HISTORY:

X-rays were discovered in 1895 by Wilhelm Roentgen who noted that this ray could blacken photographic film sealed in a container and could pass through materials opaque to light such as wood. He was able to take the first x-ray of his colleague's hand and thus became the father of diagnostic radiology as well as of radiation physics. Becquerel in 1898 accidently left 200 mg of radium in his vest pocket for 6 hours – this unfortunate, accidental first radiobiological experiment resulted in erythema and ulceration of his skin that took weeks to heal. During the early 1900’s, several researchers expanded on the field with some ingenuous experiments. Bergonie and Tribondeau demonstrated that radiosensitivity was highest in tissues with the highest mitotic index and researchers in Paris showed the beneficial effects of fractionation on normal tissues. By irradiating the testes of rams using a fractionated technique, these animals were made sterile while relatively sparing their skin. Giving them one big dose of radiation did not sterilize these animals without causing a severe skin reaction. It was thus shown early on that rapidly growing tissues appeared to react to radiation more than normal tissues. Further advances in the 1950s allowed higher energy radiation units to be built to allow further penetration of tissues with greater skin sparing properties. This was also enhanced by the advent of linear accelerators which were capable producing faster, higher energy radiation beams.

BASIS OF RADIATION FOR THERAPEUTIC APPLICATIONS

Electromagnetic radiations (x-rays and gamma rays) are able to produce biological damage indirectly. They release their energy by colliding with cells. This produces fast-moving electrons which ultimately produce the biological damage to tissues. X-rays and gamma rays enter biological material and their energy is converted into heat in the form of thermal energy which breaks chemical bonds – it these weak chemical bonds that are broken that lead to cell death. From a radiobiological point of
view, x-rays and gamma rays are similar in nature in their mode of action; the differences arise from their production. X-rays are produced extranuclearly while gamma rays are produced intranuclearly.

Photons and electrons are scattered as these x-rays reach their tissues – it takes some distance for the interactions to summate and reach a maximum, after which the energy of the beam dissipates by a constant fraction per unit depth. This fact accounts for the skin sparing properties of conventional radiation – the maximum dose occurs below the skin surface. There are several external beam radiation therapy sources. There is great overlap among several of these sources. Cobalt-60 units and lower energy linear accelerators (4 and 6 MV) essentially have the same energy in their radiation beams and have similar skin sparing properties. The difference between the cobalt-60 and the lower energy linear accelerators arises from the fact that the edge of the beam of the linear accelerator is much sharper than from cobalt units. This may be an important factor when irradiating close to critical structures, such as the lens of the eye. Thus the precision offered by a linear accelerator may be more important in circumstances such as these. Lower energy beams (electron beams) reach their maximal effect upon reaching skin and subcutaneous tissue and their energy dissipates rapidly after reaching these tissues. For this reason, these beams may be more appropriate for skin and clearly visible mucosal cancers. Also the range of electron beams vary in strength also. The lowest energy electron beams do not penetrate tissues while the higher strength beams do penetrate tissues to a moderate extent and then their energy drops off rapidly. This becomes important when irradiating certain neck lymphadenopathy – those nodes close to the spinal cord should be irradiated while sparing the spinal cord – these electron beams are able to reach the lymph nodes fairly well but then their energy drops off quickly so that the spinal cord is spared of radiation. Radiation beams employing neutrons and protons are available but the energy required to accelerate these particles is quite high and the machines needed to this are quite expensive thus these beams are not commonly employed. These beams do have some advantages – neutron beams are less affected by tumor hypoxia and repair of sublethal damage is lessened and proton beams are quite precise – this is very helpful when irradiating ocular tumors. This advantage that neutron beams have over conventional x-rays is referred to as an increased relative biological effectiveness which I will talk about later.

It is important to be accurate when quantifying radiation dose so that studies can be compared and results can be verified. For years, the unit of dose commonly referred to in treatment applications was the rad which is defined as the energy absorption corresponding to 100 ergs per gram. This has been replaced by the Gy defined as the energy absorption of 1 joule per kilogram. It has been difficult to directly determine radiation dose based on temperature rise as the rise in temperature of the tissues is very slight. Thus indirect measurements of radiation dose are now used to determine radiation dose – radiation doses are measured by the ionization of air. The pattern of energy deposition is important in determining relative biologic effectiveness.

