2017-02-27

Principles of Radiation Oncology

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Et al.

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Citation: Pieters RS, Ding L, Bushe H, Aronowitz J. Principles of Radiation Oncology. In: Pieters RS, Liebmann J, eds. *Cancer Concepts: A Guidebook for the Non-Oncologist*. 2nd ed. Worcester, MA: University of Massachusetts Medical School; 2017. doi: 10.7191/cancer_concepts.1008.

This project has been funded in whole or in part with federal funds from the National Library of Medicine, National Institutes of Health, under Contract No. HHSN276201100010C with the University of Massachusetts, Worcester.

Summary and Key Points

1. The practice of radiation oncology is based on five disciplines: clinical oncology, radiobiology, medical physics, oncologic imaging, and computer science.
2. Radiation therapy is a regional treatment that can be utilized as the sole treatment of a cancer or can be combined with surgery and/or chemotherapy in a multimodality regimen.
3. Definitive treatment (therapy with curative intent) can eradicate a tumor while sparing the organ that harbors it.
4. Severe acute effects may be acceptable if the treatment goal is cure. Supportive care and management of acute effects is critical in effective treatment delivery.
5. The impact of a given radiation dose is dependent upon the fraction size, treatment duration and treated volume.
6. Prescription radiation doses for cure are determined largely by normal tissue tolerances, the risk and acceptability of late effects.
7. The intent of palliative treatment is to relieve symptoms (rather than eliminating tumor). It is typically delivered in a relatively short treatment course, with fewer side effects.

A Brief History of Radiotherapy

Introduction

Radiation oncology uses ionizing radiation to treat cancer (and occasionally a few benign conditions). Radiotherapy or radiation therapy (RT) was initially developed in conjunction with diagnostic radiology, but has evolved into a separate specialty. Currently, more than 50% of cancer patients undergo RT at some point during the course of their cancer. Most receive treatment with curative intent (definitive therapy). Patients with incurable disease receive shorter courses of therapy to relieve cancer-induced symptoms designed to minimize acute side effects.

The acute side effects of RT are often milder than either chemotherapy or radical surgery; most patients find it the easiest portion of their therapy. While ionizing radiation damages both normal and cancerous cells, normal cells have greater capacity to repair this damage and carefully administered treatment can eradicate cancer cells while relatively sparing the organ that harbors them. For example, a laryngeal tumor and its draining nodes can be cured while sparing the voice and neck muscles.

Although RT can be used alone, it is often combined with surgery and/or chemotherapy in a multimodality regimen that benefits from the unique advantages of each modality. Combined modality therapy does run the risk of increased toxicity because of each treatment's side effects, so these regimens should be carefully designed and tested in clinical studies.

RT consists of two modalities: teletherapy and brachytherapy. Teletherapy utilizes x-ray or sub-atomic particle beams, delivered by a machine positioned a distance (typically, a meter) from the patient. Brachytherapy utilizes radiation emanating from radioactive sources implanted inside the patient's body, either temporarily or permanently. Both modalities have been in use for over a century.

In order to deliver safe and effective RT, the radiation oncologist must master five foundation disciplines: clinical oncology, radiobiology, oncologic imaging, computer science and medical physics.

Clinical Oncology

Effective practice of radiation oncology depends on a sound understanding of clinical oncology and basic sciences. This knowledge must include:

- Principles of cancer pathology, medical oncology and surgical oncology

- Gross anatomy and radiographic anatomy
- Natural history of each cancer
- General clinical care of the cancer patient including supportive care, management of cancer symptoms and treatment effects

Anatomy, the precise location of tumor in the patient and the natural history of a cancer are the basis of treatment planning for each patient. For example, careful recording of precise lymph node metastasis locations and risk of involvement of those locations in a study population dictate shape of fields to cover areas at greatest risk of microscopic tumor spread.[1]

Radiobiology

Radiobiology studies the impact of ionizing radiation on biological molecules, living cells and tissues. Whether an ionizing ray hits a molecule upon striking a cell is a random event. Statistically, a ray is most likely to strike the most common molecule in the cell, water. The ionizing ray causes water molecules to break apart into ion pairs, producing the highly reactive hydroxyl radical. Free radicals bounce around in the cell, and may strike other molecules, usually water, causing a cascade that increases the number and density of free radicals. Ultimately, one or more of these radicals may randomly strike a molecule of DNA, resulting in single or double strand DNA breaks. Without functioning DNA, the cancer cells cannot reproduce properly or repair themselves, and the cells transition to apoptosis. Apoptosis (programmed cell death) is the capacity of a cell to destroy itself if its DNA is irrevocably damaged.

A cell has several endogenous agents that are protective against radiation damage. The continued existence of free radicals depends on the concentration of the primary cellular defense- glutathione, which destroys free radicals. Enzymes that metabolize reactive oxidative species, including catalase, superoxide dismutase, and glutathione peroxidase, also may protect cells from radiation. Oxygen is a radiosensitizer because it extends the existence of free radicals by a factor of 3. Cells in a hypoxic environment are relatively radioresistant (by the same factor of 3; this is not a coincidence).

The body can usually repair single strand breaks, and sometimes can repair double strand breaks. Lethal damage results in mitotic cell death; damage that can be repaired is called 'potentially lethal damage'. Death of a cell line after lethal damage may take several mitotic cycles and therefore, depending on cell cycle time, as long as several months. A cell is most sensitive to radiation when it is undergoing mitosis; conversely, cells in G0 and the late S phase are relatively radioresistant. After cell death, the body must resorb the cell remains, and scars may form. So tumors usually shrink slowly, and sometimes a mass will remain that is simply a scar.

RT traditionally has been fractionated, which means delivered in multiple small daily doses, to maximize the effect on tumor cells and minimize the late effects on normal tissues. Acute side effects are largely due to the effect of radiation on the rapidly dividing normal cells of the body, such as skin and mucous membranes. Tumor cells are actively dividing, so tumors tend to respond in the same way as normal cells that actively divide.

Due to very different pathophysiology, occurrence of acute effects do NOT predict for occurrence of late effects. Late effects are largely due to microvascular damage that resembles that caused by diabetes mellitus, loss of parenchymal cell function and scarring. It is important to remember that late effects may occur many years after treatment.

The 4 R's of radiobiology: reoxygenation, repair, redistribution, and repopulation are the reasons radiation oncologists fractionate radiation.

Reoxygenation

When a tumor is irradiated, the better-oxygenated cells in the periphery of the tumor deposit are more likely to die. As these cells die during the course of therapy, O_2 penetrates more deeply into the tumor, and reach cells that had previously been poorly oxygenated. Hence, fractionated radiotherapy results in the induction of radiosensitivity in cells that had originally been radioresistant by the phenomenon of 'reoxygenation'.

Repair

Potentially lethal damage is damage which may be repaired; both in tumor cells and most importantly in normal, healthy, non-cancerous tissue within the radiation field. This process is felt to be largely complete in about 6 hours. Repair decreases risk of late effects.

Redistribution

Redistribution refers to the movement of cells into different phases of the cell cycle. Since cells in the late S phase and G0 are relatively resistant to radiation, multiple treatments enhance the chance that

any given cell will receive treatment during a sensitive phase in the cell cycle. Redistribution makes radiation therapy more effective.

Repopulation

Hopefully, all tumor cells are encompassed by the treatment and much normal tissue is not. In that case, normal cells can migrate from un-irradiated tissue into the target volume to replace damaged cells For example; skin cells will migrate into a denuded patch of skin, creating islands of normal skin which will enlarge to cover the open area. Surviving normal cells in the field can repopulate by cell division. Repopulation heals acute effects and also decreases risk of late effects.

Unfortunately, surviving tumor cells can also repopulate by cell division; so interruptions or extended treatment duration may decrease the probability of tumor control.

Organs that are organized in parallel (lung, kidney, liver) can tolerate the loss of large portions of their volume, while linear organs (spinal cord) cannot. Respecting radiation tolerance of these latter organs is very important. Exceeding tolerance of (sacrificing) portions of lung, liver or kidney is acceptable, providing enough functional parenchyma is left to sustain the vital function of that organ and the patient's quality of life. For example, the volume of lung that can be safely sacrificed depends on the pretreatment lung function.[2]

A radiation oncologist aims to deliver an effective dose to the tumor, while delivering as low a dose as possible to the surrounding normal tissue. Radiation dose is a very complicated concept, as it depends not only on the total dose, but also fraction size, and treatment duration. For example, 3000 cGy delivered in 5 fractions would be more potent than the same dose delivered in 10 fractions, and daily treatments are different than bi-weekly treatments. Although smaller fraction size tends to decrease late effects, if smaller daily doses are used, a higher total dose is required to achieve the same level of tumor control. However, the longer regimen is likely to decrease both acute and late effects.

