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ABSTRACT

We are studying the potential use of x-rays, which are collected by non-imaging optics and delivered through stereotactically guided needles by hollow waveguides, for irradiation of tumors. X-rays have greater transparency in tissue than most longer optical wavelengths and may provide a more uniform dose to a tumor without harming normal tissue. Dosimetry is the key to minimal damage. We are investigating the use of fiber optics, tipped with calibrated scintillators and strategically located near the tumor, to measure the delivered dose. We are testing this procedure by using a 3 ns, variable accelerator voltage Fexitron 706 to produce approximately 50 mrads of x-ray energy. We concentrate, homogenize and inject this radiation into meter length, submillimeter hollow waveguides. We place the waveguides in a simulated tumor (a phantom breast). Streak and thermal cameras monitor the energy distribution during the irradiation by observing the distribution of energy as evidenced by fluorescence and heat. Once optimum exposure conditions of placement and dose are determined, tissue studies will begin

Keywords: X-rays, Hollow waveguides, Tumor irradiation, Dosimetry, Minimally invasive therapy

1. INTRODUCTION

Eradication of cancer is most effective if it can be detected very early, before it spreads to multiple locations. It is believed that tumors begin to spread after they are one to two millimeters in size. This requires imaging resolution that can detect very small tumors as well as very accurate methods of guidance for tissue biopsy. In addition to working on higher resolution x-ray imaging systems to detect small tumors, we also are working on three-dimensional x-ray imaging for improving the guidance accuracy High resolution confocal microscopy through optical fibers for *in situ* pathological diagnosis of tissue is also being studied. This paper is concerned with the destruction of small malignant tumors. Here we focus on the delivery of x-rays through hollow waveguides to kill tumors by irradiation *in situ*. Several papers are presented in this conference on the use of *in situ* thermotherapy that uses laser energy to heat a tumor. Both methods of treatment seem to have great potential.

The method that we propose here, the use of x-rays to kill tumors, could have advantages over thermal methods in some situations. X-radiation routinely has been used to kill tumors *in situ*. Brain tumors are an example. In most cases the radiation is directed from the x-ray source without any means for concentration or precise guidance. Without precise guidance, it is sometimes necessary to pass the beam through normal tissue or, perhaps, the use of radiation is not possible because vital tissue is in the way. X-radiation delivered through millimeter size waveguides may allow the energy to go around the vital tissue and thereby make inoperable cancers operable.

In some cases the use of thermal energy, which disperses in three dimensions, may heat vital normal tissue too much for a thermal treatment. X-irradiation may be better controlled and might not diffuse to kill vital tissue nearby. The effect of x-radiation is not subject to the thermal perfusion found in tissue, i.e. blood flow limits thermal load in tissue. Limiting the energy of the x-ray photons as shown in Figure 1 also can control the depth of penetration of x-rays. The control of the energy of x-rays that are transmitted through the waveguides also might be improved by using Bragg gratings inside the waveguides.

