Radiation is a powerful tool for cancer treatment. It works by delivering focused energy (i.e., dose) to destroy chemical bonds within the genetic material (DNA) of a cell. Consequently, the cell loses its capability to duplicate itself and leads eventually to its death. In principle, the chance of controlling such tumor growth with radiation increases with the amount of dose it receives. Unfortunately, radiation particles cannot distinguish normal cells from cancerous ones, and undesirable damage to normal tissues might occur if care is not taken to precisely localize the dosage onto the intended target. This is of particular importance for cancers of the head and neck, which often mingle with or abut important normal structures that might be similarly sensitive to radiation damage.

In a traditional radiotherapy approach, the three-dimensional (3-D) volume to be covered by radiation is relatively broad and the total dose given is consequently restricted. This is due to the rather unsophisticated technology in either delineating the true extent of the tumor or ensuring the precise delivery of the radiation dose. If the dose is escalated to increase the chance of tumor control, negative side effects may ensue due to excessive damage of the normal organs. If the dose is lowered to spare normal tissues, the tumor recurrence rate may be unacceptably high due to inadequate dose.

A good example is a nasopharynx or oropharynx tumor, for which the irradiated volume usually covers both the primary site and the draining lymph nodes next to the salivary glands. After the treatment, patients may experience significant dry mouth
permanently. Other critical structures which may cause the treating physicians to curtail
the radiation dosage include cranial nerves, optic apparatus, brain stem and spinal cord.
Even temporary side effects such as inflammation of the oral and pharyngeal linings, sore
throat and swallowing difficulty could be so debilitating that patients are disheartened to
complete the prescribed treatment course despite the consequential danger of cancer
progression.

Clearly, there would be a therapeutic benefit if one could identify the precise
anatomic extent of the patient’s cancer and possess the technical ability to tailor the
radiation dose to conform tightly around the tumor while avoiding the surrounding
normal tissues. Thanks to modern advances in computer technology, significant progress
in such precision-oriented radiotherapy (PORT) techniques has been made. PORT is
now available in the treatment of many malignancies, including head and neck cancer.

Prerequisites of precision-oriented radiotherapy

Precision-oriented radiotherapy begins with the accurate localization of tumor targets as
well as normal structures that are to be protected. The first prerequisite of PORT is thus
accurate diagnostic imaging. Once the target volume is delineated, the aim of PORT is to
deposit high dose within the volume and as little dose as possible outside. Unfortunately,
the limiting resolution of typical radiological studies such as computer tomography (CT)
or magnetic resonance imaging (MRI) remains to be of the order of about one centimeter.
This means that as many as a billion tumor cells may be spared inadvertently by PORT,
due to its nature of rapid dissipation of dose beyond the edge of the intended treatment
volume.
Intuitively, PORT should be indicated whenever tumor irradiation involves substantial chance of normal tissue damage. It might hence be readily accepted when planning radiation treatment that attention to precision is always beneficial. However, sometimes a certain degree of deliberate imprecision might be necessary by allowing a generous treatment margin around the intended target volume. This stems from the fact that even if PORT were attained to “perfection”, it might at best substitute surgical resection for which one would still face the dreadful limitation a cancer surgeon typically encounters: uncertainty in the microscopic extent of the tumor. One may say that PORT is therefore analogous to an invisible knife, and such a sharp “dissection” instrument is much less forgiving in comparison with traditional radiotherapy if “geographical miss” occurs (Figure 1). Note that a malignant tumor is often infiltrative with tentacles not unlike the legs of crabs (thus the term cancer – the sign of a crab), the extent of which often remains inconspicuous clinically. This is especially true for many head and neck cancers for which relatively porous channels (e.g. nasopharyngeal cancer transgressing through skull base) or anatomical paths (e.g. lymphovascular or peri-neural invasion) exist to allow easy tumor spread. As far as cancer cells are concerned, physicians should remember that we can kill what we can see, but it is often what we cannot see that kills the patient, and getting too “cute” in tailoring treatment volume coverage might be dangerous.
Figure 1. The difference in treatment volume coverage by traditional RT vs. PORT. Note that by attempting to spare normal tissues such as blood vessel, nerve or airway (which may be safely treated by traditional RT with relatively lower dose), the border of PORT may inadvertently spare microscopic tumor cells not detected by radiological scans.