The volume of irradiated normal tissue has a major impact on treatment tolerance, even though it is not recorded in the prescription or reported in studies. Large fields will tolerate less dose. Fortunately, control of microscopic disease requires less dose than control of gross tumor deposits. Often, smaller fields will be used at the end of treatment to provide adequate dose to the tumor; this is referred to as the "shrinking field technique" and the smaller field is called "the boost".

Since radiation cell kill depends on the random distribution of energy deposition in the cell, there is no way to guarantee the effectiveness of a course of radiotherapy, nor can we accurately predict toxicity expected from a certain dose.[2] Dose response curves are asymptotic to both the 100% and the 0% probability of a given outcome. Figure 1 shows the classic S-shaped dose response curve.

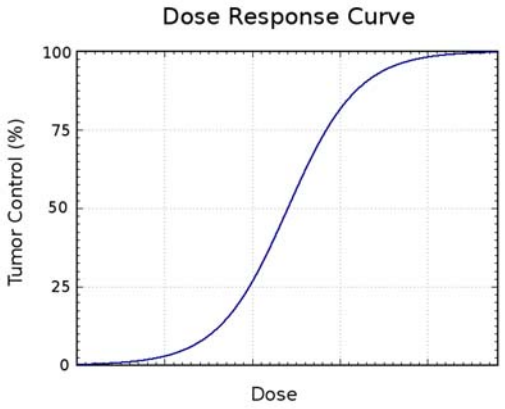


Figure 1. Dose Response Curve. Courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

When plotting both the probability of a late effect and of tumor control on the same diagram, the curves are approximately parallel. The ratio between the 50% point on the 2 curves is called the therapeutic ratio. The therapeutic ratio is favorable when the complication curve (CC) is to the right of the tumor control curve, and unfavorable when CC is to the left (Figure 2). The therapeutic ratio for complication-free survival versus tumor control is an important part of the risk/benefit analysis.

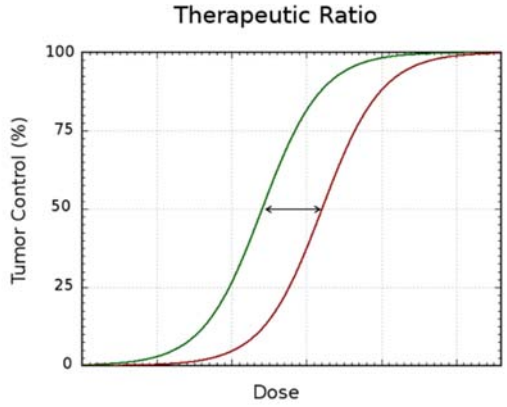


Figure 2. Therapeutic Ratio Curves. Hopefully tumor control curve is to the left and late effect curve to the right. Courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

Surgery or pre-radiation chemotherapy may improve the risk/benefit calculation by reducing tumor burden; because a lower dose of radiation is needed to eradicate residual microscopic disease than would have been needed to sterilize a bulky tumor.

Radioprotection and Radiosensitization

When the therapeutic ratio is unfavorable, attempts to control the cancer involve protection of normal tissues, radiosensitization of tumor cells, or both. Both radioprotection and radiosensitization are attempts to improve the therapeutic ration, by shifting the late effect curve to the right or the tumor control curve to the left.

Radioprotection: Decreasing the *effective* dose to normal cells, either by decreasing the fraction size or improving the normal tissue dose distribution (physical radioprotection) will improve the therapeutic ratio. Attempts to develop drugs to chemically protect cells have been largely unsuccessful (with the exception of amifostine, developed by the army for protection against nuclear attack, during the Cold War), and pilocarpine, a cholinergic agonist that protects salivary function to some extent during RT affecting salivary glands.

Radiosensitization: Since oxygen is required for effective radiotherapy, and since tumors almost always contain hypoxic areas, improving delivery of oxygen to tumor cells may improve clinical outcomes. Although pressurized oxygen has not been demonstrated to improve the therapeutic ratio, randomized data suggests that raising depressed hemoglobin levels enhances tumor control, presumably by increasing tissue oxygen levels.

Hyperthermia, either before or after irradiation, has been shown to radiosensitize tumor cells. This effect is not related to the presence of oxygen; in fact, cells in a hypoxic environment are more sensitive to hyperthermia. Delivering and maintaining heat homogenously has been challenging.

Very commonly, chemotherapy is administered concomitantly with radiation to sensitize the malignant cells to radiation. The treatment of many cancers, including anal, head and neck, lung and cervix cancer has been transformed by the use of concomitant chemoradiotherapy. The effective and safe dose of both drugs and radiation, however, must be determined for each drug or combination regimen, since radiosensitizing agents make normal cells more radiosensitive too.

Medical Imaging

The effective delivery of radiation therapy has always required an anatomic target. Originally, the target was defined by physical examination, plain radiographs, surgical findings (and metallic clips placed during surgery) (Figure 3) and analysis of patterns of disease spread demonstrated in surgical and autopsy series.

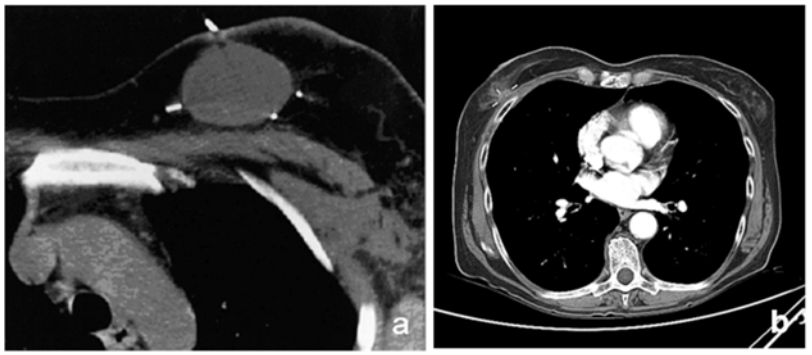


Figure 3. 3a. Surgical clips defining a tumor bed after removal of the tumor; the seroma adequately defines the tumor bed, and the clips add little additional information. **3b.**Clips defining a tumor bed after removal of the tumor; here, the clips are very useful, since the tumor bed is difficult to see on CT. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

The advent of CT, MRI and PET scanning has dramatically altered the treatment planning process.[3] Treatment planning is now done virtually, in the computer, using three-dimensional imaging from CT image sets obtained with the patient immobilized in the treatment position. MRI (Figure 4 a, b, c, d & e) and PET scans Figure 5 a-g) can be fused into these planning CT scans, enabling precise tumor delineation and close conformity to the shape of the tumor (3-D conformal RT) and technological advances in treatment delivery allow precise localization of dose in small volumes of the target and surrounding normal tissue, Intensity Modulated Radiation Therapy (IMRT). As a result of better imaging, more normal tissue is spared irradiation This physical radioprotection allows dose escalation without increasing toxicity (Figure 4 f, g & h and Movie 1).

