Radiotherapy of malignant tumors

Malignant tumors are capable to boundless growth and to extent by metastases. There are next special methods for treatment of cancer and other malignant tumors:

- surgery;
- radiation therapy;
- chemotherapy.

Today, more than 50% of patients with cancer will survive.

Establishing the diagnosis

Treatment of a malignancy can begin only after the tumor has been diagnosed. Recent radiologic techniques have dramatically improved the assessment for cancer, and we are now in the era of techniques such as computed tomography (CT), diagnostic ultrasound, and magnetic resonance imaging. Imaging procedures are invaluable in the staging of most solid tumors. Although the staging procedures used depend on tumor type and location, the underlying principle is evaluation of the local and distant extent. Local extent is usually evaluated by the primary diagnostic modalities discussed above; this section will deal with the evaluation of common areas of metastatic disease. However, the only sure way to establish the diagnosis of cancer is by pathologic confirmation.

Guide to Therapy

Accurate assessment of tumor volume and local extent is particularly important when surgery or radiation therapy is used. Generally, the imaging studies recommended for primary tumors described above and in the specific chapters will give adequate information for the surgeon or radiation therapist. In most instances, CT scanning of solid tumors will give adequate information, although, as noted, there are occasions when MRI may be more useful. However, if ultrasound has been satisfactory in delineating the primary tumor, this method should be used for following response to therapy since it is cheaper. Metastatic lesions are also best monitored using the same modality which demonstrated them at the time of presentation. Arteriography is rarely indicated other than in primary liver tumors, although it should be considered when questions of blood supply or preoperative vascular embolization are raised.

Detection of Recurrences

Recurrent disease can be defined as reappearance of tumor in its original location or as metastases in distant sites. The primary site is usually best followed with the imaging modality used for the initial tumor. Adequate evaluation for metastatic disease requires knowledge of the natural history of the tumor; chest films, head and chest CT, bone scans, and abdominal ultrasound and CT are all reasonably used, depending on the organ of origin of the original tumor.

The vexing problem that has yet to be resolved is how often follow-up studies should be obtained.

Staging of solid tumors

The original concept of "stage" in solid tumors was a system designed to describe only the extent of disease at one point in the course, usually at diagnosis. A shorthand form was used, condensing the multiple types of possible extension of the disease into categories, exemplified by the TNM (T = tumor; N = nodes; M = metastases) system. They indicated which patients went to surgery or received irradiation and what type or dose. Surgeons, radiotherapists, and pathologists frequently modified (for different tumor types) the TNM staging system, and these modifications received the endorsement of national and international (UICC) organizations. In some tumor systems, the TNM classification was divided into a clinical stage (before surgery) and pathologic stage (after surgery and histologic examination), and this continues to be employed in many adult tumors.

In the era of effective surgery, radiotherapy and chemotherapy, the staging of solid tumors is an absolute necessity for comparing multi-institutional therapy trials.

Radiation Therapy

Radiation therapy plays a major role in the management of most cancers. Because of the potential for acute and chronic side-effects, radiation must be used cautiously in patients. The severity of the side-effects is directly related to dose. Acute morbidity, such as gastrointestinal dysfunction, bone marrow suppression, and skin reactions, is seldom a limiting factor when radiation therapy is used alone, and the changes produced are generally reversible.

Radiosensitivity of tumors:

- high radiosensitivity: seminoma, lymphosarcoma, Ewings tumor, bazalioma of skin;
- average radiosensitivity: squamous cell carcinoma;
- low radiosensitivity: adenocarcinoma;
- radioresistant tumors - fibrosarcoma, melanoma, chondrosarcoma, osteogenic sarcoma.

By ionizing radiation in malignant tumor take place next changes:

– reduction measure of tumor;
– development of granulation tissue;
– reduction vessels of tumor;
– ruin all malignant cells and substitution of they by connective tissue.

Principles of radiotherapy:

1. To achieve a favorable therapeutic ratio without producing unacceptable damage to adjacent normal tissues.

2. The radiotherapy must begin timely. So much the better in I or II stages, when tumor is small.

3. For a favorable therapeutic ratio we must to irradiate all tumors cells in necessary dose and in optimal time. It is very important the first course of radiotherapy.

4. The dose is necessary if it is enough to plan effect. For radical treatment use total doses 60-70 Gy by conventional fractionation. This dose must to receive primary tumor. The regional lymphanodes must to receive 50 Gy (if they have not metastases).

5. The favorable therapeutic ratio is increase if use the factors which can increase radiosensitivity of tumor cells or to radioprotect the critical normal tissues.

7. Utilization adequate diet, vitamins, giving up smoking and alcohol.

For favorable radiotherapy of cancer the tumor must be no more 1 cm. Because for treatment of this tumor will be use 60 Gy γ-ray by conventional fractionation. More dose can not give because possible the damage of connective tissue. Tumor which has the zise 1 sm content one milliard cells (10^9).

The practical experience show what result of radiotherapy depend moreover from radiosensitivity, oxygen enhancement ratio, immunity and some other. But the zise of tumor is the principal reason for favorable radiotherapy. The limit of zise of tumor for successful treatment by radiotherapy is 6,0 cm.

There are free directions for optimization of radiation therapy:

1. Utilization of new technics and «new» types of radiation.
2. Utilization distinctive types of dose fractionation (dose fractionation schedule).
3. Utilization radiosensitization and radioprotection.

Utilization of new technics and «new» types of radiation.

External-Beam Irradiation

Radiation therapy is broadly divided into external-beam irradiation and brachytherapy. In external-beam therapy, a well-defined x-ray or gamma-ray beam is directed to a specified anatomic volume. In brachytherapy radioactive sources are applied directly within or around a given tumor site as discussed below. In oncology more radiation therapy is administered as external-beam irradiation.