PORT is thus indicated only if the treating radiation oncologist possesses the confident knowledge – though often by educated guess - of the likely microscopic extent of tumor involvement. Such judgment is facilitated initially by appreciating the macroscopic extent of the tumor via diagnostic imaging.
With the help of diagnostic imaging, the 3-D shapes of target volumes and surrounding normal structures are obtained during a process called simulation. Such anatomic information is registered electronically and fed into a treatment planning system. A professional team of radiation oncologists, physicists or dosimetrists (who specialize in radiation treatment planning) then design the treatment fields by trying to encompass the radiation dose over the desired target volume while sparing the normal tissues. Since tumors are usually irregular in shape but the basic volume assumed by each radiation beam as it is emitted from the source is often very simple such as a cube or a cylinder, an additional “beam-shaping” device is needed to modify the radiation dose coverage. Traditionally, devices such as metal blocks have been constructed manually and customized for individual patients, and the treatment planning has been rather rudimentary with a dose distribution (dosimetry) calculation in 2-D space used as a basis for extrapolation into an idealized 3-D display. When CT-based imaging technique became available and adapted for simulation, more reality-based 3-D oriented conformal radiotherapy (CRT) became common practice. Still, because of the laborious ways of constructing customized blocks and other cumbersome beam-modifying devices, the number of radiation fields employed for each patient case remains quite limited and as a consequence the volume irradiated often involves much normal tissues.

A revolutionary computer technology then arose to allow for a very slick 3-D treatment planning by using machine-driven beam-shaping devices called multileaf collimators (MLC). A target volume is basically sliced into numerous contiguous sections by the computer one beam-path at a time, each bounded by a pair of metal leaflets with a width measuring from a few millimeters to a centimeter. Within each slice
the dose delivered is calculated for the corresponding target volume the radiation beam traverses. During the treatment, these automated MLCs move swiftly to ensure that the dose coverage tightly conforms to the target, much like the old manually-made metal blocks were designed to do but in a much quicker and efficient fashion. Thus, precise dosimetric determination for any irregularly shaped tumor target or normal tissue in 3-D is feasible, and tools are available for planning physicists and dosimetrists to maximize the therapeutic benefit by a repetitive and iterative process of optimization – all done in lightening speed by the computer.

The era of PORT has thus arrived, but it assumes several divergent forms since different technical and commercial development paths have taken place that result in various approaches for the same goal. In general, PORT has been developed along two separate paths: first, with the attempt to limit patient set-up uncertainty due to motion and other technical factors, and second, with the exploitation of computer technology to help treatment plan optimization.