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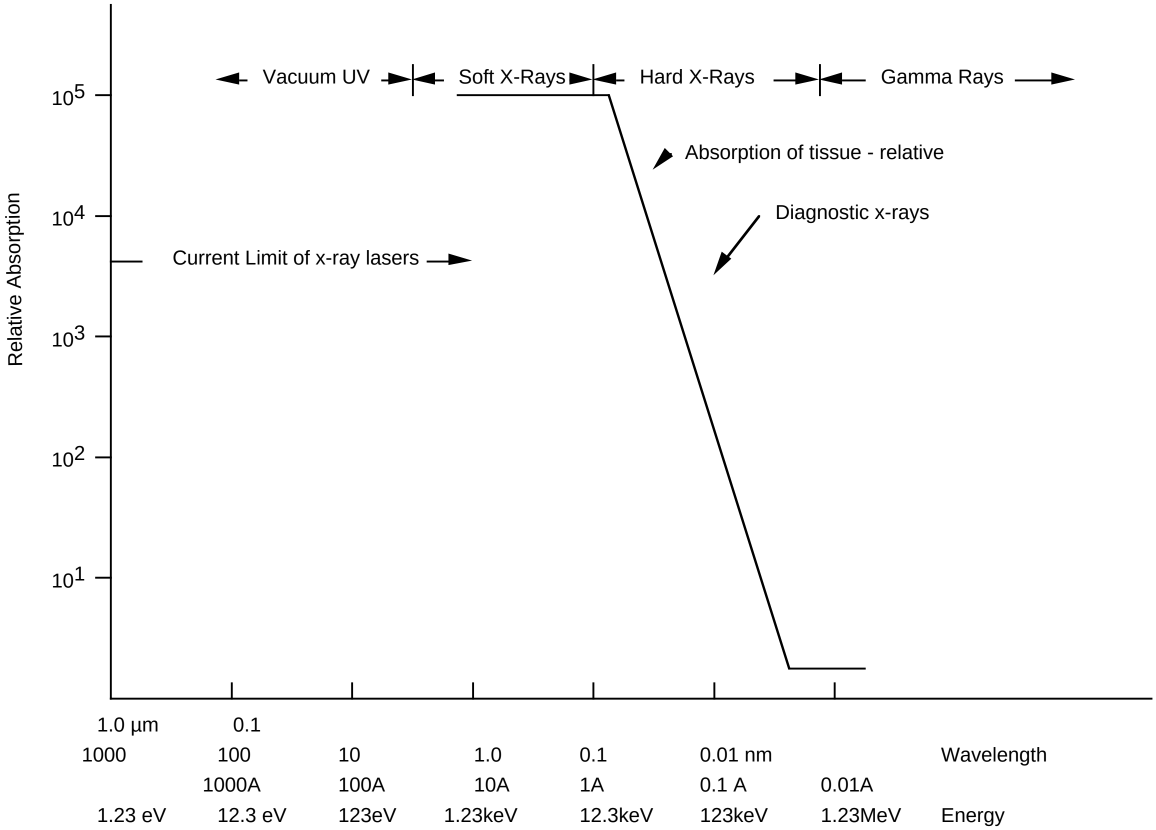


Figure 1. Absorption of energy versus photon energy.

2. CURRENT STATUS OF WAVEGUIDE DELIVERY

Much of our previous work with waveguides has been done in the mid-infrared. Here we have used coated hollow waveguides, special tapered couplers and focusing tips to deliver mid-infrared laser energy from lasers, free electron lasers (FELs) and optical parametric oscillators (OPOs) in the two to twelve micrometer wavelength region for surgical, therapeutic and diagnostic purposes.[1,2,3,4] We already have been able to translate many of the prototyped devices used in the mid-infrared into the ultraviolet with excellent performance.[5] Miyagi s group has been able to coat hollow-waveguides for use at 157 nm in the vacuum ultraviolet.[6] Hollow waveguides have been used for x-ray transmission by Mosher and Stephenakous[7,8] and by Kumakhov et. al.[9] and many others.[10,11] We believe it is possible to make use of short lengths of hollow waveguides to deliver clinically useful doses of radiation to precisely kill tissue with minimal damage to vital tissue nearby. As Kuczumow and Larsson[12] have pointed out, there has been much progress in both multilayer reflecting surfaces and in hollow capillary optic waveguides. The incorporation and assembly of practical devices and their use with precise guidance through the least invasive route to the target tissue remains to be done and made routine.

3. DESIGN OF A WAVEGUIDE DELIVERY SYSTEM FOR X-RAY THERAPY

In addition to a source of x-rays, a delivery system for x-ray exposure of a tumor inside the body would normally consist of a coupler to connect the source to a hollow waveguide that would transport the x-rays to and into the body. On the end of the hollow waveguide would be a focusing tip to further concentrate the x-rays that traverse the waveguide to be placed exactly in the proper position to irradiate the tumor. The guidance system has not been discussed, but is an integral part of clinical use. Precise guidance of the focusing tip may require three-dimensional ultrasound or x- ray imaging. This same imaging information would be needed during biopsy and it would be very efficient to combine these procedures. That is, once a tumor is located, choose a minimally invasive route to insert a guidance needle, then determine malignancy and, if malignant, keep the guidance needle in place for the treatment waveguide. This will also place emphasis on the need for a rapid biopsy analysis, such as instant optical biopsies.