Cells irradiated with 10 cGy of x-rays or 10 cGy of neutrons show differences in energy deposition. In the case of x-rays, electrons (very small particles) are set in motion whereas neutrons (larger particles) are released by neutron radiation. For neutrons, only a few cells are traversed while all cells are traversed by a number of electron particles.
So when the dose is doubled for x-rays, the average energy per cell is increased but with neutrons, this does not occur.

Biologic effects correlate with dose for a given radiation, that is, a bigger dose leads to a bigger biologic effect but the same dose of different radiations does not produce equal biologic effects because of these considerations. Neutrons start out with an inherent advantage in treating tumors because of the advantages I mentioned earlier; however, as radiation dose increases, the difference narrows as the electrons are able to produce more energy and thus more damage to cells. Also when fractionating doses, the biological effectiveness of neutrons increases in relation to electrons because it takes a while with each dose for the energy in the cell to increase – electrons are always playing catch up.

Malignant cells and normal cells differ little in their response to ionizing radiation. Both cell types are more sensitive to radiation during the mitotic phase and less so in the nuclear replication or S phase. Repair of sublethal damage from radiation can occur if sufficient time is permitted between fractionations. However fractionation also permits reassignment of cells from the less sensitive S (DNA replication) phase to the more sensitive mitotic phase. In addition only tumors have areas of relative hypoxia – these areas are relatively radioresistant because radiation’s effects are enhanced by oxygen; when sufficient doses of radiation are given to kill their oxygen rich brethren, these oxygen deprived cells redistribute into more oxygen friendly environments. Thus fractionation allows increased tumor killing by allowing the cells to redistribute into more sensitive phases and allows less oxygenated tumor cells become better oxygenated. However, normal tissues do not have these areas of hypoxia so fractionation would tend to spare these tissues. Both normal and malignant tissues have sigmoid dose-response relationships. A certain radiation dose must be given before a response is seen; initially, there is a rapid increase in the rate of response which tapers over time. Generally tissues – both malignant and normal tissues respond soon after treatment is begun; maximal reactions of both can be expected to occur about two to three weeks after initiating therapy.

SYSTEMIC EFFECTS

Data exists on systemic effects of whole body irradiation from both animal studies and accidental exposures to humans. Doses of 100 Gy or higher can cause death in hours from cardiovascular collapse and central nervous system damage. Intermediate doses (10-20 Gy) can result in death in several days by elimination of the intestinal epithelium with intractable diarrhea.

The effects of irradiation on immune responses are complex. Both humoral and cell-mediated immunity may be depressed (especially with total body irradiation); however, it is difficult to determine whether the depression in cellular immunity is caused by radiation or the malignant process itself. Nausea/vomiting and depressions of the peripheral blood counts are more particular to the types of cancers irradiated, ie. Gastrointestinal and bone marrow, respectively. Nausea that begins after a course of treatment has already begun should be explored carefully – it is usually of sign of persistence of the malignant process and not a side effect of radiation. Total body
irradiation has been used in combination with chemotherapy prior to bone marrow transplantation – the rate-limiting step with this strategy is the amount of lung fibrosis that develops with subsequent interstitial pneumonitis.

**RADIOBIOLOGY**

The important principles of radiobiology involve fractionation, repair of sublethal damage, reassortment, and accelerated repopulation.

Initially it was shown that one single large dose of radiation produced profound effects on normal tissues limiting its clinical utility. Fractionation was developed as a means of sparing normal tissue while still effectively treating tumors. Studies on ram testicles and spermatogenesis showed that fractionating the dose caused sterility in these mammals while at the same time preserving skin tissue. The sperm cells could be thought of as rapidly multiplying (much like tumors) while the skin could be thought of as slowly multiplying. Thus irradiation was shown to affect these rapidly dividing cells moreso than these slowly dividing cells. The doses were separated and given at appropriate times which allowed the skin cells to repopulate but the rapidly dividing sperm cells were exquisitely sensitive to the effects of irradiation. Fractionation also permits tumors to reassort during more sensitive phases of the cell cycle and allows cells to become better oxygenated.

