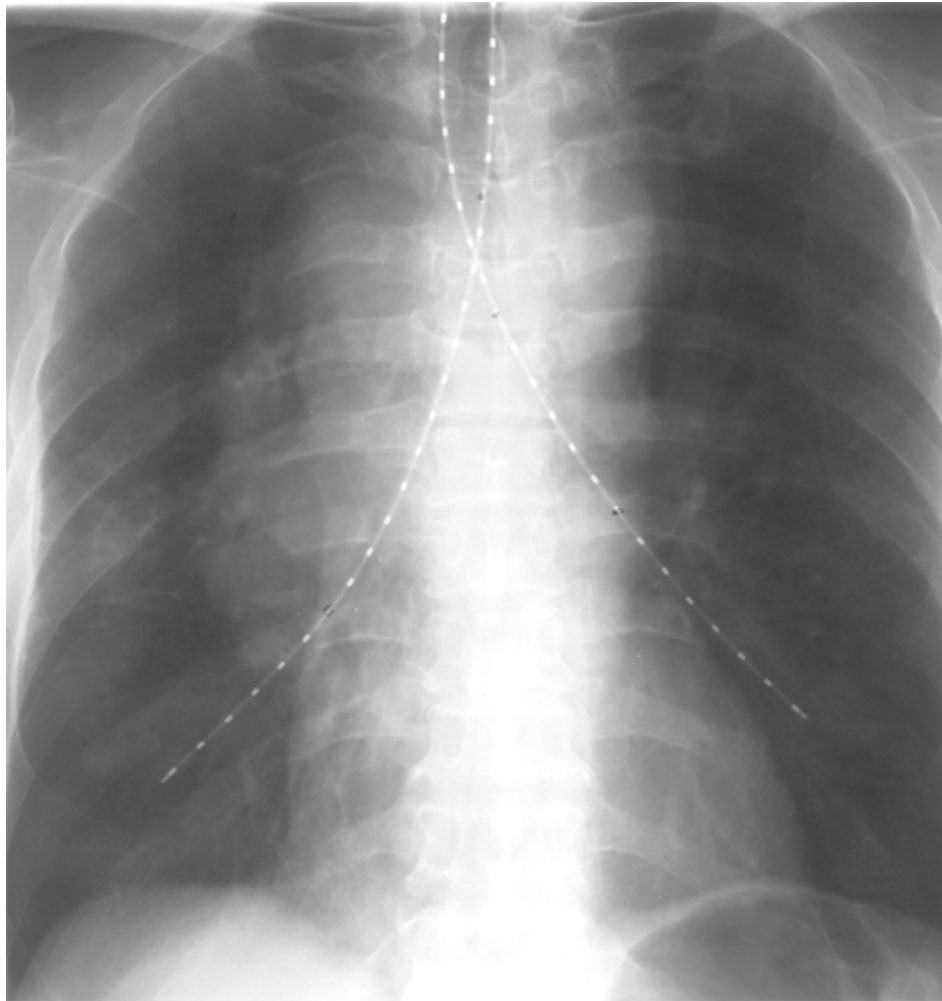


BRACHYTHERAPY

Janusz Skowronek MD, PhD



Greatpoland Cancer Center

Poznań, January 2004

1. About Brachytherapy

Derived from ancient Greek words for short distance (brachios) and treatment (therapy) and refers to the therapeutic use of encapsulated radionuclides within or close to a tumor. It is sometimes called seed implantation and is an outpatient procedure used in the treatment of different kinds of cancer.