3.1 Waveguide — The waveguide is the heart of the x-ray delivery system. These waveguides are simply very small hollow glass tubes with outer diameter usually less than a millimeter and with inner diameter ranging from hundreds of micrometers to potentially as small as a few micrometers. Typical waveguides might have a 770 micrometers outer diameter and 550 micrometers inner diameter — small enough to travel through a needle with less than a millimeter inner diameter. Ideally the inner surface of the hollow waveguide would be as smooth as possible and can sometimes be used without any coating. Coatings can be placed on the inner wall to optimize the reflection of the walls. Liquid deposition is used for some materials, but other materials require vapor deposition that is much more difficult. At this point in the development, vapor deposition of x-ray coatings inside hollow waveguides is not commercially available to our knowledge. However, high reflection coatings, or super mirrors for hard x-rays do exist and potentially could be assembled into small waveguides.

3.2 Coupler — With lasers in the infrared and ultraviolet we have been extremely successful using grazing incidence reflection from cylindrical glass tapers. Theoretical calculations tell us that a linear taper is the most efficient taper and we have been able to produce close approximations to a linear taper in the laboratory. A diagram of the coupling taper is shown in Figure 2. If our x-ray source were able to produce a well-collimated beam, we believe that a linear taper would be the best coupler for our waveguide. However, there are no x-ray lasers in the clinically relevant energy range so we are forced to use other methods, such as non-imaging optical devices, to collect x-rays to test our waveguide delivery system. In our tests here, we simply use lead apertures to collimate our test beam.

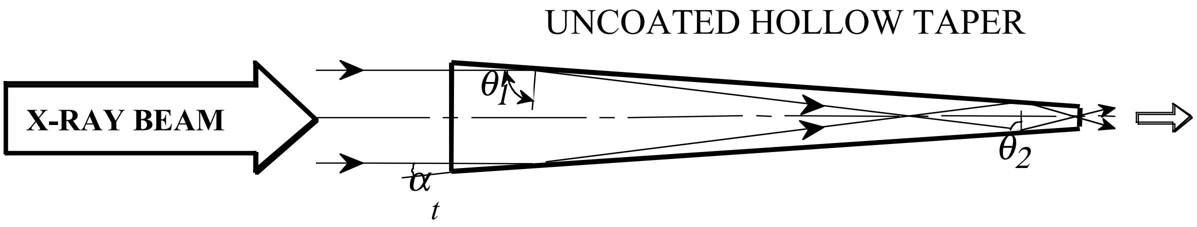


Figure 2. Hollow tapered cylinder

3.3 Focusing Tip — Further concentration or expansion of the x-rays can be done at the distal end of the fiber as the beam of radiation leaves the waveguide and irradiates the tumor. This focusing or concentration of the beam can be done with another simple linear taper. If the beam needs expansion to cover a large tumor, simply backing the taper away from the tumor and the beam will encompass the tumor. This is the simplest way of ensuring a complete exposure.

4. EXPERIMENTAL RESULTS

We have tested x-ray delivery systems using a pulsed x-ray source (a Fexitron 706 200-600keV source) that emits approximately 50 mrad of x-ray energy. We aperture the beam down, collect it with our linear tapered coupler and inject it into silver coated hollow waveguides. Figure 3 shows a schematic of the system