How is therapeutic radiation generated?

External beams of therapeutic radiation can be generated by cobalt 60 (^{60}Co) units, cesium

137 (^{137}Cs) units, linear accelerators, betatrons, and cyclotrons. Radiation for implant radiotherapy can be generated by cobalt 60 (^{60}Co) and iridium 192 (^{192}Ir).

^{60}Co external beam machine

Radioactive Co60 emits gamma rays with energies of 1.17 and 1.33 million electron volts. The ^{60}Co may be housed in a shielded box. A piston drives the ^{60}Co the "on" or exposed position. At the conclusion of the treatment session, the piston pulls the ^{60}Co back into the «off» position.

Linear accelerators

Linear accelerators may be used to produce either x-rays or electrons. Because of the sharp beam definition and the ability to generate many different electron and photon energies, linear accelerators have become the principal radiotherapy machine in many departments. Within the machine, electrons are fired from an electron gun into an accelerator tube. The electrons are swept down the tube by intense electrical fields. The electrons may be used to strike a target and produce x-rays or they can be directly emitted from the machine. Electrons are used for therapy in situations where it is desirable to administer relatively superficial irradiation. X-rays are used for therapy directed more deeply into the body.

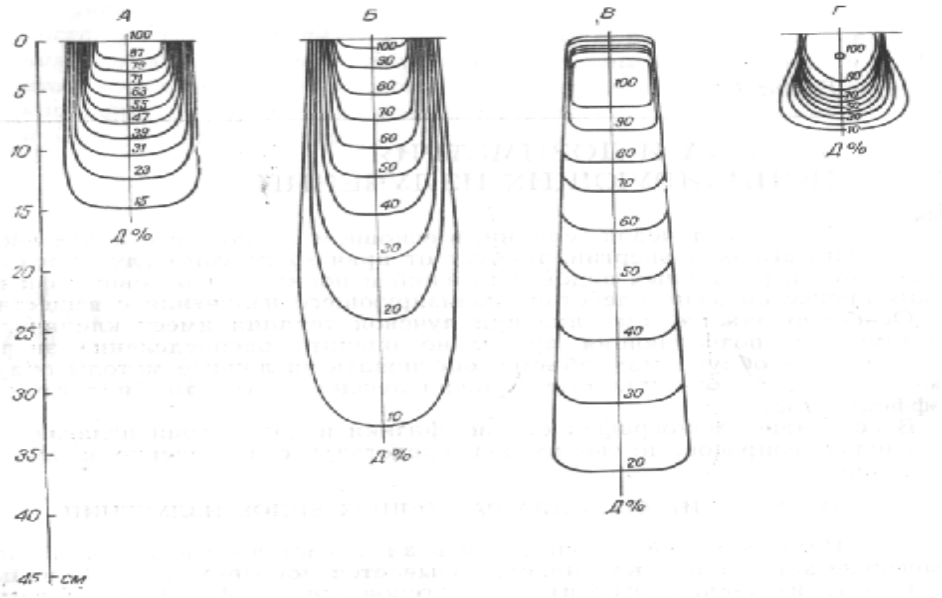
Photon-Beam Therapy

Photon beams have been used in radiation therapy since Rontgen's discovery of x-rays produced from a cathode ray tube. The maximal energy of the beam defines the quality of irradiation: orthovoltage (100-400 keV) or supervoltage (greater than 1 MeV; synonymous with megavoltage). Cobalt teletherapy units direct emitted gamma rays from the continuous decay of a radioactive ^{60}Co source. The energy level is in average 1.2 MeV. Linear accelerators use high-energy electrons, accelerated along a waveguide to 4 to 48 MeV, to produce x-rays with rather precise beam definition.

The dose distribution of photon irradiation in tissue is dependent on the energy of the beam. Orthovoltage beams deliver 100% of the energy on the surface, losing energy quickly below the superficial tissues; by 3 to 4 cm depth, the dose is 50% of the maximal dose. With 6°Co or 4 MeV x-rays, there is a skin-sparing effect: less than 60% of the maximal dose is deposited at the surface, the superficial dose building to the 100% dose level at a depth of 0.5 to 1.0 cm.

The dose in tissue diminishes less rapidly with ^{60}Co or 4 MeV photons than with orthovoltage: 50% of the maximal dosage is reached 12 to 14 cm below the surface. With higher-energy photons, one sees an increase in the depth of maximal dosage and more effective penetration: 20 MeV linear-accelerator x-rays, for example, achieves maximal dose level at 4.5 cm; the surface dose is less than 20%, and the dose is diminished to 50% of maximal at 23 to 24 cm depth.

The dose distribution in tissue is displayed as a depth dose curve or isodose plot. A single beam delivers a diminishing dose at depths beyond maximal build-up (Fig. 1).



А- orthovoltage x-rays beam (250 keV)
Б- γ-rays ^{60}Co
В – 25 MeV linear-accelerator x-rays
Г – 20 MeV electrons.

Modern techniques identify an isocenter (fixed for a specific treatment unit) at which two or more fields may focus, entering from different directions. Parallel opposed fields enter from 180° opposing angles, most often anterior and posterior or right and left lateral in position. The dose distribution in parallel opposed arrangements is relatively uniform throughout the irradiated volume.

Electron-Beam Therapy

Electron-beam irradiation provides relatively uniform doses within 1 to 5 cm of the surface, the depth of penetration varying directly with the energy of the electron beam. The unique depth dose characteristic of electrons is a relatively flat region of nearly uniform dosage (80%-100%) with rapid fall-off beyond the 80% depth. With 18 MeV electrons, for example, the dose between entry and 5 cm is uniformly between 80% and 100% of maximum; at 8 cm depth, the dose is less than 10%. There is little skin sparing with electron irradiation. The LET of electrons is equivalent to that of photons. Caution is necessary in areas of tissue inhomogeneity; bones absorb electrons preferentially (with increased dose within bone and decreased dose deep to bone), whereas air cavities (e.g., sinuses) transmit electrons, resulting in deeper penetration of the incident beam. Electron beams are available from intermediate- or high-energy (10 MeV or greater) linear accelerators.