Two general types of radiation techniques are used clinically - **brachytherapy and teletherapy**. In brachytherapy, the radiation device is placed within or close to the target volume. Teletherapy uses a device located at a distance from the patient, as is the case in most orthovoltage or supervoltage machines. The advent of high voltage teletherapy for deeper tumors and the problems associated with radiation exposure from high-energy radionuclides led to a decline in the use of brachytherapy towards the middle of last century. However, over the past three decades, there has been renewed interest in the use of brachytherapy for a number of reasons. The discovery of man-made radioisotopes and remote afterloading techniques has reduced radiation exposure hazards. Newer imaging modalities (CT scan, magnetic resonance imaging, transrectal ultrasound) and sophisticated computerized treatment planning has helped to achieve increased positional accuracy and superior, optimized dose distribution. Finally, while brachytherapy was initially used only for treatment of cancer, it has now been found to be useful in non-malignant diseases (for example, in the prevention of vascular restenosis) as well. It is clear that brachytherapy is the optimum way of delivering conformal radiotherapy tailored to the shape of the tumor while sparing surrounding normal tissues.

The **efficacy of brachytherapy**, as compared with the efficacy of external beam alone, is attributable to the ability of radioactive implants to deliver a higher concentrated radiation dose more precisely to tissues, which contributes to improved local control,

provided that the tissue is clinically delimitable and accessible. At the same time, the surrounding healthy tissues are spared irradiation.

In contrast to external-beam irradiation, **brachytherapy is invasive**, requiring insertion of site-specific applicators under sedation or anaesthesia. The surgeon who is sometimes involved in these procedures, particularly if laparotomy or craniotomy is required for the insertion of applicators, or if tumour resection is required prior to applicator insertion, should be aware of the indications for brachytherapy and the associated techniques

Brachytherapy is an internal radiation therapy that is applied either in a permanent manner, (sometimes called seed implantation), or in a temporary manner, often through the use of catheters into which the radioactive sources are placed. The radioactive materials (seeds or in catheters) are placed inside the body, and positioned in a manner that will most effectively treat the disease. When permanent brachytherapy is being employed, the radioactive “seeds” are left inside of the body. The half-life of the radioactive isotope used, gauges how long they will be radioactive within the body since the radioactivity of the seeds diminishes over time. Temporary brachytherapy usually involves either an in-patient procedure (low dose rate brachytherapy, or LDR), whereby the patient lies in bed for several days while the radioactive sources treat the disease, or in an out-patient setting (high dose rate brachytherapy, or HDR, whereby the patient usually undergoes several treatments of radiation in a short period of time.

Because the radiation source is close to or within the target volume with brachytherapy, the dose is determined largely by **inverse-square considerations**. This means that the geometry of the implant is important. Spatial arrangements have been determined for different types of applications based on the particular anatomic considerations of the tumor and important normal tissues. The dose decreases rapidly as the distance from the applicator increases. This emphasizes the importance of proper placement.

Brachytherapy has now been used for over a century. Some of the diseases now treated with brachytherapy include prostate cancer, cervical cancer, head and neck cancer, endometrial cancer, and coronary artery disease. Brachytherapy has been proven to be very effective and safe, providing a good alternative to surgical removal of the prostate, breast, and cervix , while reducing the risk of certain long-term side effects.

2. History

Historically, the removable interstitial and intracavitary sources used were **radium and radon**, the latter primarily for permanent implants. Henri Becquerel discovered natural radioactivity in 1896 when he found that Uranium produced a black spot on photographic plates that had not been exposed to sunlight. Two years later, Marie and Pierre Curie working in Becquerel's laboratory extracted Polonium from a ton of Uranium ore and later in the same year, extracted Radium. In 1901, Pierre Curie suggested to Danlos at St. Louis Hospital in Paris that a small radium tube be inserted into a tumor thus heralding the birth of brachytherapy. In 1903, Alexander Graham Bell made a similar suggestion, completely independently, in a letter to the Editor of Archives Roentgen Ray. It was found in these early experiences that inserting radioactive materials into tumors revealed that radiation caused cancers to shrink.