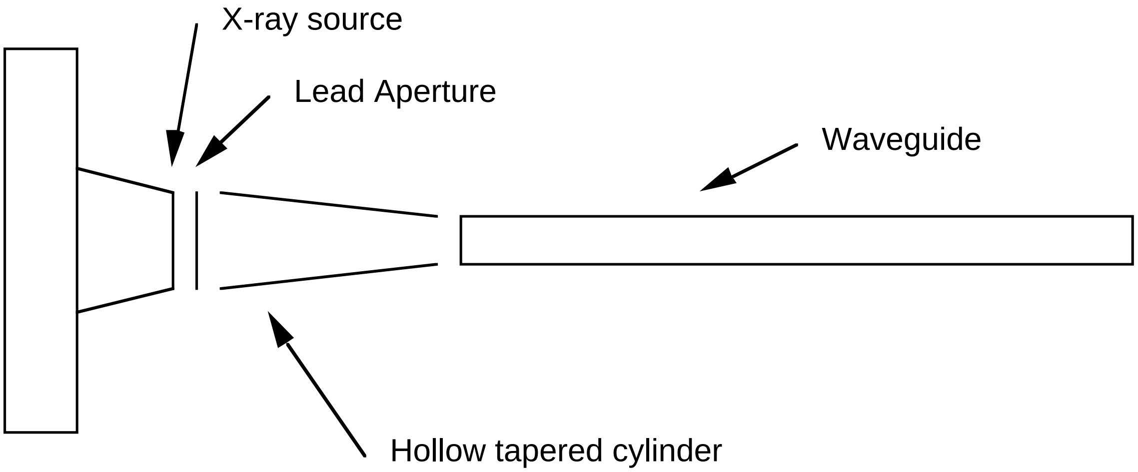


Figure 3. X-ray delivery system

and Figure 4 shows the beam profiles at the coupler input and output. The coupler input was 5 mrads and the output was 1.2 mrads. Energy measured at the waveguide input and output are. 1.1mrads and 0.2mrads, respectively. These measurements of intensity at input and output gives us a transmission of 15 - 20% for an un-bent waveguide. Measurements of loss as a function of the bending radius will also be undertaken. Note also that the coupler efficiency is about 20% using uncoated surfaces. We believe that good coatings on both coupler and waveguide can greatly improve the efficiency of both devices.

5. DOSAGE

Our planned dosage for tumor irradiation will be based on the accepted standards for radiation dose tolerance. Lethal tumor doses typically range from about 20 — 80 Gy depending on the disease, tumor stage and its location, however, the probability of adverse radiation effects must also be considered as well as specific patient condition. Since our minimally invasive procedure allows maximum exposure of tumor and minimal irradiation of surrounding normal tissue, it may be possible to give sufficient radiation for a high lethality probability and a low probability of adverse results.

To produce a modest dose of, say 50 Grays in a tumor of two millimeters in diameter or about 4 mg in weight would require about 200 millijoules of absorbed x-ray photons or about 3.12 x 10^{13} photons at 100 keV energy. Assuming we could deliver about 10^{11} photons per second with a modest x-ray source and fiber delivery, this dose would require about 5 minutes to administer. This time compares favorably with the time to deliver a thermal dose, however, the dose needed to kill a much smaller tumor is immediately distributed throughout the tumor radiatively, not conductively. As we explain below, we believe this is a much more controlled dose. We plan to test this controlled dose using fibers with scintillator tips inserted near a phantom tumor-in-tissue model.