Reassortment of cells plays a role in tumor control. When a large dose of radiation is given, most survivors are in the resistant phases of the cell cycle (S phase). A second dose of radiation would not be as effective because these cells are relatively resistant. However, if time is allowed, the cells reassort themselves into more sensitive phases of the cell cycle and a second radiation dose at this point would again be effective.

The molecular basis for sublethal damage repair is not understood. It is defined to be the increase in survival observed when a dose of radiation is split into two (or more) fractions with a time interval between them. If half a given radiation dose is given and a time interval of several hours is allowed to elapse before the remaining portion of the dose is delivered, survival increases because the cells are able to repair themselves during this period of quiescence. This has been used to explain the relative radioresistance of some tumors, particularly melanomas. They are able to repair their sublethal damage quickly so fractions must be given closer together to not allow this sublethal damage repair.

Accelerated repopulation of tumor cells occurs after a dose of irradiation. This allows tumors to quickly repopulate thus length of treatment should not be delayed. It has been shown that delaying treatment beyond 4 weeks requires an increase of 1 Gy in dose per day. Accelerated repopulation can occur when treatment is begun and delayed for whatever reason.

Fractionation of radiation dose tends to spare normal tissue because of the repair of sublethal damage between dose fractions and because of repopulation of cells. At the same time, dividing a dose into a number of fractions increases damage to the tumor as a result of reoxygenation and reassortment of cells in the cell cycle. The aim of hyperfractionation is to separate the early and late effects of radiation. Overall treatment time remains unchanged (6 to 8 weeks) but the dose may be increased because the dose per fraction has been decreased. This tends to increase the early effects of irradiation.
while reducing the late effects of radiation (those effects on the spinal cord for eg.). This
dose give better tumor control with a larger overall radiation dose.

Tumor volume is difficult to measure exactly. Assumptions need to be made that
the number of cells is directly proportional to volume and that hypoxia does not vary with
tumor size. Based on these assumptions, it has been determined the average doses of
radiation needed to eradicate tumors based on size and presumably number of cells.

**COMBINING RADIATION THERAPY AND SURGERY**

Local-regional recurrence of cancer after surgery or radiotherapy alone remains a
common problem. This subsequently leads to distant metastases and decreased survival.
In practically every anatomic site studied, improved local-regional control has been
achieved with combined radiation and surgery. This has thus led to improved survival
rates. The rationale of combining radiation therapy and surgery is based on two major
presumptions: transection of peripheral fingers of a cancerous mass is a frequent source
of postoperative recurrence, and the small size of these residual fingers renders them
readily susceptible to eradication by irradiation; also the central relatively radioresistant
hypoxic nidus of a cancerous mass is a frequent source of postirradiation recurrence.
After irradiation it can often be successfully removed by a less radical resection. It is
important for radiation oncologists to know if all “gross disease” is removed. If gross
tumor is left behind, the required high doses to large volumes may be less well tolerated
and the outcome may be less successful.

Arguments exist in favor of both preop and postop radiation treatment.
Arguments for preop radiation therapy include the fact that unresectable lesions may be
made resectable (for eg. Fixed neck lymph nodes and advanced carcinomas of the
rectum), the extent of the surgical resection may be diminished. Thus these nodes can be
removed and sphincter sparing surgery may be performed however this remains
controversial. Treatment portals preoperatively are usually smaller than would be
required postoperatively and microscopic disease is more radiosensitive preoperatively
because it has a better blood supply. Arguments against preoperative radiation therapy
include the fact that wound healing is more difficult, the dose that can be delivered safely
preoperatively is less than that which can be given postoperatively. Usually, 45 Gy in 4.5
weeks is given and this is sufficient to eradicate subclinical disease in 85% to 90% of
patients. This is less than needed to control gross disease and if positive margins exist
postoperatively, it is difficult to add a meaningful dose postoperatively.

Arguments in favor of postoperative radiation therapy include the fact that the
anatomic extent of the tumor can be determined surgically, making it easier to define the
treatment portals required. A greater dose of irradiation can be given and the total dose
can be determined based on the residual tumor burden, and surgical resection is easier
and healing is better in unirradiated tissues. Theoretic disadvantages of postoperative
radiotherapy is that distant mets can result from cells that are spread by the surgical
procedure and that postoperative irradiation may have to be postponed if surgical healing
is delayed, allowing cancer cells to repopulate. A dose of 60 to 65 Gy is administered for
6 to 7 weeks postoperatively; higher doses are usually required for gross residual cancer.
Positive margins should be regarded as evidence of gross residual disease because a
relatively large number of cells must be present. Looser found that the presence of
disease within 0.5 cm of the surgical margins has the same prognostic implication as positive margins – thus radiation treatment must be altered because of these microscopic findings.