**Stereotactic treatment techniques**

Even if a dosimetry plan is established perfectly according to the locations of the tumor and normal tissues based on the imaging results from the initial simulation, PORT loses its meaning if the positions of these structures deviate during actual treatment because of set-up uncertainty or patient motion. Thus to immobilize patient during irradiation becomes crucial, especially for tumors in the brain or the head and neck. In particular, for relatively few and small tumors, there may be a need to ablate such lesions precisely with exceptionally high and focused dose using the so-called *stereotactic radiosurgery* (SRS).
Stereotactic techniques were originally developed by neurosurgeons to locate brain
lesions with pinpoint accuracy using a 3-D coordinate system with reference to a rigid
frame attached to the patient’s skull. It is used in radiation oncology when high-dose
radiation is indicated to substitute invasive surgical resection (thus the term radio-
surgery). Commercially available systems can be distinguished along the two different
ways of radiation production, but the original purposes and the ultimate clinical results
are similar. For systems such as Gamma Knife®, about 200 Cobalt-60 radioisotope
sources emitting gamma rays (identical to x-rays) are oriented in a hemispherical fashion
or other similar geometrical pattern, and focused on a central point where the lesion
target will be placed. The second way of producing such focused radiation is via a linear
accelerator (LINAC) which generates an x-ray beam from a single electronic source that
can be rotated or moved around a central focus. Well-known commercial x-ray systems
include Cyberknife®, X-knife®, Novalis® and other similar configurations. SRS has
gained wide popularity among neurosurgeons and radiation oncologists to treat mainly
central nervous system tumors (both benign and malignant) and at times functional
targets to combat neurophysiological disorders such as trigeminal neuralgia.
Characteristically, feasible SRS targets must be small (usually 3 cm or less in diameter),
and the number of lesions to be treated must be few (usually 4 or less). Its use for head
and neck tumors is usually limited to situations where additional “boost” beyond
conventional radiation treatment or salvage for local recurrence might be beneficial.

For most head and neck malignancies, the size of primary tumor is typically larger
than what SRS can accommodate, and more importantly its edges are often mingled with
normal tissues. In such cases, stereotactic technique can be combined with the biological
advantages of *fractionation*, the process of repeating relatively small dose of radiation in many “fractions” over a long period of time. In this manner, normal tissues may be spared better than the fast-growing malignant tumors, thus therapeutically more beneficial. When used in such a way, the stereotactic treatment is truly a form of radiation therapy, i.e. *biological* therapy, and more appropriately is categorized as *stereotactic radiotherapy* (SRT). This is often done using removable body-fixation frames for reproducing a specific patient position over multiple daily treatments.

Certain general guidelines might thus be given regarding selection of SRS vs. SRT. Whenever an aggressive tumor is found located in close proximity to a critical normal tissue, SRT would probably be more beneficial than SRS since the advantage of fractionation can be exploited. On the contrary, if there is not much biological difference - as far as the response to fractionated irradiation is concerned - between the tumor and the surrounding normal tissue (a benign or low-grade lesion usually fits such criteria), SRS may be the treatment of choice, serving as a surgical tool. We should reiterate that SRT will in general have a theoretical biological advantage over SRS for most malignancies. SRS is often favored for logistic reasons rather than biological considerations per se. Perhaps due to the wide acceptance of SRS, or because SRT is simply a more tedious procedure, clinicians might develop a tendency to minimize the number of fractions for patient treatment. Only with genuinely precise treatment is it safe to do so; by spatially segregating tumors from normal tissues one can then zoom in to treat the former without too much concern of deleterious biologic effect over the latter (i.e., with PORT like SRS, the advantage of fractionation radiobiology might be justifiably ignored due to relatively little involvement of normal tissues).
Intensity modulated radiation therapy (IMRT)

Treatment planning for precision-oriented radiotherapy can be optimized with the use of computers. This method consists of inverse planning, in which the physicist feeds the anatomic information of tumors and normal organs at risk into the computer and specifies the desired outcome with dose constraint for each structure of interest. The computer then searches for the best solution to achieve the goal. The answer will dictate how the treatment machine might adjust (or “modulate”) the radiation beam intensity in an automated fashion by moving the MLCs (beam shaping devices) rapidly across the irradiated target, while constantly avoiding the normal organs. Such a technique is thus called intensity modulated radiation therapy (IMRT). This is in contrast to the traditional process of forward planning, when physicists literally had to guess and input beforehand which basic set of beam-field arrangements (each with arbitrarily chosen level of uniform intensity) might produce a good dosimetric result, then finalize on an acceptable plan only after some trials and errors. The difference can be quite remarkable, since the computer-generated IMRT plan allows for a much higher dose within the target and a more conformed dose distribution around the irregular tumor border, while the adjacent normal tissues receive relatively little dose. With the availability of IMRT, one can consider escalating the total radiation dose to the tumor as high as possible and look forward for improvement in the chance of local tumor control, meanwhile minimizing normal tissue side effects.