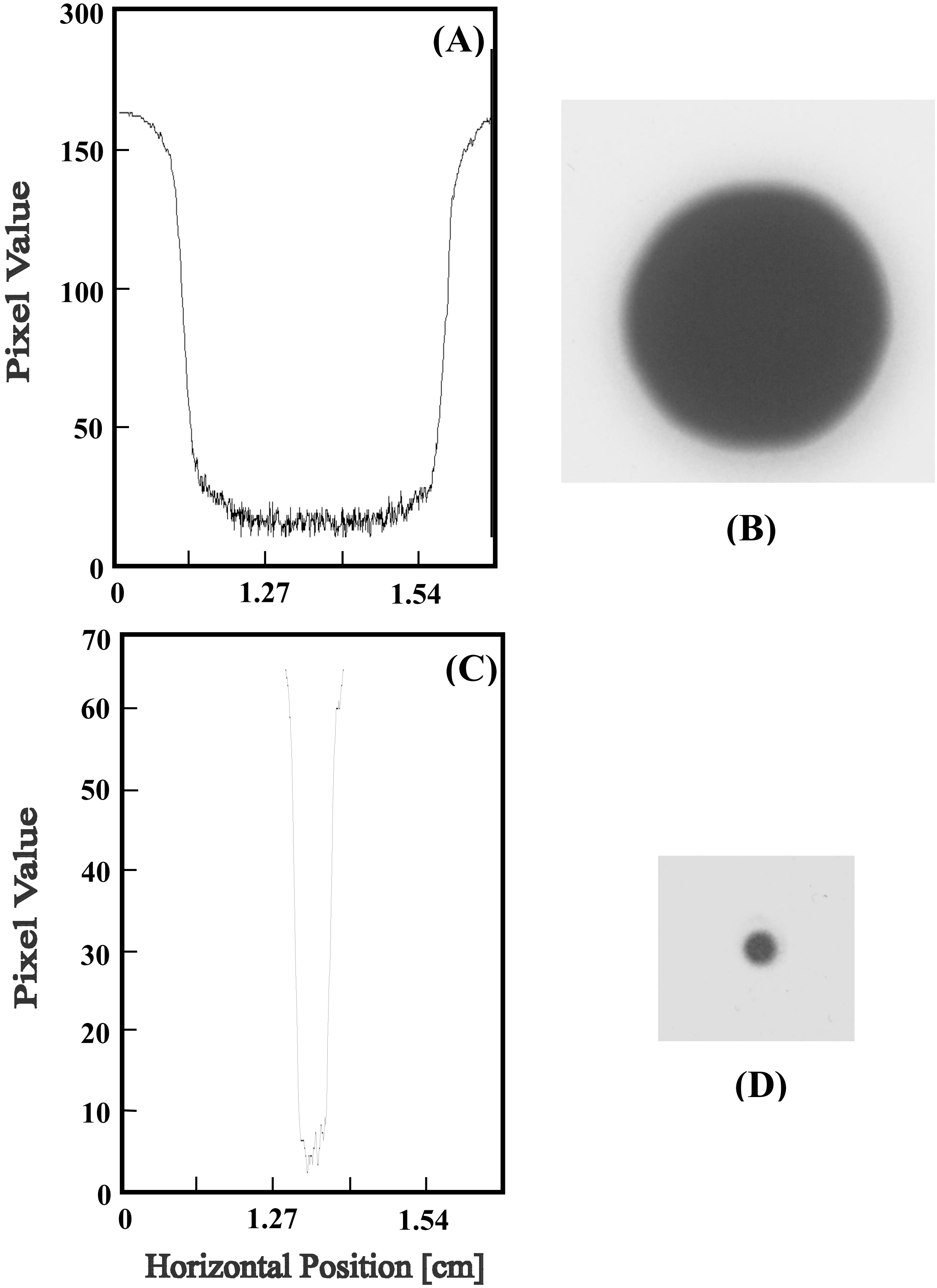


Figure 4. Comparison of the input and output x-ray beam pattern of the coupler.

6. THEORETICAL DIFFERENCES BETWEEN OPTICAL AND X-RAY TUMOR THERAPY

We believe there are signifigant differences between the outcomes of optical and x-ray therapy. The following descriptions portray how these differences may apply. The entire procedure of detecting a tumor and guiding treatment fibers or waveguides to near contact with the tumor will be similar. Differences occur when the radiation is applied.

6.1Thermal Interaction —When optical radiation is turned on, depending on its wavelength, most will be absorbed at the tumor surface. The surface will be heated and the heat will propagate through the tumor and through the normal tissue as well. Both normal and tumor tissue will be killed as the temperature of both increases. While it is permissible and prudent to kill some normal tissue as a safety margin, if vital tissue is nearby, the possibility of thermal damage may exclude this treatment method.

6.2 X-ray Interaction — When x-ray energy is used, the killing method is different. Tissue is killed by the absorption of a more powerful photon that initiates a chemical interaction that is lethal to the cell that absorbs it. A high amount of thermal energy is not required so there is no diffusion of the energy. If the beam of x-rays is precise, no killing is spread. Vital tissue, if not struck by a x-ray, continues to function. A comparison of the two techniques is given in Figure 5.