Figure 4. MRI impact on treatment planning:

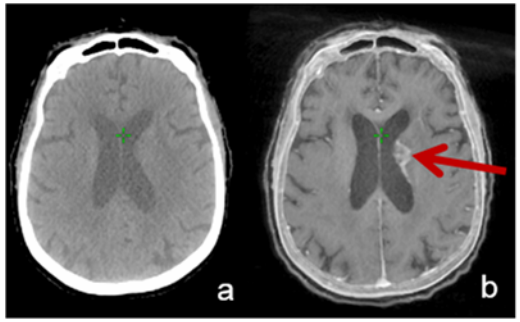


Figure 4a, b. 4a. Treatment planning CT of patient with brain metastases; no tumor is visible. **4b.** The same planning scan slice with MRI fused and displayed: 50% MRI, 50% CT. Notice tumor is now clearly visible just to left of ventricle. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

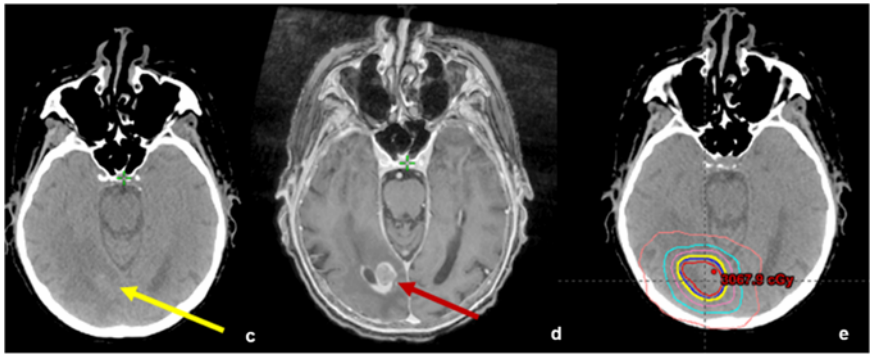


Figure 4c- e. 4c. Treatment planning CT of patient with brain metastases; no tumor is visible, but there is a hint of edema in right occipital lobe (arrow). **4d.** The same planning scan slice with MRI fused and displayed: 50% MRI, 50% CT. Notice tumor (red arrow) is now clearly visible in posterior portion of edema, which is much more visible on the MRI image. **4e.** MRI fused into treatment planning CT, with dosimetric lines defining treatment, with 100% line (yellow) (prescription dose) covering target volume. Red dot is pixel receiving maximum dose. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

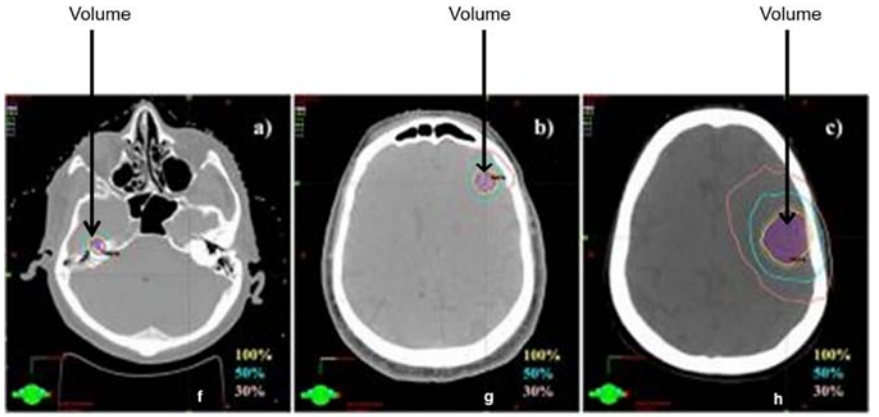
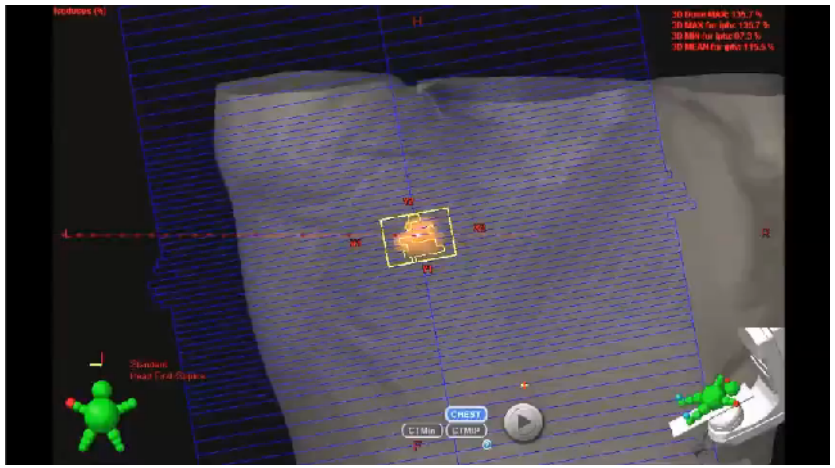


Figure 4f- h. Demonstrating transverse plane isodose distributions for a range of clinical target volumes (CTV): **4f.** 0.1 cm^3; **4g.** 1.1 cm^3; and **4h.** 12.6 cm^3. Notice how well the smaller volumes treatments can spare overlying brain. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.



Movie 1. Demonstrates intensity modulated radiation therapy treatment. Note the movement of the table and the blocks to shield organs at risk. Courtesy of the University of Massachusetts Medical School. Department of Radiation Oncology.

If you have problems loading the movies, try installing the Flash plug-in found at: http://helpx.adobe.com/acrobat/kb/reader-acrobat-flash-player-download.html.

Figure 5. PET impact on treatment planning:

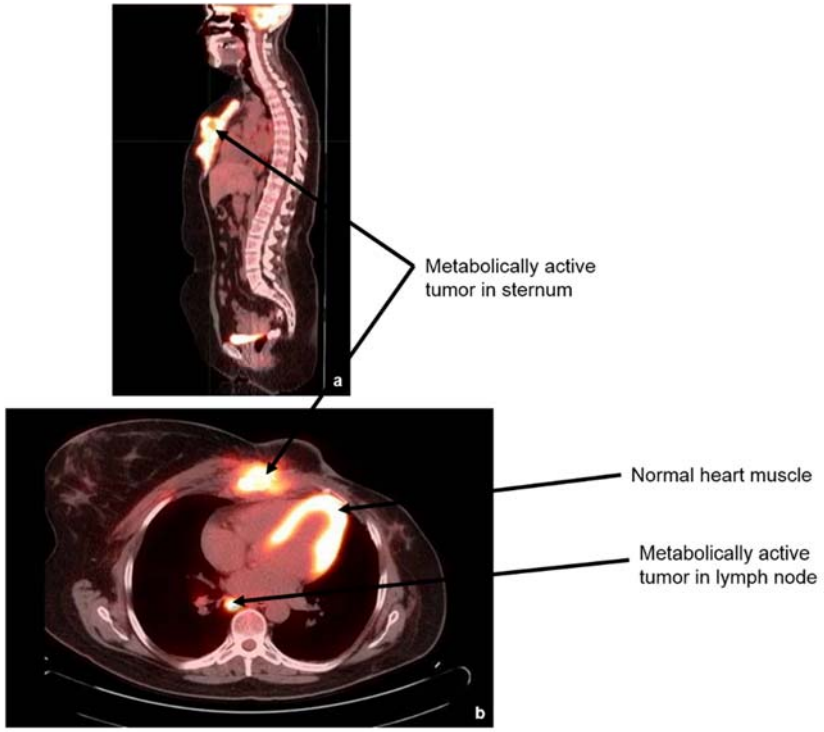


Figure 5a, b. Diagnostic tomographic PET/CT fused images. Images courtesy of the University of Massachusetts Medical School, Department of Radiology.

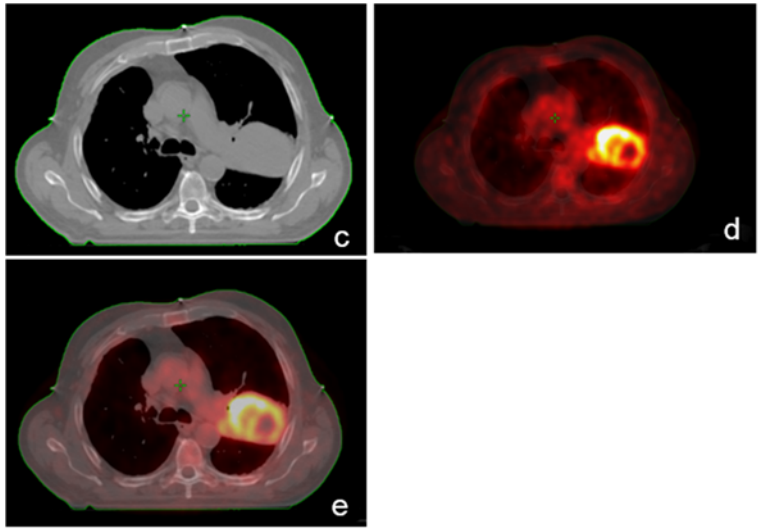


Figure 5c- e. 5c. CT slice through chest demonstrating a mass, possibly collapsed lung tissue. **5d.** PET slice demonstrating FDG avidity in the mass. Note the limited anatomic specificity seen on PET alone. **5e.** Fused PET/CT of above slices, demonstrating that entire mass is involved, therefore tumor, but the hilum is not. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