**SPECIFIC TYPES OF HEAD AND NECK CANCER AND THEIR RADIATION TREATMENT**

**Oral Cavity and Oropharynx:**

Squamous cell carcinomas are the most prevalent type of neoplasm affecting the oral cavity and oropharynx. Histopathology of these tumors plays some role in radiation treatment. Cancers with infiltrating borders have a higher probability of developing neck metastases which should be taken into account when planning radiation. Generally, radiation should be considered for treatment of neck metastases when the risk is greater than 15% and should be used when that risk is greater than 20%. Also poorly differentiated neoplasms show a higher incidence of lymph node metastases while verrucous carcinomas have a very low incidence. Microinvasive carcinoma (depth of invasion is less than 1.0 mm) has been shown to rarely metastasize. And nonkeratinizing squamous cell lesions respond more dramatically to a combination of irradiation and concurrent chemotherapy. General treatment policies vary on whether surgery or irradiation should be used for oral cavity and oropharyngeal tumors. Usually, oropharyngeal tumors respond better to irradiation than do oral cavity tumors. Thus primary irradiation has been used more often in the treatment of oropharyngeal neoplasms.

Treatment must be tailored to the location and size of the lesion, its extension to surrounding structures, presence of lymph node metastases and other patient factors. Surgery has the advantage of being expeditious and generally results in few significant dental or salivary gland deficiencies. Except for smaller lesions, surgery sometimes requires removal of significant amounts of tissue which may alter the appearance and function of the patient. Radiation takes more time, produces dryness of the oral cavity that is usually manageable but can sometimes lead to radionecrosis of soft tissue or bone.

Postoperative radiation is needed for larger lesions, those with close or positive margins, and for perineural invasion. It is also recommended for those patients with initially positive margins who later have negative surgical margins on reexcision.

For neck disease, if the initial tumor was small with a thickness of less than 2 mm and completely excised with no poor prognostic factors, radiation is not necessary if the neck is clinically and radiographically negative. If a neck dissection has been performed with the surgical procedure, radiation may also be deferred if only one positive lymph node was noted with no extracapsular extension. Optimal oral hygiene and pretreatment dental care are very important in preparing patients for radiation. Indiscriminate dental extractions are not indicated – dental extractions should be tailored to pretreatment dental status and the ability of the patient to maintain dental hygiene. About 8 to 10 days are needed after tooth extraction for complete recovery before starting radiation therapy. Generally, the molars must be extracted and the incisors and canines may remain if not carious and patients are vigilant about brushing their teeth twice daily and fluoride treatment with a dentist.
Radiation is accomplished usually with opposing lateral portal fields (this may reduce the incidence of bone exposure and osteoradionecrosis) including the upper necks if indicated. The tongue is depressed away from the palate with an individually constructed bite block. The portal or field of treatment includes generally level I (submandibular and submental lymph nodes), level II, level III and lower levels depending on the degree of nodal involvement. Submental coverage is more important for lesions at the tip of the tongue, anterior floor of mouth or lower lip. The upper border is about 2 cm above the dorsum of the tongue – try to spare the hard palate and parotids. The posterior border is 2 cm behind the scm and the inferior part usually lies at the thyroid notch.