In the early twentieth century, major brachytherapy work was done at the Curie Institute in Paris and at Memorial Hospital in New York. Dr. Robert Abbe, the chief surgeon at St. Lukes Hospital of New York, placed tubes into tumor beds after resection, and later inserted removable Radium sources thus introducing the afterloading technique as early as 1905. Dr. William Myers at Ohio State University developed several radioisotopes, including $^{198}\text{Gold}$, $^{60}\text{Cobalt}$, $^{125}\text{Iodine}$, and $^{32}\text{Phosphorus}$ for clinical brachytherapy. These were

implanted surgically by Drs. Arthur James (surgeon) and Ulrich Henschke (radiation oncologist).

Marie Curie, the discoverer of radium, recognized its importance early and championed the medical use of these isotopes. They were important tools in early cancer therapy but now have been largely replaced by manmade isotopes, which overcome most of the disadvantages of the naturally occurring ones.

Initially, even removable isotopes were used by directly applying the isotope, and thereby exposing the operator to significant radiation doses. This problem has largely been circumvented through the use of ^{137}Cs , ^{192}Ir , and ^{60}Co . The first two have a lower energy and are much easier to shield. Afterloading techniques are used for removable implants as often as possible. Receptacles for the radioactive material are placed in the patient in the form of needles, tubes, or intracavitary applicators. When they have been satisfactorily placed they are afterloaded with the radiation sources.

Permanent implants are primarily done today with ^{198}Au and ^{125}I . In the treatment of prostate cancer, the radioactive seeds are about the size of a grain of rice, and give off radiation that travels only a few millimeters to kill nearby cancer cells. With permanent implants (for example, prostate) the radioactivity of the seeds decays with time while the actual seeds permanently stay within the treatment area.

3. Kinds of brachytherapy

a. characterized by the duration of the irradiation:

there are 2 different kinds of brachytherapy: **permanent**, when the seeds remain inside of the body, and **temporary**, when the seeds are inside of the body and then removed.

b. characterized by the positioning of the radionuclides:

- **interstitial brachytherapy**: radioactive sources are inside the tumour

- **contact brachytherapy or plesiobrachytherapy**: radioactive sources are close to the tumour. Contact brachytherapy is divided into four different kinds of brachytherapy:

intracavitary, intraluminal, endovascular and surface brachytherapy

c. characterized by the dose rate (ICRU definitions):

- **low dose rate (LDR) 0.4 - 2.0 Gy/h**

- **pulsed dose rate (PDR) 0.5 - 1.0 Gy/h**

- **medium dose rate (MDR) 2 - 12 Gy/h**

- **high dose rate (HDR) > 12 Gy/h**

Low Dose Rate (LDR) remote afterloading systems radiation protection, but do not provide as much flexibility in the design of alter native isodose volumes as that obtained with higher dose rate sources with adjustable stepping positions and dwell times.

At the other end of the spectrum of brachytherapy methods is the use of **High Dose Rate (HDR)** afterloading with a single source of ^{192}Ir moved by computer to a series of dwell positions. In that case the choice of isodose volume is very flexible. Large doses can be given within a few minutes. Sources of that kind require well-shielded bunkers similar to linear accelerator rooms.

One radiobiological disadvantage in the use of such high dose rates, of 1-3 Gy/min (greater ratio of late tissue effects), can in practice be overcome by careful placement of catheters and by good immobility achievable with very short exposures.

Pulsed Dose Rate (PDR) treatment is a recent brachytherapy modality that combines physical advantages of high-dose-rate (HDR) technology (isodose optimization, planning flexibility and radiation safety) with radiobiological advantages of low-dose-rate (LDR) brachytherapy (repair advantages).

PDR uses a single stepping ¹⁹²Iridium source of 15-37 GBq (0,5 – 1Ci). This produces treatment dose rates of up to about 3 Gy per hour, which can be utilized (pulsed) every hour, 24 pulses per day. The source is enclosed in a 2,5 mm long capsule 1.1 mm in diameter. The single radioactive stepping source moves through all the implanted catheters during each pulse. A typical pulse length lasts 10 minutes per hour, which may be increased to approximately 30 minutes three month later when the ¹⁹²Ir source has decayed.