Neutron Irradiation

Neutrons are most commonly produced by cyclotrons, with depth dose characteristics for 7 to 14 MeV neutrons being similar to those of ^{60}Co. Neutrons are high-LET radiations and are of interest because of the relative lack of oxygen dependence as summarized above. Initial neutron trials resulted in disastrous late effects owing to a lack of data regarding the differences in relative biological effectiveness (RBE) with small fraction sizes. In recent studies using appropriately adjusted RBE values, there has been evidence of various degrees of effectiveness for specific tumor sites (soft-tissue sarcomas).

Heavy-Particle Irradiation

High-energy cyclotrons produce energetic charged particles of potential value in radiation therapy. Protons, for example, yield a discrete volume of increased dose at a depth that varies with the energy of the incident proton beam. The dose distribution is characterized by a Bragg peak resulting from relatively dense nuclear reactions as the particle loses velocity. Therapeutically useful proton energies (e.g., 160 MeV) have an RBE only slightly higher than that of photons. Other particles (e.g., high-energy carbon, neon, or argon ions) have a similar dose distribution. In addition, the liner energy transfer (LET) of the latter particles is increased in the region of peak physical dosage, resulting in an even greater biological dose differential at the depth of the agg peak . Protons have produced intriguing results in focal intraocular tumors such as choroidal melanoma and in pituitary adenomas.

Brachytherapy

Direct application of radioactive materials to localized accessible tumor sites is termed brachytherapy. The principal types of brachytherapy include intracavitary applications (within body cavities such as the vagina or nasopharynx), interstitial implants (directly into tissue), and mold applications (adjacent to tumor sites such as skin or eye). Brachytherapy has been used in adults for decades, most often for cancers of the female genital tract, upper aerodigestive tract, breast, and soft tissues. Pediatric applications have been described more recently, primarily for retinoblastoma and soft-tissue tumors.

The primary advantage of brachytherapy is the ability to achieve a concentrated high dose volume with relative sparing of adjacent normal tissues. The dose distribution in brachyther-apy is governed largely by the inverse square law. A typical dose distribution of interstitial therapy with high dose levels near the sources and rapid fall-off. By geometric planning, one can achieve a dose distribution encompassing the desired target volume with far less irradiation of surrounding normal tissues than can be achieved with external-beam irradiation. To assure relative dose homogeneiry within the target volume, brachytherapy applications are used primarily for tumors less than 5 cm in greatest diameter.

Initial experience with brachytherapy used ^{226}Ra. Rigid needles or tubes limited attainable geometry, while handling the radioactive sources for direct implantation created radiation safety problems for personnel. Current practice most commonly uses ^{192}Ir, an artificially produced radio-nuclide imbedded in wire or seeds that can be afterloaded into hollow Silastic tubes. Interstitial placement of the tubes is performed by direct positioning or by stereotactic localization using computed tomographic (CT) guidance. The geometry of the implant can be planned before insertion, confirmed by radiographs during the procedure, and altered if necessary; when it is satisfactory, the tubes are loaded with the radioactive sources. This sequence allows greater accuracy while limiting exposure of medical personnel. The implant remains in place for a calculated period of time, typically 2 to 5 days, and is subsequently removed with little difficulty. Problems of radiation safety are magnified in children, but procedures to assure personnel and parental exposures within established limits can be achieved even in young children.

Iodine-125 sources have the advantage of emitting lower-energy photons, simplifying radiation safety procedures. Iodine-125 has been used predominately in permanent low-activity implants in adults, small seeds remaining in place with gradual decay over several months. The lack of data regarding potential somatic and carcinogenic effects of long-term exposure to low-dose irradiation in children limits consideration of permanent implants for pediatric cancer. High-activity ^{125}I has recently been introduced for use in removable implants with potential advantages in pediatrics due to the limited penetration of the lower-energy photons beyond the immediate implant volume.

Brachytherapy also has potential radiobiological advantages compared with external-beam irradiation. Dose rates in brachytherapy are generally 30 to 100 cGy/hour in comparison to 100 to 300 cGy/minute with external therapy. Low dose rates appear to achieve reduction in tumor cell proliferation while permitting repair of sublethal damage in normal tissues. In addition, low-dose-rate irradiation has a much lower oxygen enhancement ratio (OER) compared with acute exposures during external beam therapy.

Brachytherapy experience has been well documented in cancer of uterus, rectum, mouth cavity. Recent series document successful applications of both intracavitary and interstitial brachytherapy in soft-tissue sarcomas.

Implant radiotherapy

Direct implantation of sealed sources of radioactive material into or adjacent to a tumor is a technique for cancer treatment. Radioactive needles or small radioactive seeds may be placed directly into tissue. Alternatively, sealed sources may be placed in a body cavity or on a body surface immediately adjacent to the malignant area. Several types of radioactive material are commercially available for these purposes. The most commonly used are radium 226, cesium 137, radon 222, gold 198, iodine 125, and iridium 192. There is a general trend away from the use of radium and radon because of shielding and storage problems. Therefore cesium, iodine, and iridium have become more popular.

Treatment Planning

The treatment planning of radiotherapy must begin with establishing the diagnosis of malignant tumor by clinical, radiology and oblige histologic examination. After that must be the consultation with a radiation oncologist, a surgeon, a chemotherapeutist. Those actions are necessary because the treatment of malignant tumors is difficult and compound, complications are very hard.