For oropharyngeal portals, the margin should project posteriorly around the external auditory canal to a line joining the tip of the mastoid to about one cm above the foramen magnum. Anterior margin is usually 2 cm anterior to any evidence of clinical disease. This margin should also project 2 to 3 cm forward of the anterior cortex of the ascending ramus of the mandible, depending on tumor extent. After 45 Gy, the posterior margin is brought to the midportion of the vertebral bodies to spare the spinal cord. Also after a minimum tumor dose of 60 Gy is delivered to the oropharynx, portals can be reduced by 1 to 2 cm and an additional dose is delivered to complete treatment to 65 to 75 Gy. For lower nodes, the larynx is shielded and these nodes can be treated. Generally 65 to 70 Gy in 6.5 to 7 weeks is recommended for T1 and T2 lesions. For oral tongue lesions, these are usually best dealt with surgery. However irradiation may be considered for small, posteriorly situated, ill-defined lesions that are relatively inaccessible surgically. Again considering that surgery is usually the mainstay of oral cavity and oral tongue cancers, patients may still opt for radiation. For T2 lesions of the tongue, irradiation should be given in doses of 70 to 75 Gy in 7 to 8 weeks with decreasing fields to the primary site and neck. Irradiation rarely cures T3 and T4 oral tongue lesions and thus should be used in conjunction with surgery. For floor of mouth lesions, small superficial lesions can be cured by radiation or surgery. Again for larger T3 or T4 lesions, radiation should usually be used in conjunction with surgery. In the oropharynx, primary radiation plays a more important role in treatment. Fauclal and tonsillar fossa tumors are generally advanced (90% of lesions may be T3 or greater) – these tumors are particularly amenable to radiation; however with deep muscle or bone involvement, irradiation assumes a secondary role. Similarly, the base of tongue can be treated with irradiation alone if there is not any deep muscular or bony invasion.

Sequelae of treatment include oropharyngeal mucositis and moderate to severe dysphagia. Occasionally, laryngeal edema, fibrosis, hearing loss and trismus may occur. Osteoradionecrosis of the mandible is rare but depends mainly on the proximity of the tumor to the mandible and dose of radiation given. It is affected by prophylactic dental care, trauma and irradiation technique. Soft tissue necrosis can occur about 10% of patients treated with external irradiation alone or in about 20% of those treated with external and interstitial irradiation. Mandibular necrosis rarely develops in doses less than 60 Gy in 6 weeks. It increases to about 2% with doses under 70 Gy in 7 weeks and to 9% with doses over 70 Gy. Lhermitte’s syndrome is defined as electric like sensations that occur down the body when the neck is flexed – this syndrome occurs after the spinal cord has been irradiated to a dose greater than 45 Gy. It occurs 1 to 3 months after irradiation and usually subsides after 1 to 9 months without any longterm effects.
Radiation myelitis can lead to paraplegia because of radiation’s effect on the microvasculature – the dose required is usually 50 Gy given in 1.8 to 2.0 Gy fractions 5 times per week. The risk with treatment of oral cavity and oropharyngeal lesions is estimated to be at 5% after 60 Gy given in 7 weeks.

Nasopharyngeal carcinoma because of its relation to the skull base, cranial nerves and major vessels has generally been treated with irradiation. Poor prognostic factors include lower cervical lymphadenopathy, bilateral adenopathy and cell histology (nonkeratizing and squamous cell carcinoma have increased risk compared to undifferentiated). Occasionally neck dissection is required to treat neck node metastases but irradiation is often all that is necessary for tumors metastatic to the neck. Improved tumor control results with neoadjuvant chemotherapy. The area to be treated includes the nasopharynx, adjacent parapharyngeal space and all of the cervical lymphatics. Standard fields include the posterior ethmoid cells, the posterior one-third of the maxillary antrum, and the nasal cavity, but usually not the orbit. Lateral fields are generally used with about a 5 degree posterior angulation to avoid direct irradiation of the external and middle ear. The upper level of treatment splits the pituitary fossa and extends along the sphenoidal plate. Posteriorly, the clivus is included with a 1 cm margin. Special considerations should be made for skull base involvement and anterior extension with coverage of the posterior orbit if necessary. Again as with oropharyngeal tumors, the posterior border of the lateral field is displaced anteriorly to shield the spinal cord. High energy photons may be used for deeper penetration so that less of a dose is given to the mandible and temporomandibular joints. There is a very high likelihood of cervical metastases (about 80%) so all cervical lymphatics should be treated. Ho showed that survival was no better for N0 patients receiving radiation to their cervical lymphatics but other studies have shown local regional failure is greater (40% vs. 11%) in those who were not electively treated to their necks. Complications of treatment include an incidence of cranial and sympathetic nerve palsy of about 1%. The incidence of radiation myelitis may be as high as 2%. Hypopituitarism is not commonly reported although this potential exists. Ocular side effects occur after 60 Gy and can include radiation cataract and retinopathy. Trismus can be reduced by using high energy x-rays or an anterior field for the nasopharyngeal boost. This would avoid direct irradiation of the temporomandibular joint.