Pulsed brachytherapy uses a stronger radiation source than that employed in LDR brachytherapy and gives a series of short 10 to 30 minute exposure long every hour amounting to approximately the same total dose in the same overall time as that in LDR. The trajectory of a single high activity source through the implanted catheter can be precisely programmed by a dedicated computer and carried out by a remote source projector.

The resulting isodoses can be optimized by modulating the dwell time of the source as a function of its trajectory within the implanted volume. This allows individualization of dose distributions, while essentially eliminating radiation exposure to the medical staff.

The source strength is 10 to 20 times lower than that used in HDR, and the requirements for shielding are less stringent. An ordinary brachytherapy room would require less than two extra half, value thickness of protection, and an accelerator type bunker is not necessary.

Nursing care is facilitated compared with LDR brachytherapy, since patients can be attended between the treatment sessions, without concern about problems of radioprotection.

PDR brachytherapy offers several advantages over conventional LDR brachytherapy:

(1) The distribution of radiation doses can be more easily controlled and tailored permitting the following improvements:

(a)/ more precise application (then LDR) of the prescribed dose to the treatment volume,

(b) better reproducibility of treatment plans,

(c) greater flexibility to change the dose distribution through the course of treatment if necessary,

(2) Improved radiation safety for clinical and physics staff,

(3) Only one source to replace every three months, and

(4) All brachytherapy procedure feasible with one machine: intracavitary, interstitial, intraoperative and intraluminal.

Compared with HDR brachytherapy

(1) PDR offers similar quality of treatment,

(2) Similar treatment procedure and technical verification,

(3) Improved radiation safety for clinical and physics staff,

(4) Requirements for shielding are less stringent - an accelerator type bunker is not necessary,

(5) Theoretical radiobiological advantage: the technique allows some repair in late-reacting normal tissue due to intervals between pulses,

(6) patient comfort is believed to be worse, and

(7) few indications for palliative treatment.

4. Indications for brachytherapy.

a. prostate brachytherapy

Prostate brachytherapy usually involves an out-patient procedure for either permanent seed implantation or HDR brachytherapy to the prostate gland. It has been shown to have comparable 10-year survival rates to radical prostatectomy, and has fewer side effects including a lower incidence of impotence and incontinence.

According to the American Cancer Society, prostate cancer is one of the most common forms of cancer among American men, mainly affecting men over the age of 65. As men get older, the likelihood of developing prostate cancer increases, therefore, physicians usually recommend that prostate cancer screening begin at age 50. For African American men, or men with a family history of prostate cancer, physicians recommend screening beginning at age 40.

b. breast brachytherapy

Treatment of breast cancer with brachytherapy usually involves a five-day treatment course with either LDR (in-patient) or HDR (out-patient) brachytherapy, rather than six weeks as with traditional radiation treatment following a lumpectomy. This offers excellent cure rates without the need for a mastectomy.

Breast conservation treatment has long since been established as an effective treatment alternative to mastectomy for early stage breast cancer. Standard breast conservation treatment consists of breast conserving surgery for tumor removal (lumpectomy) followed by external radiation to the whole breast. Although this treatment approach offers many advantages over mastectomy and provides in-breast cancer control rates that approach 95-100% with good to excellent cosmetic results in nearly all patients, six weeks of daily treatment has proved prohibitive for some patients. As a result, some women refuse external radiation (putting themselves at higher risk for recurrence) or choose mastectomy and have

the breast unnecessarily removed. Those finding six weeks of daily treatment inconvenient or impossible include working women, elderly patients, and those who live a significant distance from a treatment center. Breast brachytherapy as the sole method of radiation following lumpectomy is a new treatment approach that offers equivalent local control, breast conservation and improved convenience of treatment delivery. Although most women with breast cancer are appropriate candidates for standard breast conservation treatment and can be treated with lumpectomy and external radiation, only a subgroup of these women will be appropriate candidates for breast brachytherapy. However, even with strict selection criteria it is estimated that 71,000 women each year in USA would be appropriate candidates for breast brachytherapy.