The initial process in planning radiation therapy is to identify the target volume. For curative irradiation, the target volume usually includes the primary tumor site and immediately adjacent area(s) of potential microscopic extension. Inclusion of adjacent or regional lymph nodes is dependent on tumor type and extent. Data from clinical examination, radiographic studies, and operative assessment may be used to define the target volume. Knowledge of the natural history of specific tumor presentations is critical in determining the appropriate irradiation volume.

Once the target volume has been determined, an interactive process of patient simulation and dosimetry defines the treatment plan. Simulation permits accurate localization of the target volume from one or several directions; the simulator is a diagnostic-quality x-ray unit structured to mimic the treatment machine geometrically. The position and divergence of the photon beam are identical to those of the linear accelerator, allowing the radiation oncologist to plan accurately treatment strategies that have been identified by and may be later confirmed by computerized dosimetry. Planning seeks to maximize dose homogeneity within the target volume and permit appropriate dose limitation for critical normal structures.

Dosimetry provides a detailed analysis of the dose distribution within a given plane. CT-based treatment planning accurately displays the dose relation based on the planned field configuration. The simplest technique to provide homogeneous dosage is a parallel opposed pair of treatment fields. Such uniformity is ideal when treating the cranium (to encompass the subarachnoid space), the abdomen (especially when treating the entire peritoneal cavity), or more localized central anatomic areas (such as the nasopharynx or mediastinum). The energy of the photon beam determines the depth of maximal dosage and the distribution, specific indications often requiring low-energy (e.g., treatment of the subarachnoid space) or high-energy (e.g., para-aortic) megavoltage beams.

Simulator is ancillary radiation equipment. There must be a mechanism of converting the concept of irradiating a certain amount of tissue into a practical plan. The specific number of

radiation beams (also called radiation ports), their size, and their angles of entry into the body must be determined. The simulator is a machine that assists in the development of an actual treatment approach.

The simulator reproduces, or "simulates," the radiotherapy treatment machine (i.e., ^{60}Co or linear accelerator). The simulator contains, however, a diagnostic x-ray tube instead of a high-energy radiation source. The physician may plot the angles of the radiation beams and determine the beam size required and document each proposed "port" with a diagnostic x-ray. This diagnostic film is used to show the tumor volume and the location of any appropriate lead blocks. In this way a high energy treatment plan can be developed without exposing the patient unnecessarily to radiation from cobalt or the linear accelerator.

More complex field arrangements are often desirable, concentrating the high-dose volume or limiting doses to specific structures. In addition, blocks are customarily used to define the treatment volume. Customized blocks are fabricated from a lead alloy that provides precise beam definition to limit the irradiation volume to the desired anatomic region.

With treatment volumes extending beyond one body cavity, one must use adjoining-field configurations such as mantle and para-aortic fields in Hodgkin's disease. Field junctions require exquisite attention to avoid areas of overdosage and underdosage, which may be associated with local recurrence or unnecessary toxicity.

Optimization of treatment techniques

Since the beginning of radiation therapy a very extensive number of methods, beam modalities and irradiation techniques have been developed. Beside the choice of radiation modality there are a large number of degrees of freedom that can be used for treatment optimization including: beam energy, beam directions, beam collimation, beam profiles and the irradiation technique in general as determined by the type of equipment used.

Radiation modality. Photon beams from external radiation sources have dominated radiation therapy closely followed by external electron beams and intracavitary and interstitial therapy with sealed sources. During the last decades also heavy charged particle therapy with neutrons, protons and heavy ions have been used more extensively. A further reason for leaving out the heavy high liner energy transfer (LET) particles are that they are not universally applicable. Due to their high ion density the damage to the genome is more severe and generally not repairable. Since the more efficient repair capacity of the normal tissues is one of the corner stones of radiation therapy, high LET radiations are not really suitable for treating the often extensive microscopic disease. Furthermore, brachytherapy will be left out too due to the greatly differing irradiation techniques even if most of the optimization methods particularly those using biological objectives, apply to both these latter modalities.

Conformation, conformed and generalized conformal therapy. The former generally used rectangular wedged fields from a large number of beam directions even though it for practical reasons generally was less than 20. The ultimate step in the therapy development is to allow full freedom in the shape of the delivered beams both with regard to beam energy, beam direction and beam profiles. However, such treatments are quite complicated both to plan and deliver so a more practical treatment optimization requires some treatment parameters or degrees of freedom to be locked to make planning and dose delivery practical and manageable. For many simple target volumes few field techniques with uniform beams are quite sufficient whereas for more complex shapes non uniform dose delivery is generally much more advantageous. In fact, it can be shown that the classical conformation therapy method with uniform beams is almost equal to the fully optimized generalized conformal method only for the special case of homogeneous circular symmetric target volumes. For most other target volumes non uniform dose delivery will be clearly advantageous.

In very general terms the function of non uniform dose delivery is to protect normal tissues in front of, inside or beyond the target volume whereas organs at risk outside or lateral to the target volume are speared by irregular field collimation. From the beam s point of view the

function of non uniform beams are therefore to save organs at risk longitudinal to the target volume whereas the collimation system saves normal tissues transversal to the target volume.

General methods for non uniform dose delivery. The best methods for non uniform dose delivery are dynamic multileaf collimation and scanned elementary beams. The dynamic jaw collimation method allows in principle full modulation of the incident beam but at the cost of very extended treatment times. Furthermore, it requires that both the upper and lower jaw pairs are fully asymmetric so that a narrow rectangular beam spot could be scanned arbitrarily across the entire target volume. If very high dose rates were available and the speed of motion of the collimator jaws was very fast the time required could be reduced but this is not a very realistic method with present accelerator systems.