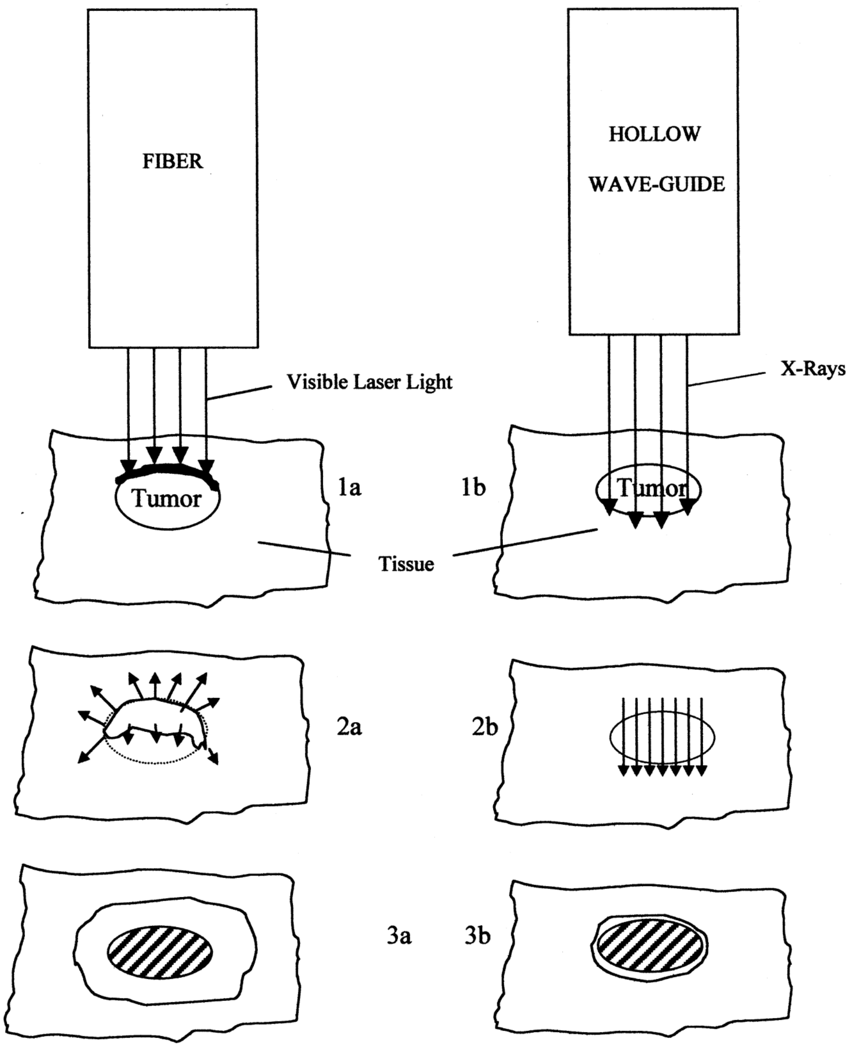
7. FUTURE DIRECTION OF HOLLOW-WAVEGUIDE X-RAY DELIVERY

This preliminary work shows that hollow waveguides can play a practical role in delivering x-rays into the body. A considerable amount of work remains to be done to implement both the delivery system and the clinical application of the energy. First of all, little has been said about the source of x-rays. The conventional methods of generating x-rays are not very suitable for getting them into waveguides. We are working on methods of developing very short pulses of optical energy and then using these optical pulses to generate x-rays from plasmas. We believe short pulses might be less harmful to tissue than longer pulses, but we must prove this. We also think that short, intense optical pulses can be injected into x-ray emitting structures that can be used to feed waveguides, but we must also show what structures are useful for this. As we have shown, tapers work well with narrow beams, but other collecting methods are needed for wide beams. We speculate that laser generation of x-rays might be done in a manner that takes advantage of light focusing to condense the energy into a narrow beam before generating the x-rays. Also, for control, we d like to have monochromatic x-rays, but strong sources of monochromatic x-rays have not yet been produced in the medically relevant energy region. Once a good source is found, coupling to the waveguide needs to be finalized. If the source produces a narrow beam, a cylindrical taper will work. If the beam is spread, a parabolic collector will be needed. Once x-rays are in the waveguide, surface smoothness and reflectivity are the important criteria. Finally, at the distal end, a simple tapered end can be used for focusing the radiation on the tumor.

The clinical side of the problem is also interesting. Finding smaller tumors may require better imaging systems and better screening methods. Also guidance techniques capable of placing a needle in position to insert biopsy equipment and a x-ray waveguide also will require excellent three-dimensional imaging. Once that has been done, the clinician must be able to determine whether an appropriate dose has been given to achieve the best outcome. None of these problems have been solved.

8. CONCLUSIONS

We believe these studies show that waveguide delivery of x-ray radiation to kill small tumors *in situ* can be carried out. We also believe waveguide delivery is a controllable means of killing tumors and may be valuable therapy for tumors located close to vital tissue that might otherwise be destroyed by thermal therapy or by other more aggressive radiation therapy.



1a	Time exposure begins- depth stops at tumor margin, heat must propagate to kill entire tumor	1b	Depth controlled by energy, much less heat- cells killed by radiation and not by heat
2a	Heat goes in all directions eventually and kills the tumor	2b	X-rays penetrate the entire tumor, kills the tumor and a small margin beyond
3a	Dead tumor plus large margin beyond	3b	Dead tumor and a small margin beyond

Figure 5. Comparision of thermal versus x-ray killing of a tumor.

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