For head and cancer cancers, IMRT is fast gaining wide acceptance world wide. Higher dose can be given via IMRT as a “boost” to the primary tumor bed sequentially.
after a course of radiation therapy aimed at a broader coverage of the head and neck region. This follows the traditional practice of the “shrinking-field technique”, with the dosages of various structures (including the tumor) prescribed to commonly accepted values among different practitioners. More often now, IMRT is used from the very beginning of the treatment course with the so-called simultaneous integrated boost (SIB) technique. For each fraction of treatment, the subclinical (undetected but perceived to be microscopically present) spread of cancer cells in the broad head and neck area is treated to a relatively lower dose, while the primary tumor is irradiated simultaneously with a higher dose. Because of this unorthodox approach, the total dose received at any structure of interest and its subsequent clinical effect can vary widely depending on the fractionation schemes used. It is therefore less meaningful to use total physical doses for inter-comparison of treatment results using different SIB techniques. Instead, some sort of quantitative biological correction is usually needed. Furthermore, IMRT has the potential of introducing dose inhomogeneity within a specific structure because of intensity modulation. The biological and clinical consequence due to such effect is still not very well understood, since clinicians have traditionally been trained to be familiar with the consequences of only homogeneous dose distribution across an anatomic object. These issues are at the forefront of clinical radiation oncology research currently, and the art of implementing IMRT is continually being refined.

One of the pitfalls of IMRT is the lack of uniform treatment planning approach among different radiation oncologists or physicists. The computer-assisted inverse planning process introduces way too many dosimetric variables for individuals to manipulate in unison. As a consequence, different planner can result in very different
treatment plan. Furthermore, treatment planning software and delivery hardware also vary widely from center to center, thus patients can rarely transfer their radiotherapy care freely without suffering some kind of miscommunication in the technical details. From radiobiological consideration, different levels of physical dosage per fraction cannot be added simply to predict the ultimate clinical consequences. Therefore, unless absolutely necessary, it is not advisable for any IMRT patient to switch doctors or treatment facilities once the treatment begins.

By the same token, when local tumor recurrence unfortunately happens despite the completion of the entire IMRT course, it is wise to remember the old Chinese saying that “the best person to untie the knot is still the one who tied it” – the original radiation oncologist would still be the most appropriate one to plan any conceivable salvage irradiation with another course of IMRT (or other form of PORT) if indicated. This may not be readily acceptable by the patient who might have become disappointed in the original physician or center that failed the first try and now seeks new help.

While avoiding excessive dose to the normal tissues, IMRT allows precise dose delivery to the target typically via more beam paths, in effect spreading extremely small amount of dose to a wider area of the body as compared to the conventional forward-planned 3-D CRT. Thus, while the total dose received at the designated organs at risk may be minimized, the integral dose - total dose deposited in the whole body – might still be significant. The health hazard of such pervasive low dose, in particular the induction of second malignancies, remains uncertain and debatable. It might take a few more years, even decades, before we realize the degree of such danger. Regardless of the quantitative
risk, ways to minimize the integral dose should be beneficial and are being developed by modifying the existing PORT techniques or using entirely different technologies.

**Image guided radiation therapy (IGRT) and adaptive radiation therapy (ART)**

*Image guided radiation therapy* (IGRT) is a recent development in radiation oncology beyond IMRT and SRS/SRT. Just like the stereotactic techniques, IGRT is preoccupied with precise tracing of the radiation target in order to compensate for motion uncertainty. An example is to implement *respiratory gating* for tumors in the trunk during each fraction of irradiation by synchronizing the treatment field coverage precisely over a tumor which moves with the patient’s respiration. Another frequent application of IGRT is for prostate cancer, since the prostate gland can move slightly (mostly depending on the content of the rectum behind it) from day to day through the long course of radiation therapy. These internal soft-tissue structures which ordinarily will escape radiographic detection can be illuminated if, say, metal seeds could be inserted beforehand as “fiducial markers”.