The classical filter and block techniques have the flexibility but they are probably not realistic for more than some 3 portals per patient. In recent years several compensator optimization techniques have been developed which are quite useful to handle few field techniques provided suitable beam directions can be identified. In reality the optimal choice of beam direction is one of the most difficult problems of treatment optimization since it involves a restriction on the phase space of feasible beam combinations. This can not be achieved without having tested all possible beam combinations which in practice is equal to a global optimization. It also accentuates a difficult radiobiological problem, in a way the Scylla and Charybdis of radiation therapy: With a single beam the small volumes of normal tissues in the entrance region receive a rather high local dose, whereas on the other extreme, with a continuum of arc beams, large volumes receive rather low doses. To allow a strict optimization realistic radiobiological objective functions capable of distinguishing between these extremes are needed.

Scanning beam therapy. Radiation therapy is traditionally performed with stationary beams and flattening filters to make the beam uniform. The fastest and probably safest way to deliver non uniform beams in real time is today by moving a small elementary electron, photon or proton beam over the patient similar to the electron beam in a TV monitor (scanning beam therapy). Despite this shortcoming the scanned beams are very useful and many times sufficient at least for beam compensation. In combination with dynamic multileaf collimation a very fast and flexible dose delivery is possible and ideal for few field non uniform generalized conformal therapy with treatment times of the order of a few minutes in most cases.

Fan beam therapy. There are a large number of projects centered around the use of uniform or non uniform fan beams. The earliest was probably in the computer controlled therapy in Boston where the length of a narrow elongated slit beam through the isocenter (fanbeam) was varied as the gantry rotated and the patient was slowly moved through the beam. The treatment time was often long of the order of 20 min and the set up time was also considerable. This problem is shared with all small volume irradiation techniques, unless the dose rate and speed of rotation is increased by about one order of magnitude.

A similar technique has been investigated in Galveston but keeping the patient fixed and moving an oblique fan beam by using a dynamic pair of asymmetric collimator jaws. More recently a special modulated fan beam collimator has been developed. This device allows temporal modulation of the treatment time along the fan beam for non uniform dose delivery.

The latest development has been suggested by the group in Madison. Then- idea is to use a fan beam modulating collimator for "spiral irradiation" much in the same way as used as spiral computed tomography. The patient is then being moved through a continuously rotating modulated fan beam. Unless the accelerator output is very high all the fan beam approaches described here unfortunately suffer from long treatment times.

Pencil beam therapy. At the cost of a further increase in treatment time it is possible to use a moving narrow collimated beam (pencil beam) to deliver non uniform dose distributions. The pioneering work for uniform beam delivery was done in Chicago using a mechanically moving bending magnet in a rotary gantry. Since the dose rate in the electron beam was quite high the treatment time was not too much increased.

More recently a robot mounted linear accelerator has been developed (Accuray, MainW., Private communication, 1993). This device has the advantage of a high degree of freedom since the computer controlled dynamic dose delivery is performed by the robot. However, for large target volumes this device requires very long irradiation times since the beam is narrow (4 cm) and the dose rate is normal (3 Gy/min).

Development of algorithms for radiation therapy optimization.

From a mathematical point of view classical radiation therapy planning has been treated as a forward process as it tries to answer the question: how will the absorbed dose in the target volume and surrounding normal tissues be distributed for a given target volume, associated patient geometry and suggested configuration of the incident beams? Classical radiation therapy optimization is therefore generally a trial and error process, where gradually improved dose plans can be found by trying out an increasing number of beam configurations.

However, in mathematical terminology radiation therapy planning is fundamentally an inverse problem. This is so, because what we really want to find, is the optimum combination of incident beams for a given target volume. More exactly, the planning process should answer the question: which configuration and shape of the incident beams is best for controlling the tumor growth with minimal damage to normal tissues? At least under the assumption that the desired dose to the target volume or the geometrical and radiobiological properties of the tumor and normal tissues of the patient are known, it should be possible to find the optimal irradiation technique.

The question mark indicates the principal quantity calculated, the isodose distribution in the patient and the optimal incident beam profiles by the two methods respectively. Obviously the absorbed dose distribution in the patient is also obtained by the inverse calculation either by an ordinary forward calculation or by the inversion method itself.

Immobilization

Immobilization is critical for proper simulation and daily treatment. Infants and children younger than 2 or 3 years old may require sedation. Most older children can be reassured with appropriate explanations, gaining sufficient confidence to maintain the necessary position unattended for the 30- to 90-second period of each treatment field. For anatomic sites other than the torso, specific devices are often used to achieve stabilization and reproducibility, including headholders (chin supports, fixed mesh casts) and removable casts to assure consistent positioning of an extremity.

For neuraxis therapy, a cast or mold is necessary to support the patient in a reproducible prone position. Plaster or self-setting acrylics may be used.

Utilization distinctive types of dose fractionation (dose fractionation schedule).

Dose, Fractionation, and Time

For most tumors, the dose of radiotherapy is influenced by both the need for tumor control and the tolerance of normal brain. This tolerance, in turn, depends on a number of factors including the anatomic location (the brain stem and hypothalamus are more sensitive than other areas), the volume irradiated. Doses of 60 Gy given at a rate of 2 Gy daily 5 days per week. The fractionation schedule and total treatment time are also of considerable importance. Late effects on normal tissue seem to depend largely on the size of the dose per fraction. Thus, there may be a theoretical advantage to the use of a larger number of smaller fractions ("hyperfractionation") to reduce late damage. With "accelerated hyperfractionation," a higher total radiation dose is given in a similar or shorter time than in conventional therapy. This technique is postulated to increase tumor control.

