorption and small angle scattering by the object. A simple algorithm has been developed to separate refractive index effects from absorption effects. The measured quantity is really an apparent absorption since it the combination of absorption and extinction processes. Extinction is the loss of intensity due to diffraction occurring as the beam traveses the object. In some phantom details, enhancement in the apparent absorption of an object has been as much as a factor of 17 when compared with a conventional synchrotron radiograph. Direct comparisons between the synchrotron DEI system and conventional systems being made using mammography phantoms and tissue samples obtained from patient specimens containing different types of cancers (masses, calcifications, and architectural distortions). In the long term, it may be possible to advance the program to human studies in the medical research facility at the NSLS.

Coronary Angiography

Certainly the most advanced of the applied medical research programs at synchrotron facilities are those doing human coronary angiography. The field traces its origins back to the proposal that the intensity of the synchrotron x-ray beams would be high enough to allow imaging of the coronary arteries following venous injection of an iodine containing contrast agent [14]. Differences in the x-ray optics and the types of detectors appear among the experimental groups depending upon the needs of the technology. The pioneering work in angiography in Russia at the Institute of Nuclear Physics [15] and the programs at the NSLS [16] and HASYLAB [17], as well as the planned work at the ESRF [4], move the patient through a stationary one-dimensional fan beam. The programs in Japan at the Photon Factory are taking very rapid, two-dimensional exposures [18,19]. They use a single energy above the K-edge of iodine with transvenous injection. Thus far, four patients have been imaged.

The concept of synchrotron based coronary angiography was first developed at Stanford University and the early human studies were done at the Stanford Synchrotron Radiation Laboratory [20]. The NSLS program has been a collaboration between Stanford University, North Shore University Hospital and SUNY Stony Brook. Thus far a total of 28 patients have been imaged, 7 at SSRL and 21 at the NSLS [21].

In Germany at HASYLAB the researchers have developed a system similar to the Stanford/NSLS system. Two of the major goals of the transvenous imaging have been to advance to where the contrast agent can be injected into a peripheral vein and the images can be gated on the ECG signal. The German group headed by Dr. W.-R. Dix has made major advances in each of these areas of the technology having imaged over 150 patients [22,23]. Excellent images of the right coronary artery and of the left anterior descending coronary artery have been obtained at the NSLS and HASYLAB, but the circumflex artery has been more difficult to image, although the HASYLAB group is making significant progress. The technology is now at a point where definitive medical research can begin. In order to evaluate the true clinical potential of synchrotron coronary angiography, the HASYLAB team is carrying out a major study involving over 400 patients [6]. The outcome of that study will certainly influence the continuation or commencement of projects around the world.

Bronchography

Recently, Rubenstein, et al have described a medical imaging procedure using xenon as a contrast agent for K-edge dichromography of the respiratory air passages [24]. The process could provide the opportunity to image anatomic structures and pathologic processes that cannot be visualized by conventional x-ray based imaging methods. For example, detection of lung cancer, the leading cause of cancer related deaths in the US, is an important application. At present, standard x-ray procedures cannot detect tumors less than 1 cm in diameter. It has been calculated that synchrotron imaging with xenon could detect significantly smaller, earlier tumors leading to enhanced five-year survival. For the synchrotron bronchography, the airway structures are imaged after inhalation of a gas mixture containing stable xenon. The amount of inhaled gas is limited to the anatomic dead space volume of the upper and lower air passages. The subjects hold their breath for several seconds while the images are recorded using the dual-energy imaging system developed at SSRL and the NSLS for coronary angiography. Initial studies on human volunteers have been carried out at the NSLS in recent experiments [25]. For these studies, the X17 beamline was aligned to bracket the xenon K-edge at 34.56 keV. The procedure was identical to the angiography imaging except that the contrast agent was inhaled instead of being injected. In these preliminary experiments the trachea and bronchi to the tertiary level could be seen.

Microbeam Radiation Therapy

The application of synchrotron radiation to radiotherapy was first suggested by Larsson [26]. The inherent collimation of the synchrotron beams allows the creation of beams which optimize dose delivery to the tumor site but may also effectively spare intervening normal tissue. The synchrotron geometry is ideal for stereotactic radiosurgery and the monochromatic beams will not beam harden. Hence, the radiation dose to the patient will be efficiently delivered. Microbeam Radiation Therapy (MRT) is a concept developed at Brookhaven National Laboratory by which a lesion is irradiated in a stereotactic fashion using bundles of multiple, parallel, microscopically narrow beams of x-rays [27]. The energy range required is 50-150 keV. The microbeams are planes several millimeters high and 25-75 μm wide. The beams in each bundle are separated by 75-200 μm on center. The central phenomenon is that endothelium and other kinds of vital self-renewing cell systems that are destroyed by high absorbed doses within the paths of microbeams regenerate from similar cells in the minimally irradiated contiguous segments between the microbeams. Tissue necrosis is thus avoided except in the crossfired zone.

Experiments have been carried out at the NSLS in which it has been shown that MRT is effective in increasing the survival of rats with imminently lethal brain tumors [28]. The present efforts at the NSLS and in Grenoble at the ESRF [4,29] are continuing both experimentally and theoretically in order to understand optimal beam parameters for MRT and to study dose distributions theoretically.

DISCUSSION

The projects discussed in this paper are, for the most part, still in their infancies. There is a lot of competition from advances in conventional imaging with the development of digital angiography, advanced mammography systems, magnetic resonance imaging and fast computed tomography. The synchrotron programs will have to provide significant advantages over these modalities in order to be accepted by the medical profession The development of compact sources will be required in order to move the synchrotron developed imaging technologies into the clinical world. In any event, it can be expected that the images produced by the synchrotron technologies will establish "gold standards" to be targeted by conventional modalities. A lot more work needs to be done in order to bring synchrotron radiation therapy and surgery to the level of human studies and, subsequently, to clinical applications.

ACKNOWLEDGMENT

This work was supported by the US Department of Energy under contract #DE-AC02-76CH00016.

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M98000290

Report Number (14) BNL--64697
CONF-970891--

Publ. Date (11) 199708
Sponsor Code (18) DOE/ER, XF
UC Category (19) UC-410, DOE/ER

DOE