Fortunately, for head and neck cancer, target motion is of relatively low concern since the currently existing immobilization devices for the head are generally adequate and the tumors are often fixed to internal structures. Once simulation is performed and the target is identified, its location will often be assumed to be constant in relation to the surrounding bones. When IGRT is used, one needs only to check the bony landmarks within the skull for position verification before proceeding with daily irradiation.

On the other hand, bulky tumors of the head and neck often shrink readily during the long course of radiation and chemotherapy treatment. The anatomic uncertainty is thus
introduced not because of patient motion or set-up error, but the significant anatomic deviations of relevant internal structures due to the progressive change of the tumor bulk (or the patient’s significant weight loss). To keep track of this dynamic situation and issue appropriate countermeasure as frequently as possible, adaptive radiation therapy (ART) is indicated. The aim of this therapy is to modify sequentially in time the original treatment plan based on the initial simulation scan and the subsequent daily image verification, using sophisticated mathematical algorithm for mitigation of the geometrical incongruities and variations, without actually repeating the laborious simulation and treatment planning. Active research in this regard is on-going.

**Other techniques of PORT**

Radiation particles other than x-rays (or photons) used for PORT include protons and heavy ions such as alpha particles (helium nucleus) or carbon anions. These particles are characterized by the so-called linear energy transfer-(LET), a quantity measuring the rate of energy loss per length of path. Heavy ions have high LET and thus are “densely ionizing”, in comparison with the low-LET photons which are “sparsely ionizing”. Particle therapy, especially using protons, is making news headlines nowadays due to the recent commercialization of its use in several nationally known cancer centers.

Protons have a level of LET similar to photons, thus no significant biological advantage (measured as relative biological effect, RBE) over high-energy photons or electrons (another kind of radiation commonly used in all radiation oncology centers). A proton beam, however, has a special physical property of releasing very little energy as it traverses into tissue until a fixed depth is reached where almost all the dose is deposited
(called a “Bragg peak”). The depth of this dose peak can be manipulated electronically to coincide with the target by varying the energy of the protons. Thus, proton radiation has the dosimetric advantage when treating a deep seated tumor next to a critical normal structure. Heavy ions have both high LET and the presence of a Bragg peak. If utilized properly, they possess both the physical and biological advantages as the PORT particle of choice for highly “radioresistant” tumors, as long as normal tissue tolerance is also respected (a lesson learned painfully from past research trials using another high-LET particle, neutrons). Both proton and heavy-ion treatment planning may be done in an inverse manner, with intensity modulation amounting to “dose painting”. Such may represent the most sophisticated form of PORT, although much technical details remain to be worked out and is under intense investigation at a few treatment centers worldwide. The main disadvantage is their extremely high cost of production and operation.

Another form of PORT is implant (brachytherapy), which has been practiced by radiation oncologists for decades. It involves the manual or machine-driven placement of radioactive sources that emit extremely short-ranged radiation within the tumor volume, usually temporarily over single or multiple sessions. The main advantage of brachytherapy is its relatively low dose to the rest of the patient’s body since no external radiation beam traversing the body is involved. Its disadvantages mainly stem from the fact that it involves invasive procedures with operative risks similar to surgery (risks of anesthesia, bleeding, infection, etc.). With the popularity of external beam treatment using IMRT, brachytherapy for head and neck cancer is becoming a rarity and should be performed by experienced hands in selected centers of excellence.
Functional image guided PORT

The recent developments of functional imaging studies like positron emission tomography (PET) or magnetic resonance spectroscopy (MRS) imaging have allowed physicians to consider dose escalation to metabolically-active or radiation-resistant spots within a tumor to help raise the local tumor control rate. These sophisticated imaging techniques may unite modern molecular biology to clinical radiation oncology using IMRT or particle beams for dose painting purpose. As it stands today, much remains to be researched before their clinical application becomes routine.