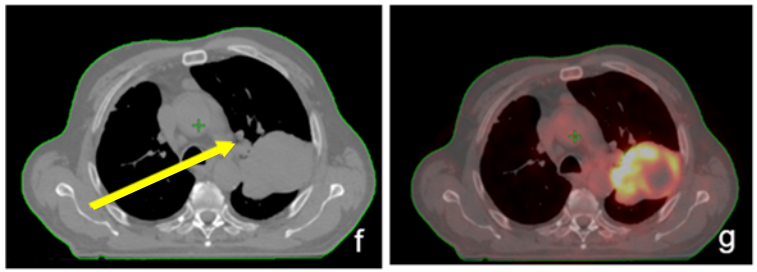
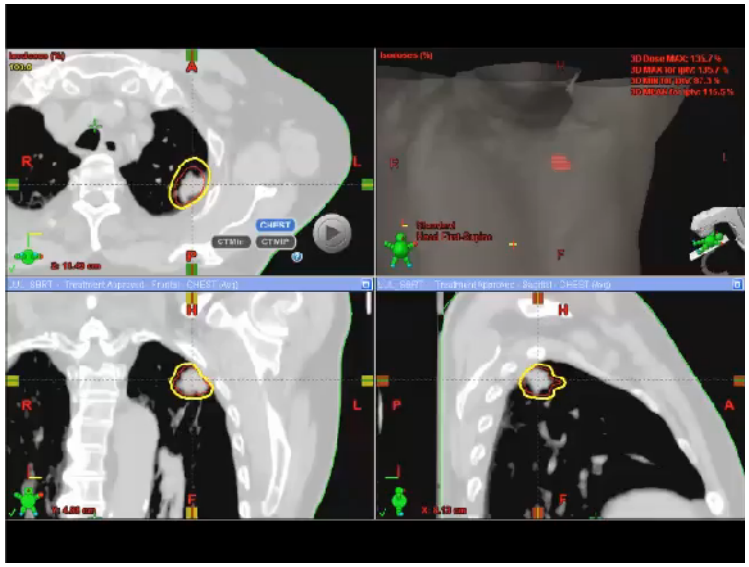


Figure 5f- g. 5f. CT slice, same patient, cephalad to previous images. Arrow points at lymph nodes. **5g.** PET/CT fusion demonstrates that these nodes are NOT FDG avid, therefore probably not involved. Images courtesy of the University of Massachusetts Medical School. Department of Radiation Oncology.

Respiratory motion is taken into account with 4D treatment planning (the fourth dimension is time). Further precision of treatment is ensured by confirming that tumor is contained within the high dose volume despite physiologic motion, and knowing the extent of this motion allows use of tighter margins, sparing normal tissue.[4] Four dimensional (4D) treatment planning may entail the use of advanced treatment techniques such as respiratory gating, which turns the beam on only during a specific portion of the respiratory cycle (Movie 2).



Movie 2. Demonstrates the respiratory motion taken into account with 4D radiation treatment planning. Courtesy of the University of Massachusetts Medical School. Department of Radiation Oncology.

If you have problems loading the movies, try installing the Flash plug-in found at: http://helpx.adobe.com/acrobat/kb/reader-acrobat-flash-player-download.html.

Daily target localization on the treatment machine (Image Guided RT - IGRT), either by localizing implanted radio-opaque markers (fiducials) (Figure 6) or by imaging with an on board CT-scanner, called cone-beam CT (Figure 7) has greatly improved the accuracy of treatment delivery, because the prostate actually moves a bit in a living patient, largely as bowel and bladder variably fill and empty from day to day.

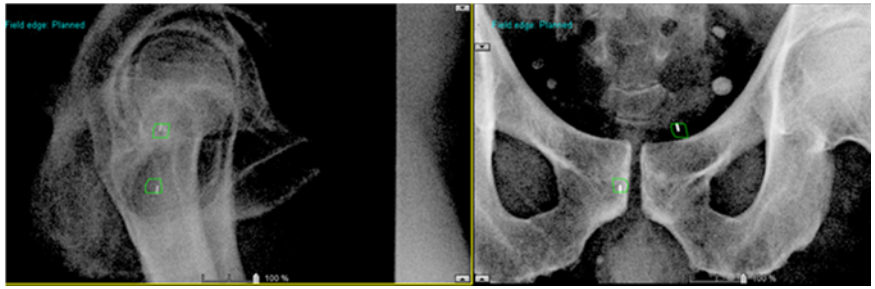


Figure 6. Lateral and AP radiographs of a male pelvis obtained with diagnostic energy x-rays on the treatment linear accelerator. Inert (not radioactive) medal wires were inserted into the prostate prior to treatment planning CT scan and outlined on the scan. The green boxes are from the outline on the planning CT scan. By shifting the patient so the wires are within the boxes, the radiation oncologist can assure that the planned dose distribution is being delivered to the prostate. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

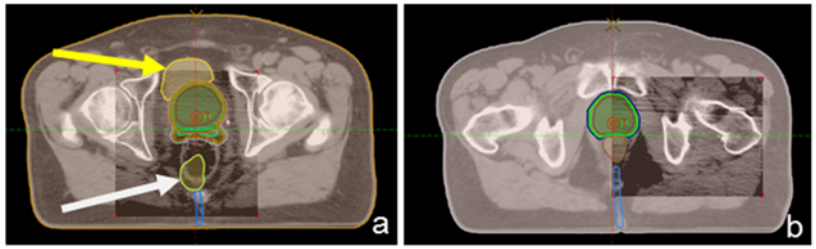


Figure 7. Cone beam CT of prostate showing location of prostate. Daily cone-beam images enable the same adjustment of patient as fiducial markers to place dose distribution accurately as prostate shifts. The cone beam CT is fused with and beneath the planning CT, visible through viewing windows (slightly darker rectangles in each image above. Notice how close posterior edge of prostate and seminal vesicle volume is to rectum. Daily image guidance has dramatically decreased the incidence of post treatment rectal bleeding. **7a.** Upper slice showing seminal vesicles, rectum (white arrow) and bladder (yellow arrow). Notice rectum has shifted on cone beam CT scan from planning scan in this slice. **7b.** Lower slice showing prostate and rectum. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

Cone beam CT has also enhanced the accuracy of treatment of lung tumors, permitting greater sparing of normal lung tissue, which is important as most lung cancer patients also have chronic obstructive pulmonary disease to one extent or another (Figure 8).

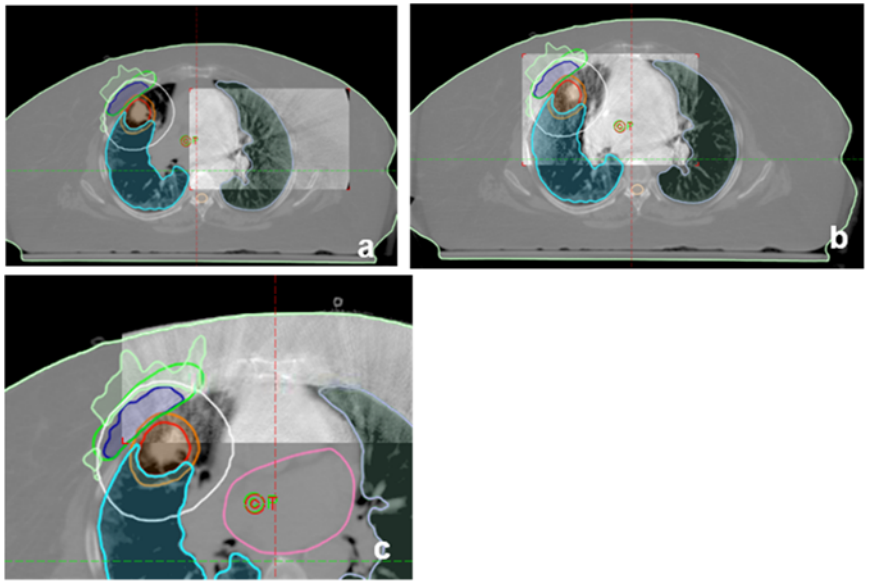


Figure 8. CT of chest, right upper lobe lung tumor. Treatment planning CT on top of a cone beam CT taken just before a daily treatment at the end of a treatment course.The rectangular viewing window shows the cone beam CT information. **8a.** Viewing window is on right side; tumor is seen on treatment planning CT before the start of treatment. **8b.** Same slice as 8a. Viewing window now includes RUL tumor. Notice tumor is smaller and is encompased by target dose lines drawn on planning scan even though the lung has retracted and pulled the tumor noticeably medially. **8c**. Viewing window splits tumor; bottom half of tumor is seen on treatment planning CTand top half is seen on cone beam CT, smaller and pulled medially. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

Computer Science

The great recent advances in radiotherapy (3D Conformal RT, Intensity Modulated RT- IMRT, IGRT) would not have been possible without the explosion in computer technology. Today, treatment planning is done almost entirely by computer. Computers also control the actual treatment delivery, including the positioning and motion of the leaves that shape and texture the treatment beams. Multi-leaf collimators have replaced lead

blocks for beam shaping, and can move during the actual treatment (IMRT). IMRT paints dose into the body, permitting tight control of dose distribution within the body by shaping dose around critical structures and the tumor. This technology enables even greater dose conformity and treatment of tiny volumes, as in Figures 4f and 4g. This precision allows for safe delivery of much higher doses than possible with traditional treatment planning and delivery techniques.