Tumors of the hypopharynx may involve the pyriform sinus, postcricoid area or pharyngeal wall. Whether radiation or surgery is selected, goals of treatment include preservation of respiration, deglutition and phonation. Most T1 and selected T2 lesions can be treated with irradiation or conservation surgery – vocal cord fixation is a general contraindication to sole irradiation. For larger lesions that usually require surgery, postoperative irradiation increases local regional control. Treatment consists of opposed lateral fields encompassing the primary tumor from skull base to the anterior low neck fields and tracheostoma. The neck and pharynx are irradiated with opposed upper-lateral fields and a single anterioposterior low-neck field. The spinal cord is shielded posterior to the pharynx by a small shield in the posterior-inferior corner of the field. This prevents the possibility of excessive dose from overlap of the two upper lateral and anterior low-neck field. A beam splitter is routinely used for the upper half of the lower-neck field to prevent overlap by the upward divergence of the beam. Shrinking field technique is used and the neck and pharynx routinely receive doses of 60 Gy in 6 weeks.
postoperatively. When irradiation is used alone with curative intent, 70 Gy in 7 weeks should be administered. Side effects of treatment are as outlined above with the additional risk of pharyngocutaneous fistula. The incidence of these fistulas is the same whether the pharynx has been irradiated before surgery or not but the time required to heal is significantly greater for irradiated fistulas.

Early laryngeal carcinoma (T1) is usually treated with radiation. T2 lesions are better treated with conservation laryngectomy procedures but radiation may also be used. This remains controversial so a decision needs to be made with the patient, surgeon and radiotherapist. Control rate of T1 lesions is 90% and T2 lesions is about 70 to 80%. Advanced vocal cord carcinomas have been historically treated with laryngectomy with or without postoperative irradiation. Indications for postoperative irradiation include close or positive margins, significant subglottic extension (>1 cm), cartilage invasion, extension into soft tissues of the neck, multiple positive neck nodes or extracapsular extension. For T1 lesions, irradiation extends from the thyroid notch to the inferior border of the cricoid. For T2 lesions, the field size ranges from 4 X 4 cm to 6 X 6 cm for a large T2 lesion. Treatment usually employs 4 or 6 MV x-rays with parallel opposed lateral fields. T3 and T4 lesions require larger portals with inclusion of the jugulodigastric and level III lymph nodes. These lesions can be treated to 72 Gy in 36 fractions or twice daily fractions at 1.2 Gy per fraction to a dose of up to 76.8 Gy. Supraglottic tumors are treated similarly except that because of the rich lymphatics, regional lymphatics should be included in tumors T2 or greater. Poorer results are generally achieved for supraglottic tumors. Subglottic extension requires treatment of the tracheostoma otherwise this area may be shielded. Side effects of irradiation can involve the voice. Usually, in the first two to three weeks, the voice may improve as the tumor regresses but it generally becomes hoarse again as radiation changes set in. About 3 weeks after completion of treatment, the voice generally improves and reaches a plateau in 2 to 3 months. Laryngeal edema is the most common sequela after irradiation and can take up to 6 to 12 months to subside. Patients treated with twice daily techniques develop more severe acute radiation reactions (severe mucositis and dysphagia) sometimes necessitating nasogastric feedings. Up to 10% of patients will require this because of this acute reaction.

Brachytherapy refers to a technique where the radioactive sources are placed close to the target. They can be placed in tissues, into cavities or onto skin surfaces. Both temporary and permanent implants exist although permanent implants should have short lived isotopes because the radiation must decay quickly to negligible levels. Advantages of brachytherapy are that radiation is delivered closer to the tumor while sparing normal tissue and treatment is given continuously – this may be more effective in hypoxic or slowly proliferating tumors. It is only effective if the entire tumor is accessible and can be implanted. Poorly defined cancers are thus poor candidates. If there is a risk of regional node metastases, brachytherapy also cannot be used as the sole therapy.

In conclusion, radiotherapy offers an opportunity for curative management of cancer. A one size fits all approach does not work in this field and treatment techniques and modalities vary from one radiotherapist to another and from institution to institution. A good radiotherapist understands the rewards and limitations of radiotherapy and chooses to use their techniques widely and with great skill.