Radiation Fractionation

The most important variables influencing the therapeutic ratio in clinical radiation

oncology are the total dose, the number of radiation fractions (and hence the dose per fraction), and the interval between radiation fractions (and hence the overall treatment time). The application of radiation therapy evolved rapidly to fractionated, protracted treatment based on early radiobiological experiments and clinical observations. Fractionated treatment using small daily doses of radiation (1.8-2.2 Gy per day) over 5 to 7 weeks to total doses of 50 to 70 Gy produced local control of many epithelial carcinomas in adults with relative sparing of normal tissues.

The relation between the radiation fractionation schedule and the tumor control dose has been established clinically in certain neoplasms in which tumor control doses have been measured for different fractionation schedules.

Multiple small radiation fractions separated by at least 4 hours (typically 24 hours) permit the repair of sublethal damage. Because each radiation fraction provides another opportunity for sublethal damage to be repaired, both tumors and tissues become more resistant to irradiation as the number of radiation fractions increases. It has been argued that tumors might repair damage less well than normal tissues because the hypoxic cells in tumors are repair deficient, but there is little direct evidence to support this hypothesis. There is evidence that late-responding normal tissues accumulate and repair more sublethal damage than do tumors or rapidly responding normal tissues; this finding is the basis of trials with larger-than-conventional numbers of smaller-than-usual radiation fractions (hyperfractionation).

Prolonging the overall treatment time may allow a portion of the hypoxic tumor cells to reoxygenate and become more radiosensitive. Reoxygenation of hypoxic (radiation-resistant) tumor cells appears to occur rapidly after the start of a course of radiation. Although neither the kinetics nor the mechanisms underlying reoxygenation are clearly known, it appears that this phenomenon is an important reason for the increased efficacy of fractionated radiation therapy.

Protraction of irradiation will also allow the more rapidly proliferating normal tissues and tumors to repopulate. Repopulation during the course of fractionated radiotherapy is a significant cause of the apparent radioresistance of rapidly proliferating tissues such as skin, gut, and oral mucosa. Rapid repopulation is not a factor for tissues such as lung, spinal cord, or kidney. Repopulation can also increase the radioresistance of tumors if the growth rate is sufficiently high and the radiation schedule is sufficiently prolonged.

During protracted irradiation, cells may redistribute through the cell cycle as populations become partially synchronized by radiation. In addition, cells that were nonproliferating (quiescent) may be recruited into proliferation. Redistribution and recruitment of cells occur in both tumors and normal tissues and may be a factor in fractionated radiotherapy However, we currently lack the detailed knowledge of cell kinetics required to exploit redistribution and recruitment.

Unconventional Radiation Fractionation

In practice, most radiation therapy is delivered once a day,5 days per week, with daily doses of 1.8 to 2.2 Gy; such a course is now termed standard or conventional fractionation. A number of other schedules have been tried. Clinical trials over the past few decades have generally shown that hypofractionation (fewer, larger radiation fractions) and split-course radiotherapy (where a break of 1-4 weeks is planned near the middle of an otherwise conventional schedule) produce poor clinical results.

Some clinical and laboratory data support the concept or dividing the daily dose into two or three smaller treatments, the hyperfractionated schedule. Laboratori studies suggest that late-responding normal tissues are spared more by fractionation than either tumors or acutely responding tissues. Hyperfractionation allows larger numbers of fractions to be given without the problems associated with prolonging treatment. These hyperfractionated treatments must be separated by at least 4-6 hours to ensure repair of sublethal damage in normal tissues between

fractions. Clinical trials indicate that daily doses of 2 Gy can be replaced with twice-daily doses of 1.2 to 1.3 Gy (to total doses 20%-30% higher than those used in conventional fractionation), without exceeding late normal tissue tolerance, although these schedules often produce in-creased acute normal tissue reactions. It is not yet clear whether the hyperfractionated schedules are enhancing tumor response.

Because of the variation in daily doses and radiation schedules encountered in clinical practice, attempts have been made to develop models or formulas for equating different schedules.

The concept of a "tolerable" dose. The dose of radiation tolerable by an organ cannot be characterized as an absolute number. Rather, a dose of radiation to the entire substance of an organ may be associated with a certain probability of a radiation-induced complication. This concept is referred to as the minimal tissue tolerance dose (TTD).

The $TTD_{5/5}$ is usually used in clinical practice and is defined as that dose of radiation associated with a 5% rate of complications occurring within 5 years of treatment. The use of the $TTD_{5/5}$ concept is fraught with pitfalls. In general, $TTD_{5/5}$ refers to "whole organ" doses of which the clinician must be aware. For example, the $TTD_{5/5}$ is usually higher if less than 100% of an organ is irradiated. The $TTD_{5/5}$ when the entire heart is irradiated is 4500 cGy. When, however, only 20% of the heart is irradiated, the $TTD_{5/5}$,, is 6000 cGy. Before invoking a $TTD_{5/5}$ in practice, one must be aware of how much of an organ was treated. In addition, $TTD_{5/5}$ is usually used in the context of 180 to 200 cGy/ fraction. That is to say that the $TTD_{5/5}$,, of the heart is approximately 180 cGy/fraction for 25 fractions or 200 cGy/fraction for 22 fractions. As the dose/ fraction increases, the $TTD_{5/5}$ decreases.

The best known of these models are the nominal standard dose (NSD or ret) model proposed by Ellis:

$$NSD = D/(N^{0,24} \cdot T^{0,11}), \quad \text{where}$$

D – total absorption dose (cGy);

N – number of fractions;

T – overall treatment time (days).

The radioresistance of connective tissue is 1800 rad equivalent therapy (ret) by NSD conception. Despite widespread interest in this approach, neither NSD nor any of the alternative models is accurate enough, or sufficiently general in scope, to be used to calculate tolerance doses or tumor control doses in nonstandard schedules.

Utilization radiosensitization and radioprotection.