c. cervical brachytherapy

Historically, cervical cancer has been treated with a hysterectomy (the surgical removal of the uterus), which carries many side effects for the patient. Brachytherapy is usually used in combination with external beam radiation therapy in the treatment of cervical cancer and has been found to be at least as effective as a hysterectomy.

d. head and neck brachytherapy

The use of brachytherapy in the treatment of head and neck cancers causes practitioners hesitation, owing to the proximity to vital structures including the carotid arteries, the jugular veins, other major blood vessels and in some cases the brain. There is a limited amount of clinical data available but, there are several safe and efficacious ways to use brachytherapy in the treatment of head and neck cancers.

e. skin brachytherapy

f. lung cancer

The use of brachytherapy in the treatment of lung cancer dates to the 1920s, though the applications varied widely. Brachytherapy is one of the most efficient methods in the

overcoming difficulties in breathing caused by endobronchial obstruction in palliative treatment of lung cancer. Depending on the location of the lesion in some cases brachytherapy is a treatment of choice. Because of the uncontrolled local or recurrent disease, patients may have significant symptoms: cough, dyspnoea, haemoptysis, obstructive pneumonia or atelectasis. In many patients, these symptoms are primarily attributable to endobronchial obstruction. Efforts to relieve this obstructive process are worthwhile because patients may experience a significantly improved quality of life. However, many of these patients have a poor performance status and have received multiple other therapies. As a result, treatment options are often limited.

In most cases brachytherapy has a palliative aim due to the advanced clinical stage. Lack of clear consensus regarding the value of doses used in brachytherapy is the reason why different fraction doses are used in clinical treatment

g. oesophageal brachytherapy

The aim of palliative brachytherapy is to reduce dysphagia, diminish pain and bleeding, as well as improve the patient's well-being. Endoesophageal brachytherapy makes it possible to use high doses of radiation to the tumour itself with concurrent protection of the adjoining healthy tissues due to the rapid fall in the dose with the square of the distance from the centre of the dose. The above treatment also leads to a smaller proportion of late radiation complications.

However, there have been only few reports to confirm that the number of local remissions and long-term survival rates have been increased in patients treated with teletherapy combined with brachytherapy. Doses used in teletherapy were as high as 35-60 Gy, whereas those in HDR brachytherapy ranged between 10 and 25 Gy administered in 2-4 fractions. The combined treatment can be radical or palliative. Positive results of HDR brachytherapy have been observed in patients who had not been treated surgically. In these

patients, the radioisotope source is inserted through the mouth to the esophagus if the applicator can be passed through the stenotic region. In general, in brachytherapy a sufficient dose distribution in the tumour can only be achieved in tumours that are smaller than 1.5 cm in diameter, and only in patients whose esophageal lumen is kept sufficiently wide to allow passage of the applicator,

h. brain brachytherapy

Brachytherapy for recurrent malignant gliomas represents an increasing part of indications for brachytherapy in central nervous system tumors. Indications for brachytherapy are tumors with a maximum tumor diameter of 5 cm without involvement of the corpus callosum, without brain stem involvement, not in proximity with the motor strip. Primary malignant tumors, recurrent brain tumors, metastatic brain tumors and benign brain tumors have been considered for brachytherapy.

i. soft-tissue sarcomas

Brachytherapy can be used alone or in combination with external beam radiation therapy for soft tissue sarcomas as an effective means to enhance therapeutic ratio (ratio of effectiveness when compared to toxicity of treatment).

j. brachytherapy is also used to treat coronary artery disease and external artery restenosis to prevent restenosis after angioplasty. Early clinical studies indicate that intravascular brachytherapy can help reduce the rate of restenosis after angioplasty procedures. Based on these results, devices for intracoronary brachytherapy have been approved by the FDA for widespread use.