Medical Physics

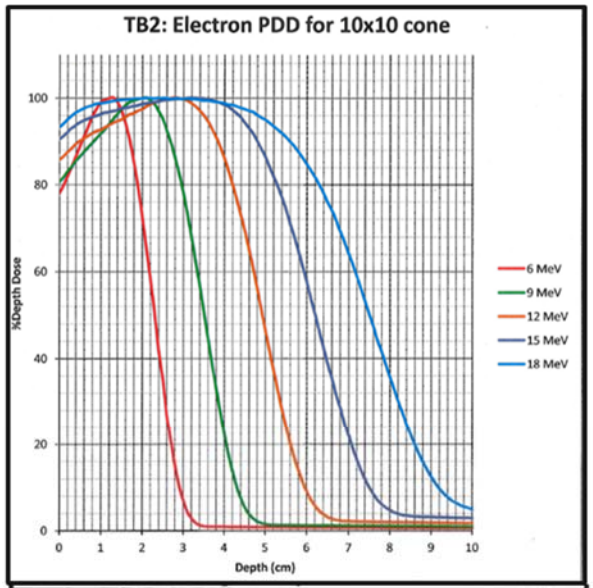
The physics of ionizing radiation is the final body of knowledge required. X-rays, heavy particles (such as protons) and electrons are beams produced by machines; gamma rays are the product of radioactive decay. Remember, from Physics 101, that the density of any radiation (visible light, ultraviolet light, ionizing radiation, etc.) falls off with the square of the distance. This fundamental property is referred to as the Inverse Square Law.

Diagnostic radiography typically uses low energy (kilovoltage) x-rays. Diagnostic energy x-rays (kilovoltage) can treat superficial tumors, but the deposition pattern delivers full dose to the skin, increases acute skin reaction and preferential absorption of these low energy beams in bone increases the risk of late bone damage. In addition, the dose delivered by these beams decreases (falls off) rapidly as depth in tissue increases. Today, electrons are more commonly used, because the dose delivered decrease rapidly with increasing depth in tissue, to the point of almost no dose deep in the body (Figure 9).

Treatment of deep-seated tumors requires high-energy beams (megavoltage) that have greater penetrating power, so dose delivered at depth falls off more slowly than with kilovoltage radiation. Both the amount of skin sparing and the depth of penetration depend on the energy of the megavoltage beam. Megavoltage x-rays have this greater penetration, are not preferentially absorbed in bone, and do not deliver full dose to skin. This skin sparing effect is due to build-up of the free radicals generated as the beam penetrates into tissue Figure 10.

Use of multiple megavoltage fields permits protection of overlying tissue as seen in Figure 11, a simple four field plan, by geographic dose distribution; before IMRT, this was commonly used for the treatment of prostate cancer. These techniques may still be seen in old patient records or in emerging countries, where contemporary technology is not yet available. When patients who have received radiation treatment in the past are seen, it is important to be aware of how they were treated.

The ultimate use of many fields is arc therapy, using, in essence, up to 360 fields, where the treatment head rotates around the patient; before IMRT, this was the best tissue sparing plan available (Figure 12).



Electron Depth (cm) for 10x10 cone			
Energy (MeV)	Dmax	90%	80%
6	1.3	1.7	1.9
9	2.0	2.7	3.0
12	2.8	3.8	4.2
15	3.2	4.8	5.3
18	2.5	5.6	6.3

Figure 9. Depth dose curve for the clinically useful range of electron energies. Courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

Figure 10. Depth dose curve for photons:

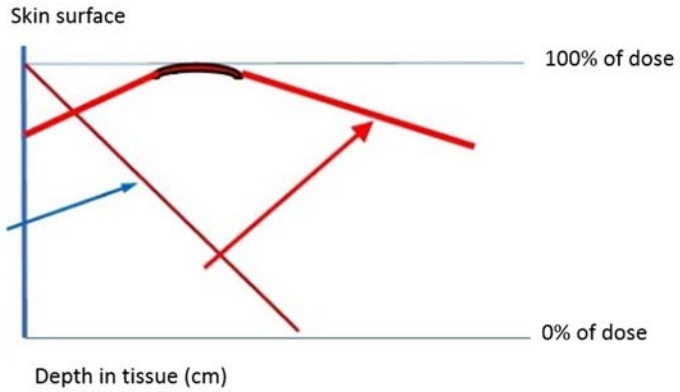


Figure 10a. Kilovoltage versus megavoltage, notice kilovoltage delivers 100% at the surface (skin), while megavoltage spares skin, maximum dose is at a depth, referred to as Dmax. Blue arrow represents kilovoltage beam, also called orthovoltage. Red arrow represents 18 MV beam with about 3.5 cm skin sparing. Courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

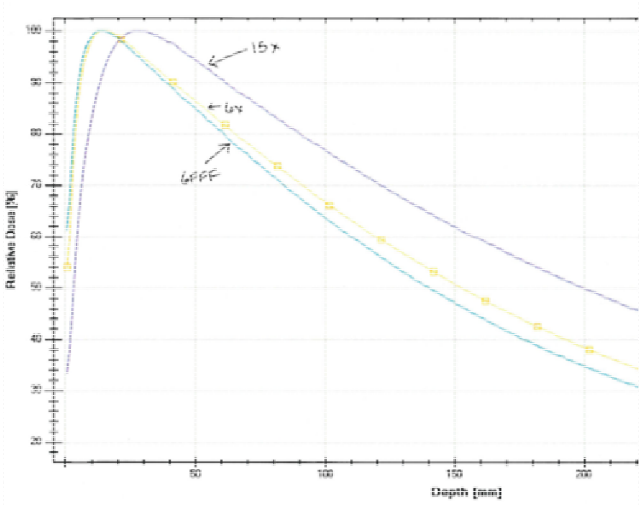
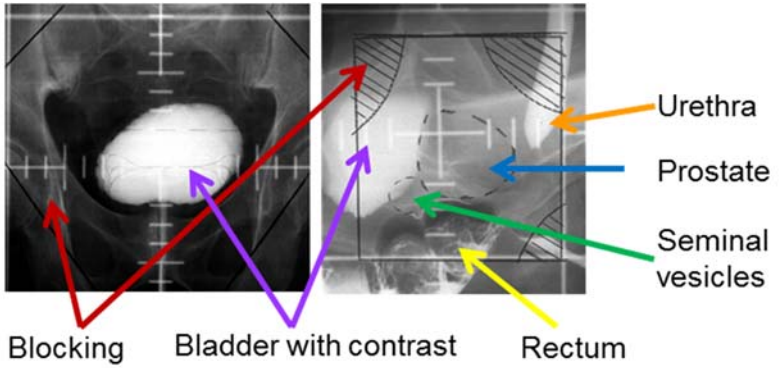


Figure 10b. Depth dose curves for 2 megavoltage x-ray beams, 6 MV & 15 MV. Courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

Figure 11. Use of multiple beams to spare overlying normal tissue. Simplest example, four fields: Treatment fields and dose distributions for a 4 field plan, showing sparing of overlying tissue. With the use of four fields, AP, PA and laterals, 100% of prescription dose can be delivered to the target volume, while the tissue in front and back receives 50-60%, the tissue laterally 40%and the 4 outside corners very little. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.