Hyperbaric oxygen and the hypoxic cell sensitizers metronidazole and misonidazole have been used in an attempt to overcome the problem of reduced radiation sensitivity of poorly oxygenated tissues, which make up a significant portion of many solid tumors. Other attempts at overcoming this problem, such as the use of neutrons, which have less dependence on an ionizing interaction with oxygen for their biological effects, have been accompanied by unacceptable brain damage in spite of good local tumor control.

An attractive approach to improving the ttherapeutic ratio is to use chemical to radiosensitize the tumor or to radioprotect the critical normal tissues. Recent efforts to radiosensitize tumors have been based, for the most part, on electron-affinic drugs(e.g. mizonidazole and metronidazole), which preferentialljy radiosensitize hypoxic cells. Clinical use of the nitroimidazole can radionsesitizers has been limited by their cumulative neurotoxicity. At the doses that can be tolerated by humans, mesonidazole can sensitize tumors *in vivo* to single doses of radiation by factor of 1, 1 to 1, 4.

Numerous other strategies also have been employed in attempts to minimize the effect of tumor hypoxia, including transfusion of anemic patients, modifications of standard radiation schedules, radiotherapy with hyperbaric oxygen, and irradiation with particles (neutrons, heave charged particles) that have lower OERs. A new approach to solving the problem of hypoxic cells is to use of perfluorochemical emulsions plus oxygen breathing to increase the oxygen –

carrying capacity of the blood.

Efforts to protect normal tissues have based on sulfhydryl compounds such as cysteamine analogue WR-2721. Attempts to improve the therapeutic ratio (i,e., to protect normal tissues specifically) with these agents are based on both decreased drug uptake by tumors and on decreased radioprotection under hypoxic conditions. Clinical trials of WR-2721 are in progress.

The possible goals of radiotherapy

To proceed from problems of treatment of cancer, radiation therapy can use: 1) as independent mode of treatment; 2) combination of surgery and irradiation; 3) combination of chemotherapy and irradiation.

Radiotherapy as independent mode of treatment use in next cases:

- if radiotherapy is more better other modes;
- if radiotherapy is only possible mode of treatment to patient with malignant tumors;
- if patient to refuse a surgery treatment.

Radiotherapy with *radical goal* to demand of dose which can kill all malignant cells (60 Gy by conventional fractionation).

Radiotherapy with *palliative goal* to demand of dose (40 Gy by conventional fractionation) which can kill part of malignant cells, hamper the grow of tumor, to take off pain and tumors narrow and squeeze.

Radiotherapy with *symptomatic goal* to demand of dose 30-40 Gy by conventional fractionation for take off pain and tumors narrow and squeeze, only.

Radiotherapy does not conduct in next cases (contra-indicated):

1. Disintegration of tumor with abscess or bleeding, sprouting into hollow organs.
2. Present of many distant metastasis.
3. Bad condition of patient.
4. Exhausted.
5. Anaemia, low level of leucocytes ($< 3\times10^9$/litre).
6. Sepsis diseases, active tuberculoses of lung.
7. Infarct of heart (< 1 year ago).
8. Insufficiency of heart, liver, kidneys.

Intraoperative Radiotherapy

The use of intraoperative radiotherapy (IOR) is under consideration for patients with cancer of stomach and possibly other tumors.

The aim of the current procedure is to deliver a single high-dose exposure to an unresected segment of a tumor or total tumor identified under direct vision. Thus, the margins of the tumor and hence the radiation portals can be determined with precision. The technique of maintaining anesthesia and physiologic support with both the operating and the anesthesia teams momentarily out of the operating room presents problems. The surgical techniques are standard. The intraoperative treatment cones are introduced as sterile instruments directly into the surgical field. Scatter from such therapy can be strictly limited. Animal studies suggest that irradiation doses must be limited to 1500 to 2000 rad if intestine is in the field, but, if the intestine can be excluded, large vessel walls will tolerate single doses exceeding 3000 rad. Supervoltage technique has been used.

Combinations of surgery and irradiation

The combined use of surgery and radiation therapy has been a basic principle of cancer management since the early 1900s. The rationale for preoperative or postoperative irradiation has been based on the failure patterns of the two modalities. Recurrence after local or radical surgical excision implies residual microscopic disease at the operative margins; recurrence after radiation therapy in general relates to large tumor volume, with an excess of clonogenic tumor cells beyond the number that can be destroyed by locally tolerated doses of radiation. The presence of hypoxic foci increases with tumor size; even a small proportion of hypoxic cells substantially

affects the dose necessary to eradicate the clonogenic population.

With combined therapy, the goal of surgery is to remove all macroscopic disease, reducing the proportion of clonogenic cells and eliminating the hypoxic cell fraction. Radiation therapy seeks to eradicate peripheral extensions of disease beyond the operative margins, destroying the normally oxygenated microscopic foci. Planned surgery and postoperative irradiation must include a reasonable likelihood of complete surgical resection of macroscopic disease; little is gained by debulking if surgery removes only a portion of the identifiable tumor, thereby reducing the clonogenic cells, introducing tumor cells into a broader area by contaminating the entire operative bed, and altering vascularity of the residual tumor, thus potentially increasing the number of hypoxic cells. A laboratory model of rhabdomyosarcoma has confirmed the clinical observation that surgery contributes to local control only if complete resection of macroscopic disease is achieved.

Preoperative irradiation is often preferable to postoperative therapy. Irradiation is more effective with intact vascularity; in practice, preoperative doses are generally 75% to 80% of postoperative doses. In addition, preoperative treatment reduces the likelihood of surgical implantation or dissemination. In Wilms' tumor, for example, preoperative irradiation diminishes the frequency of intraoperative tumor rupture, decreasing both abdominal recurrence and disease-related mortality. In some tumor systems, preoperative irradiation may reduce the volume of normal tissue necessarily resected to assure adequate tumor removal. Suit and associates have shown excellent local tumor control with preoperative irradiation and wide local resection of extremity soft-tissue sarcomas using irradiation doses below those indicated for postoperative management and avoiding amputation.