Even though PORT such as SRS can be used at times to substitute for real surgical resection, a fundamental tenet in surgical oncology still needs to be observed: that is, partial tumor resection (tumor debulking, equivalent to partial radiation field coverage of the tumor) is rarely helpful. Thus, it is important to ensure that the radiation field coverage of the lesion be as complete, with adequate margins, as possible. It is crucial that radiographic imaging be used to help clinicians delineate precisely the extent of the tumor. In fact, functional imaging studies may likely augment the efficacy of PORT better if they could help detect previously unseen tumor edges rather than, or in addition to, identifying metabolically active spots within a tumor.

Conclusion

Because of the technical complexity involved, planning for PORT takes time and requires patience and skill. Since the process involves judgmental call to weigh the balance between tumor dose escalation vs. minimizing normal tissue damage, a certain art of the
trade is at display by the treating doctors and physicists. For any patient, it is crucial to allow the radiation oncology team sufficient time to plan the treatment carefully, rather than urging them to rush through at the possible expense of suboptimal planning. Such minor time delays to ensure the best planning outcome is a worthy investment despite the possible tumor progression during the waiting period. For head and neck cancers, much preparation is usually required including dental evaluation and prophylaxis, construction of intraoral shielding device if indicated, and medical oncology consultation with possible insertion of deep vein catheter or gastrointestinal feeding tube. Once the radiation treatment commences, it is also prudent to avoid significant interruption of the planned therapy schedule since, from clinical radiobiological teaching, cancer cells can exhibit the treatment-induced phenomenon of accelerated growth as overall time course gets prolonged. Despite the use of PORT, treatment induced acute toxicities (e.g. skin irritation, sore throat or swallowing difficulty) are still expected to occur but fortunately are transient, since the dose planned is tailored to limit predominantly permanent late effects (e.g. dry mouth or nerve damage). A strong personal will of the patient is usually required to finish the entire course of prescribed treatment, and psychosocial support from family and friends is also helpful. Frequently, a team approach involving professional healthcare staff makes a significant difference in ensuring a favorable therapeutic outcome.

With the advent of computer technology, PORT techniques like SRS, SRT, or IMRT have certainly fulfilled the goal long-held by radiation oncologists to deliver adequate dose for tumor control while minimizing toxicity to the normal tissues. PORT is thus inherently beneficial, but with the technological improvement its cost has also escalated.
Yet, radiation oncology practice remains one of the most profitable investments a hospital can make. This is due to the fact that radiation therapy works very well in what it is purported to do – controlling local tumor growth. It is not surprising that our society is willing to pay for an efficacious cancer fighting weapon, when the disease ranks one of the most egregious killers of its citizens. This also applies to many new chemotherapy or molecular-targeted drugs. With specific regard to PORT, the ultimate fruition is the local control of the tumor, which may or may not lead to the enhancement of survival rate for which the determining factor is the often unknown extent of microscopic disease throughout the patient’s body (a dreadful term called metastasis). In the case of patients having known systemic metastasis, treatment by PORT can also provide meaningful alleviation of local symptoms and thereby improve quality of life. Above all, there is no cure by systemic therapy without the simultaneous control of local tumors, and PORT may be used to supplement chemotherapy for such purpose, particularly if the tumors are few in number but too large to be controlled by drugs alone. The general question is to what extent our society should bear the financial burden as the cost of the high-tech cancer treatment continues to skyrocket. Furthermore, the equal accessibility for patients with less ability to pay will remain a hot political item to deal with. The recent surge of many well- and lesser known institutes to build proton or particle treatment facilities (each requiring tens to hundreds of million dollars) will likely push these issues to repeated public debates in medical meetings as well as political gatherings.