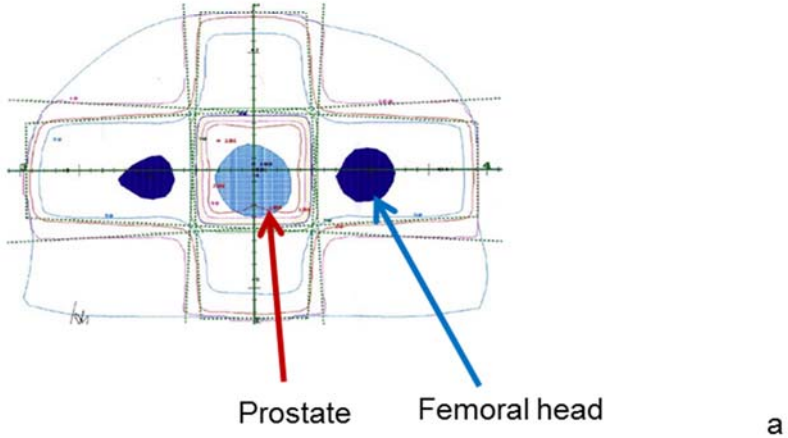


Figure 11a. Old fashioned orthogonal treatment planning images & 2D plan, based on wire contour. Notes blocks drawn with crayon, which were cut out of styrofoam and lead alloy poured to create custom blocks, to shape treatment fields to protect uninvolved normal tissue. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

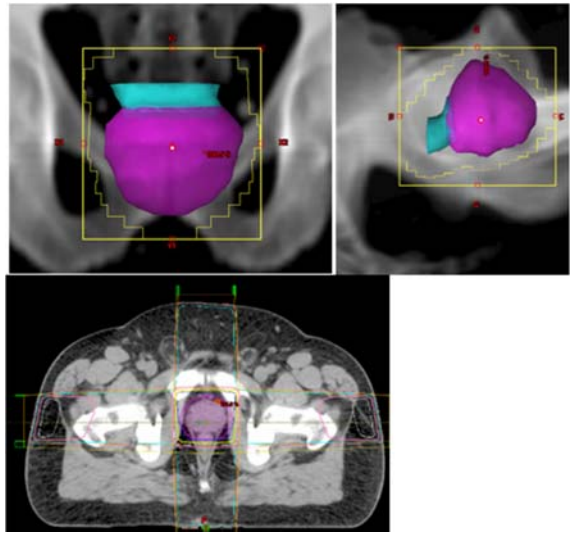


Figure 11b. Contemporary digitally reconstructed radiographs (DRR) from planning CT, with prostate a seminal vesicles reconstructed from contouring on successive CT slices and single CT slice dose distribution demonstrating coverage of prostate, & anterior wall of rectum, with sparing of femurs and remainder of rectal circumference. Image courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

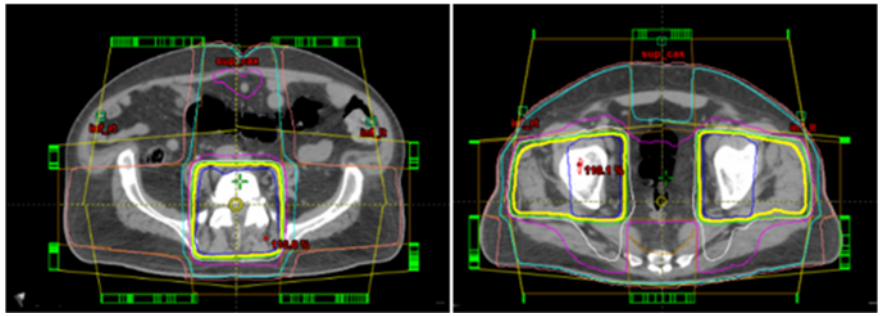


Figure 11c. A four field plan on patient CT slice for XRT for bone metastasis. Left image shows 100% line encompassing sacrum; notice uninvolved psoas muscles are partially in 100% volume. Right image shows 100% line encompassing femoral heads (which are treatment targets) with relative sparing of pelvic contents (which are not). Image courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

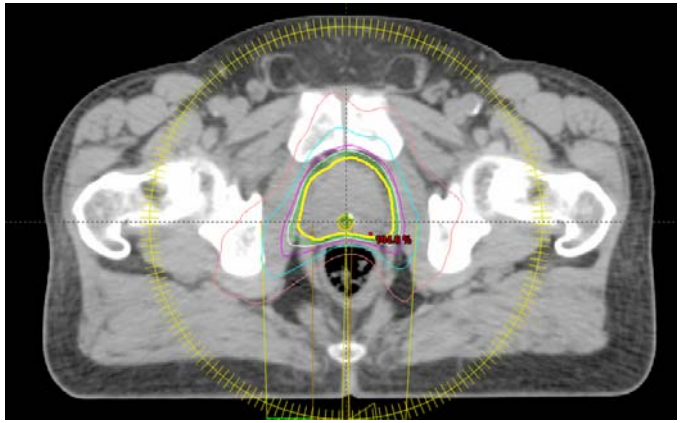


Figure 12. A dose distribution for a 360º arc plan. Notice the yellow 100% line tightly hugs the prostate, and the anterior wall of rectum is relatively spared because the dosimetry lines are concave behind the prostate. University of Massachusetts Medical School. Department of Radiation Oncology.

Various heavy atomic particles have been used for radiation therapy as well; the only one in much use today is the proton. At great cost, proton beams provide great precision of conformal dose delivery, which is felt to be important in treating tumors close to critical structures such as the brainstem, and perhaps in children.

Brachytherapy (the temporary or permanent implantation of tumors or body cavities with radioactive sources) is a method of focusing high doses of radiation into tumor while reducing dose to surrounding tissues (Figure 13 and 14). Dose distribution depends on precise positioning of the radioactive sources and the physical characteristics of the individual isotope disintegration products. Dose rate depends on the initial radioactivity strength of the source and the half-life of the particular isotope.

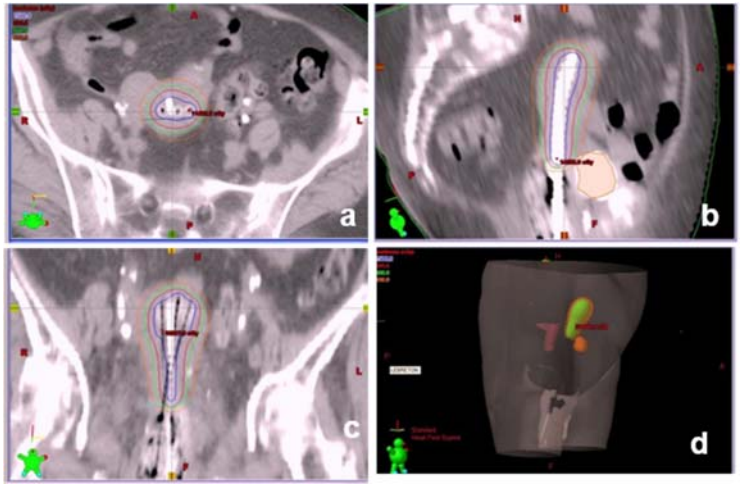


Figure 13. CT slices through the uterus showing radioactive tube placement for treatment of endometrial cancer. **a)** Axial; **b)** Sagittal; **c)** Coronal; **d)** Dose cloud. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

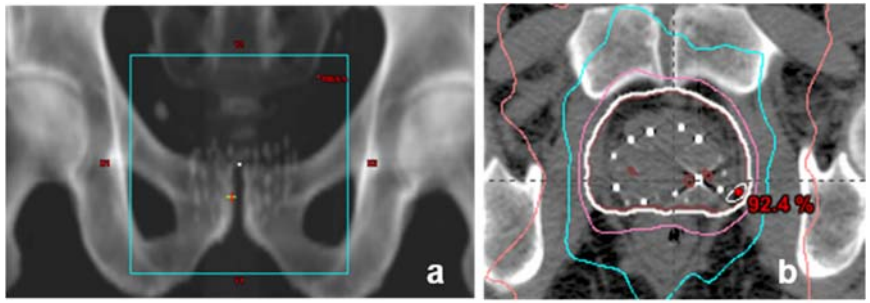


Figure 14. a. DRR: AP view of I131 permanent interstitial prostate implant **b.** Axial CT slice through this implant, showing seed placement. This patient also received external beam therapy as a portion of his treatment. So the white line is the 100% line from the brachytherapy. Note sparing of anterior rectal wall and careful seed placement away from urethra. University of Massachusetts Medical School. Department of Radiation Oncology.