5. Benefits of brachytherapy

The benefits of brachytherapy vary depending on the patient, their priorities, and preferences, though as a minimally invasive treatment method, the benefits of avoiding surgery are universal.

These include a quicker recovery time, less time spent in the hospital, and a reduced risk of postoperative infections. The benefits of using brachytherapy in the treatment of early stage prostate cancer are quite pronounced. There is a much lower incidence of impotence and incontinence than occurs with a radical prostatectomy, and most men resume walking within a few hours of the procedure and other normal activity within a few days. In the case of breast cancer, the course of traditional radiation treatment following a lumpectomy lasts six weeks, with daily installments given at a hospital or clinic, whereas brachytherapy treatment lasts for five days. Due to heightened convenience of brachytherapy, more women are likely to participate in adjuvant therapy, reducing the risk of the recurrence and the possible need for a mastectomy, therefore increasing breast conservation.

6. Glossary of Terms

Listed below are the definitions of brachytherapy and cancer-related terms in alphabetical order.

Adjuvant therapy – A necessary addition to current treatments. An example is chemotherapy or radiation therapy after surgery to prevent the return of cancer.

Anesthesia – The loss of feeling or sensation as a result of drugs. General anesthesia causes temporary loss of consciousness (“puts you to sleep”). Local or regional anesthesia numbs only a certain area.

Angioplasty – Dilatation of an occluded blood vessel. This can be done by inflating a balloon catheter to restore blood supply.

Benign tumor – An abnormal noncancerous growth that doesn’t spread to other places in the body.

Biopsy – The removal of a sample of tissue to see whether cancer cells are present. There are several kinds of biopsies. In some, a very thin needle is used to draw fluid and cells from a lump. In a core biopsy, a larger needle is used to remove significantly more tissue.

Brachytherapy – Internal radiation treatment given by placing radioactive material directly into a tumor or close to it. Also called interstitial radiation therapy, intracavitary radiation therapy, intravascular radiation therapy, or seed implantation.

Cancer – Cancer develops when cells in the body begin to grow out of control. Normal cells grow, divide, and die. Instead of dying, cancer cells continue to grow and form new abnormal cells. Cancer cells often travel to other body parts where they grow and replace normal tissue. This process, called metastasis, occurs as the cancer cells get into the bloodstream or lymph vessels.

Carcinogen – A substance known to cause cancer.

Carcinoma – A malignant tumor that begins in the lining layer (epithelial cells) of organs. At least 80% of all cancers are carcinomas.

Catheter – A thin, flexible hollow tube. Catheters can be used to allow fluids to enter or leave the body. Catheters can also be used to insert temporary radioactive sources into tumors, as in breast brachytherapy or high dose rate prostate brachytherapy.

Cervix – The lower, narrow end of the uterus that forms a canal between the uterus and vagina.

Chemotherapy – Treatment with drugs to destroy cancer cells. Chemotherapy is often used alone or with surgery or radiation to treat cancer.

CT scan – Computed tomography scan. A series of detailed pictures of areas inside the body taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized tomography and computerized axial tomography (CAT) scan.

External beam radiation therapy (External radiation) – Radiation therapy that uses a machine outside of the body to deliver high-energy rays directed at the cancer or tumor.

Gleason score – A system of grading prostate cancer cells describing how aggressive the cancer appears. It is used to determine the best treatment and to predict how well a person is likely to respond to treatment. The lower the Gleason score, the closer the cancer cells are to normal cells, the higher the Gleason score, the more abnormal the cancer cells.

High dose rate remote brachytherapy (HDR) – HDR temporary brachytherapy involves placing very tiny plastic catheters into the treatment area, and then giving radiation treatments through these catheters over a temporary period. With HDR temporary brachytherapy, a computer-controlled machine pushes a single highly radioactive source into the catheters one by one.

Internal radiation – A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near a tumor. Also called brachytherapy, implant radiation, or interstitial radiation therapy.