Combined surgery and radiation therapy may be utilized solely to address regional lymph-node metastases. In several tumor systems, such as ovarian dysgerminoma, testicular seminoma, or, potentially, paratesticular rhabdomyosarcoma, surgery is used for the primary tumor with radiation therapy employed to eradicate microscopic foci in regional nodes.

Intraoperative irradiation has recently engendered considerable interest Direct irradiation of the tumor bed during the operative procedure offers theoretical advantages in localization and immediate treatment of residual microscopic deposits. In practice, large electron fields are used to deliver 15 to 20 Gy in one fraction to the operative bed, most often for intra-abdominal cancers in adults (e.g., those of the pancreas, stomach, rectum, and retroperitoneum). Problems include the technical availability of irradiation in the operative amphitheater and assurance of appropriate field alignment with limited visual exposure. In addition, radiobiological data indicate that single large radiation fractions are limited in achieving tumor sterilization by the presence of hypoxic cell fractions. Late effects on hollow viscera (biliary tract, bowel, ureter) and peripheral nerves appear to be the dose-limiting phenomena in regard to normal tissue tolerance.

Combinations of chemotherapy and irradiation

The coordinated use of irradiation and chemotherapy is fundamental to modern cancer management, especially in children. The interactions between radiation therapy and cytotoxic chemotherapy are complex. Improvement in the therapeutic ratio results from combined effects categorized by Steel, as shown in Table 1. Diminution in the therapeutic ratio can occur with combined therapy, defined by Fu either as inbibition (combined effect less than that of the more-active modaliry alone) or antagonism (combined effect less than that achieved by the less-active agent alone).

Table 1

Interactions of Chemotherapy and Radiation Therapy
That Potentially Improve the Therapeutic Ratio

1 . Spatial cooperation — independent actions of local irradiation and systemic chemotherapy, the latter addressing occult or overt disease beyond the irradiated volume; no true "interaction" is apparent in this mechanism, typifying the term "adjuvant chemotherapy."
2. Additive antitumor effects — independent tumor cell kill in excess of that achieved by either modality alone, different mechanisms affecting the same tissue; toxicities of the two modalities must not overlap to a degree requiring significant dose reduction in either radiation therapy or chemotherapy.
3. Enhancement of tumor response — "true interaction," resulting in a combined antitumor effect greater than would be achieved by simple addition of the tumor cell kill of each modality if used separately.
4. Protection of normal tissues — use of drugs to protect against irradiation effects on normal tissues with little or no similar protection against tumor cell kill.

It is difficult to prove true radiosensitization when combining cytotoxic drugs with irradiation; increased radiation cell kill per dose level is more easily identified as an effect of chemical agents that cannot destroy tumor cells themselves (e.g., hypoxic-cell sensitizers).

Spatial cooperation is readily apparent in pediatric oncology, best typified by irradiation of sanctuaries in acute lymphoblastic leukemia and by combined-modality therapy for apparently localized or metastatic presentations, including Wilms tumor, Ewing's sarcoma, and rhabdomyosarcoma. Additive effects are also apparent in the latter group of solid tumors, both radiation therapy and chemotherapy reducing the local clonogenie tumor-cell population. There is a variable degree of chemotherapy-induced enhancement of radiation damage to normal tissues. Improvement of the therapeutic ratio by additive local interactions may be limited by overlapping toxicities, necessitating dose reductions or interruption depending on the target tissues, the agent(s) used, and the time between chemotherapy and irradiation.

Several mechanisms explain the potential enhancing interactions of chemotherapy combined with irradiation. In-creased slope of the radiation dose-response curve (the classic definition of "radiosensitization") has been noted with DNA intercalating agents such as dactinomycin and cisplatin. Dactinomycin also typically inhibits repair of subletbal damage, enhancing tumor and normal tissue effects equally during fractionated irradiation.

Adriamycin has similar clinical interactions; in the laboratory, it seems to affect predominately the accumulation of sublethal damage rather than its repair.

Chemotherapy-induced alterations in cell kinetics may produce synchronization toward the more radiation-sensitive phases of the cell cycle; hydroxyurea has most often been used in this manner, although a differential effect between tumor and normal tissue has not been confirmed. Preirradiation tumor reduction has potential effects beyond additive clonogenic cell kill, decreasing the hypoxic cell fraction and recruiting intermitotic cells into the more sensitive proliferative phase along with the reduction in tumor volume.

Protection of normal tissue has been described following time-dependent preirradiation administration of cytarabine, ciclophosphamide, or methotrexate. Laboratory evidence of bone-marrow sparing in this setting has been difficult to confirm in the clinic.

To enhance the therapeutic ratio, combinations of radiation therapy and chemotherapy must potentiate antitumor effects selectively with quantitatively less increase in normal tissue effects. It has been difficult, for example, to show an improved therapeutic ratio with dactinomycin or Adriamycin, the noted sensitization being shared equally by normal tissues and tumors. Increased normal tissue reactions have been quantified in the laboratory, Phillips and Fu defining the dose-effect factor (DEF) as the radiation dose divided by the radiation dose in the presence of drug to produce the same biological effect. Normal tissue interactions may be site specific (.e.g., increased bladder toxicity with cyclophosphamide and irradiation, methotrexate-irradiation interactions in the central nervous system). Additive normal-tissue effects may be

secondary to similar effects on the target tissue (e.g., bleomycin and irradiation effects on lung) or different tissue changes affecting the same organ (e.g., cardiac effects of Adriamycin on the myocyte and indirect effects of irradiation on cardiac function secondary to vascular changes).