Stereotactic Radiosurgery (SRS) or Stereotactic Radiotherapy (SRT)

The advent of CT and MRI based 3-dimensional treatment planning has made it possible to focus high doses of radiation accurately. SRS delivers an ablative dose of radiation in a single fraction, destroying both tumor and tissue. SRT utilizes the same technology, but fractionates therapy into 2-5 treatments, thereby taking advantage of the 4 R's of radiobiology. Precise target definition and patient immobilization are critical. Individually designed restraints are used to assure patient positioning.

Stereotactic treatments rely on several technologies:

- three-dimensional imaging that determines the exact coordinates of the target within the body
- systems to immobilize and carefully position the patient
- highly focused gamma-ray or x-ray beams that converge on a tumor or abnormality
- image-guidance on the treatment table

SRS is usually used for treating small lesions. Both SRS & SRT were originally used to treat brain lesions because the skull is easily immobilized. These treatments have been useful for the treatment of some non-cancerous conditions, including intracranial arteriovenous malformations (AVM's) and trigeminal neuralgia.

More recently, stereotactic technology has been applied to treat extracranial lesions, such as liver and lung; this is called stereotactic body radiotherapy, (SBRT). Extracranial lesions are harder to immobilize, as organs move with respiration; 4D planning is necessary where respiratory motion is expected, as in lung and liver.

SRS and SBRT have become much more common in the last few years. SRS replaces whole brain radiotherapy for many cases with limited (1 to 4 lesions) brain metastases[5] (Figure 5). SBRT for small lung lesions without apparent nodal metastases (T1N0M0) appears to have comparable survival to surgical removal of these tumors, with local control in the range of 90%. It is now being used routinely in medically inoperable patients or those who refuse thoracotomy[6]. It has been studied against lobectomy, with comparable results in small studies[7] additional studies are ongoing. SBRT is also proving to be useful for treatment of liver tumors, whether primary or metastatic[8] (Figures 15 & 16).

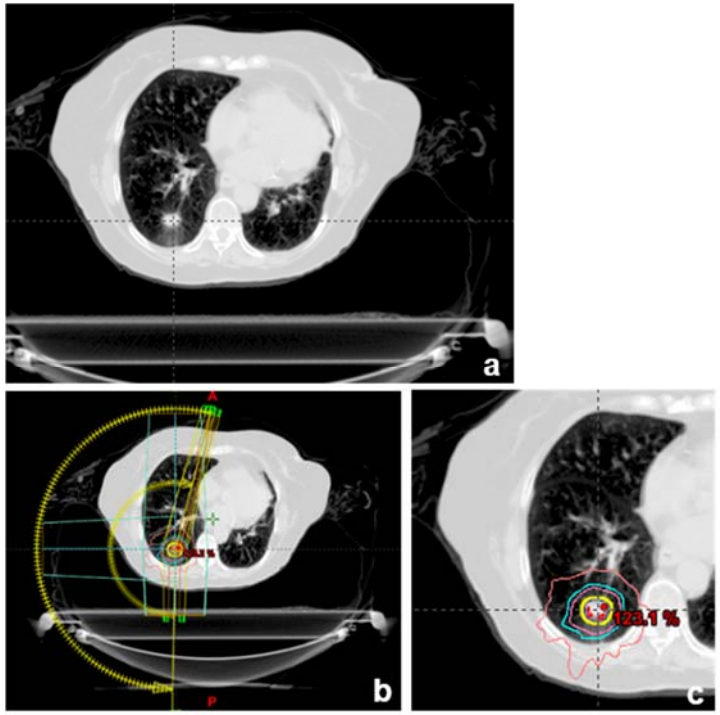


Figure 15. SBRT of a Stage I cT1N0M0 lung tumor. **15a.** CT Slice showing target lesion (under cross hairs). **15b.** Same CT slice showing arcs used to treat the tumor, during treatment the linear accelerator rotates around patient as beam is on, and dose distribution improved from traditional arcs because IMRT is used as well as rotation. (Blocking leaves move as well to make dose as homogenous as possible.) **15 c.** Dose distribution around tumor. Prescription dose line (100%) is yellow. Outermost dose line is 50%. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

Figure 16. SBRT liver:

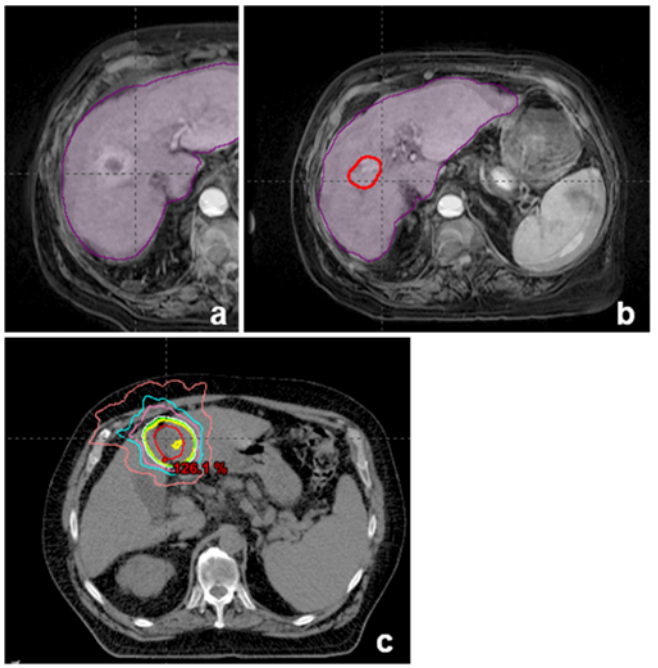


Figure 16a. MRI of liver, notice whitish metastasis with necrotic core. **15b.** Same patient, MRI fused with planning CT, with metastasis outlined in red (slightly different slice) **16c.** Planning CT of another patient with liver metastasis, with target outlined in red, and prescription dose (100%) in yellow. Notice margin between red and yellow lines, to allow for respiratory motion. Images courtesy of the University of Massachusetts Medical School, Department of Radiation Oncology.

The biology of SRS and SBRT are not well understood yet. It is clear that these treatments are ablative- they are designed to entirely kill the volume treated, so treatment of adjacent normal tissue must be minimized, and the new ability to do that makes use of these treatments possible. In addition to direct cell kill, vascular damage and immune effects are believed to contribute to the efficacy of SRS and SRT.[9] The biology of ablative therapies is an active area of research in radiobiology.

Goals of Radical Treatments

Radical RT seeks to permanently control primary tumors (often, with the draining lymph nodes), while limiting toxicity to acceptable levels. If the tumor has not already spread, eradication of the primary (and regional nodes) will cure the patient. RT has the capacity to achieve control while preserving the affected organ, thereby enhancing long-term quality of life.

Goals of Palliative Treatments

Palliative RT seeks to relieve specific symptoms (such as pain or bleeding) while minimizing patient inconvenience and side effects. It is an effective modality for reducing or eliminating many tumor-associated symptoms requiring relief, and is often the most effective, least invasive and least expensive option. Unfortunately, it has been estimated that half of patients in the United States who might benefit from palliative radiation therapy have not been referred to a radiation oncologist.

Treatment should relieve the targeted symptom for a significant length of time, often for the remainder of a patient's life, while causing few, if any, side effects. The treatment should be planned to minimize patient imposition and cost (the latter is usually born by society through health insurance). Radiation oncologists must balance efficacy against cost, through the judicious use of fractionation and choice of technique. The use of prolonged is typically unwarranted, as symptom relief requires a lower radiation dose than is necessary for tumor eradication. However, acute normal tissue tolerances must be accounted for; a high daily dose to bowel may cause significant gastrointestinal symptoms, impacting quality of life.

The mechanism of palliative radiation is incompletely understood; it more likely secondary to alteration of humoral factors (perhaps an anti-inflammatory effect) rather than tumor shrinkage, as a patient may enjoy dramatic pain relief without any change in tumor volume. In most cases, the likelihood of response is not dependent upon tumor histology (although there are exceptions). On the other hand, maximal pain relief may take 6-8 weeks for some bone metastases. This seems to be due to bone healing after tumor cell death. Partial or complete pain relief can be expected in at least 60% of patients; reduction or elimination of tumor bleeding occurs in 90%. Certain tumors (lymphoma, for example) are so radiosensitive that lower doses of radiation can be utilized.

Most commonly, radiotherapy is used for palliation of pain; the second most common palliative use is to relieve the symptoms of brain metastases, and other neurologic signs & symptoms. It is also useful for relief of tumor bleeding, obstruction of most hollow visci, (except the biliary tree), and respiratory compromise due to airway obstruction or post obstructive pneumonia. Disfiguring lesions of Kaposi's sarcoma reliably respond to palliative RT. The efficacy of RT in palliating painful, draining chest wall recurrences of breast cancer was recognized more than a century ago.