Interstitial radiation – A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near a tumor. Also called brachytherapy, internal radiation, or implant radiation.

Intracavitary radiation – A radioactive source (implant) placed in a body cavity such as the cervix or esophagus.

Low dose rate brachytherapy (LDR) – Brachytherapy in which sources are left in place for the duration of treatment. This includes temporary LDR in which patients are hospitalized for several days of temporary brachytherapy. It also includes permanent LDR in which seeds are permanently placed.

Lymph node (lymph gland) – A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). Lymph nodes are part of the body's immune system.

Malignant – A cancerous growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body.

Medical oncologist – A doctor who specializes in diagnosing and treating cancer using chemotherapy, hormonal therapy, and biological therapy. A medical oncologist often serves as the main caretaker of someone who has cancer and coordinates treatment provided by other specialists.

Metastasis – The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called “secondary tumors” and contain cells that are like those in the original (primary) tumor.

Oncologist – A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer treatment. For example, a radiation oncologist specializes in treating cancer with radiation.

Palliative care – Treatment given to relieve symptoms of pain caused by advanced cancer. Palliative therapy does not alter the course of a disease but can improve the quality of life.

Permanent interstitial implant – A procedure in which radioactive material sealed in seeds is placed directly into or near a tumor. Also called brachytherapy, internal radiation, or implant radiation. While the radioactivity decays away the actual seeds remain forever.

Prostate – A gland in the male reproductive system just below the bladder. The prostate surrounds part of the urethra, the canal that empties the bladder, and produces a fluid that forms part of semen.

Radiation – Radiant energy given off by x-ray machines, radioactive substances, rays that enter the Earth's atmosphere, and other sources.

Radiation dosimetrist – A specialist who measures the amount of radiation exposure during treatment procedures.

Radiation oncologist – A doctor who specializes in using radiation to treat a variety of diseases including cancer.

Radiation physicist – A person who makes sure that the radiation machine or implant delivers the right amount of radiation to the correct site in the body. The physicist works with the radiation oncologist to choose the treatment schedule and dose that has the best chance of killing the most cancer cells.

Radiation therapist – A health professional who gives radiation treatment.

Radiation therapy – The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external beam radiation therapy), or it may come from radioactive material

placed in the body near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body.

Restenosis – Narrowing of a blood vessel (usually a coronary artery) following the removal or reduction of a previous narrowing (angioplasty).

Seeds – Radioactive pellets, approximately the size of a grain of rice, used in brachytherapy.

Stage – The extent of a cancer within the body, especially whether the disease has spread from the original site to other parts of the body.

Stent – A device placed in a body structure (such as a blood vessel or the gastrointestinal tract) to provide support and keep the structure open.

Temporary interstitial implant – A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is temporarily placed directly into or near a tumor.

Tumor – An abnormal mass of tissue that results from excessive cell division. Tumors perform no useful body function. They may be benign (not cancerous) or malignant (cancerous).

Tumor staging – This is an important step in the management of cancer. Typically, several tests are performed to determine 3 things. The first part is to quantify the size and extent of a primary cancer. The second is to determine whether nearby lymph nodes are involved by the cancer. The third is to check whether cancer has spread through the blood stream to other parts of the body. Using this information, people with cancer are assigned a stage. This helps to determine the best course of treatment and it also predicts the response to treatment. Each type of cancer has a specific staging system.

Ultrasound – A test that bounces sound waves off tissues and internal organs and changes the echoes into sonograms (pictures).

Unsealed internal radiation therapy – Radiation therapy given by injecting a radioactive substance into the bloodstream or a body cavity, or by swallowing it. This substance is not sealed in a container.

Vascular – Relating to or containing blood vessels.

Volume study – This is a procedure used in prostate brachytherapy to map out the prostate gland. An ultrasound probe is placed in the rectum to get images of the prostate. Once the map is made, a computer plan is generated to show the best place to put radioactive seeds in and around the prostate. This is often done before or during a prostate implant procedure.