It is a myth that radiotherapy cannot be repeated. Many patients will require treatment of multiple sites over the terminal portion of their illness, which sometimes can last for several years, particularly for bone metastases, and retreatment of the same site is often possible. The brain will only perceive pain from 1-3 sites at a time. So it is not uncommon for patients to achieve good pain palliation from a course of radiotherapy and shortly thereafter require treatment to another site or sites, sometimes many times over the course of illness.

To summarize this section: Radiotherapy is a powerful tool for palliation, and can improve the quality of even a short life. Retreatment is often possible, especially in patients for whom late effects are less of a concern.

Conclusion

Radiation Oncology is the medical specialty concerned with the prescription and delivery of RT, one of the three main modalities for treating cancer. Computer technology has revolutionized the field over the past decade, and the physicians who manage cancer patients must keep abreast with the changes so that their patients are not deprived of these advances. Although acute or long-term adverse effects may result, it is important to balance these risks against the risks of surgery or chemotherapy and for the patient and referring physicians to remember the goal of treatment when late effects do occur.

Thought Questions

1. Why do many patients fear radiation therapy?
   Your answer:

Expert Answer

2. Why do most American Radiation Oncologists always prefer to fractionate (spread out dose over several treatments) rather than give a single fraction as the total treatment?
   Your answer:

Expert Answer

3. When should a diagnosis of a late effect of radiation therapy be considered and when is such a diagnosis completely inappropriate?

   Your answer:

Expert Answer

4. Why have SRS and SRT become more commonly used in treatment?

   Your answer:

Expert Answer

Glossary

Armamentarium- All of the medicines, biologics, equipment and techniques available to a doctor

Benign conditions- Non-cancer diseases

Brachytherapy- Placement of radioactive isotopes in body cavities (nasopharynx, gyn tract) [intracavitary brachytherapy] or tissues (prostate, breast) [interstitial brachytherapy]

cGy- (centiGray)- A unit of radiation measurement: 100 cGy=1 Gy

Conventional fractionation- A defined schedule for delivering small doses of the total radiotherapy dose at regular intervals

Course of radiation- A complete treatment delivered to a single volume, whether in one sitting or over several months

Dose cloud- An image of a dose distribution in the body, often shown in a 3-dimensional image

Fractionated radiation therapy- A course of radiation delivered in multiple daily or several times/day doses, called fractions

Fraction size- Number of centiGray (cGy) delivered in a single radiation therapy treatment session

Glutathione- A naturally occurring compound; cellular defense against free radical damage of DNA

Half-life- The time for half of the radioactive atoms in a sample to undergo radioactive decay

Hyperthermia- Heating tumor, to about 43^{o} C for a defined time

Potentially lethal damage- Genetically damaged cell can repair

Radiosensitizer- An agent that increases the damage a specified dose of radiation does to a cell

Teletherapy- External beam radiotherapy given from a distance

Therapeutic ratio- The ratio between the dose providing a 50% probability of tumor control and the dose for a 50% probability of a given complication

Tumorcidal- Dose that will kill tumor cells

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A Brief History of Radiotherapy

Jesse Aronowitz, MD

Western medicine had been dominated for almost two millennia by the concepts of Hippocrates as codified by Galen. Disease was believed to be secondary to an imbalance of 'humours' that could be righted by purgings, bleedings, diaphoresis, and emesis. But discoveries in anatomy, physiology, microbiology, and immunology in the 18th and 19th century rendered the Galenic system of medicine untenable. Appearing in its place was the revival of folk healing arts (herbology, therapeutic baths, massage) as well as the appearance of new therapies (homeopathy, electrotherapy, osteopathy). In the last decade of the 19th century, a Dane, Nils Finsen, introduced a system of light therapy for which he was awarded a Nobel Prize. Utilizing intense, focused ultra-violet light, he was able to successfully treat a variety of skin disorders, such as lupus vulgaris (cutaneous tuberculosis) and basal cell carcinoma. After Wilhelm Röntgen announced his discovery of a 'new kind of ray' in 1895, it seemed appropriate to apply this ultra-short wavelength light in the treatment of cutaneous ailments that had responded to Finsen's light. The results were gratifying and, within a decade, there were over a hundred medical applications for x-rays. Although mostly used for benign skin disorders, radiotherapy proved to be effective in palliating breast cancer recurrence, bone metastases, and lymphomatous masses. Biologists began studying the effects of radiation on normal and tumor cells over a century ago, establishing the field of Radiobiology, which has been used to optimize treatment.

Over the ensuing decades, several important discoveries expanded radiotherapy's utility. Initially, therapy was delivered in a few large treatments. By the 1920's, however, it was learned that 'fractionating' a treatment over an extended course was gentler on the tissues the rays traversed. Higher energy tubes allowed x-rays to penetrate more deeply, so that subsurface tumors could be targeted. Extremely powerful 'megavoltage' units began appearing in the 1930's, culminating in the appearance of linear accelerators in the 1960's. Certain tumors, such as lymphoma and Hodgkin disease, were no longer considered hopeless; diseases such as laryngeal and bladder cancers could be cured without mutilating surgery.

Within a few years of Röntgen's discovery, the Curies isolated radium (^{226}Ra), a material that emitted deeply penetrating γ rays with similar physical and biological characteristics as x-rays. Radium's scarcity, however, and the expense of refining it, delayed its broad use. The watershed event in the therapeutic use of radioactive materials was the 1913 Gynecologic Congress in Halle (Germany) in 1913, in which several papers related the dramatic response of gynecologic tumors to implanted mesothorium (^{228}Ra). Radium or mesothorium could be encapsulated in small capsules or needles that could be temporarily implanted into tumors or an involved viscous. Within a decade, major institutions had refined the practice of brachytherapy (treatment by implantation of radioactive materials) and the radium industry had lowered the cost of the product. Brachytherapy was soon recognized as curative treatment for oral, urological, and gynecologic tumors; as well as palliative for esophageal, breast, and rectal tumors.

Despite the demonstrated efficacy of ionizing radiation for destroying cancer, the practice was at risk of disappearing in the second half of the 20th century, for several reasons:

1. Radiation damages normal, as well as cancerous tissue
2. Treatment providers (physicians, nurses, and ancillary personnel) were at risk of developing complications (including malignancy) from chronic radiation exposure
3. The appearance of more skilled surgeons, as well as more effective surgical techniques, that rivaled radiotherapy
4. The introduction of chemotherapy, replacing radiotherapy as treatment for lymphoma and as an adjuvant to surgery.

Perhaps the most important development to advance radiotherapy was its transformation into a separate specialty, radiation oncology. Until fifty years ago, teletherapy (radiotherapy utilizing beams from an x-ray generator) was the provenance of dermatologists and 'general radiologists' (whose major interest was diagnostic radiology). Brachytherapy was utilized primarily by surgeons, for whom it was only of secondary interest. Radiologists solely involved in the practice of the treatment of cancer established their own specialty organizations, the International Club of Radiotherapists (1953) and its American counterpart (the predecessor of ASTRO, in 1958). Training programs for radiotherapy specialists began appearing. Academic Radiation Oncology departments explored and developed safer and more effective techniques and treatment regimens. The 'Patterns of Care' studies have gathered practice

and outcome data from academic and private practice, leading to the recognition and implementation of optimal therapies. The introduction of low-energy radionuclides and afterloading equipment has made brachytherapy safer for the provider. Finally, the development of imaging and computer technology has resulted in more focused therapy that spares normal tissue to an unprecedented extent.

Radiotherapy is used more frequently today to treat malignancy than at any time in its history. In certain diseases (as locally-advanced cervical cancer) it remains the most effective therapy. It can be used to spare the patient from mutilating surgery (tongue, larynx, bladder, penis), or by preserving tissues by limiting the extent of surgical procedures (breast, sarcoma, brain). It offers an effective alternative for patients unsuitable for curative operative procedures (lung, esophagus). It improves survival as an adjuvant to surgery (rectum, esophagus) and allows reduced doses of chemotherapy (thereby reducing toxicity) when used as an adjuvant in the treatment of lymphoma. And it is frequently the most effective and best tolerated palliative therapy for patients with incurable disease. Radiotherapy has entered its second century as a vital form of cancer treatment.

Return to Introduction