Paparella: Volume IV: Plastic and Reconstructive Surgery and Interrelated Disciplines

Section 2: Disciplines Closely Associated With Otolaryngology

Chapter 31: Radiation Therapy of Head and Neck Cancer

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The Radiation Prescription

Dose, Time, Fractionation

The basic radiation prescription specifies a certain dose to be delivered in a particular number of treatments or fractions over a specific period of time. The biologic efficacy of a given type of radiation is dependent on all three of these dose-time-fractionation factors and not just on the dose.

Dose is simply the amount of energy deposited in tissue per unit mass from the radiation. It is commonly measured in rad: one rad equals one-hundredth of a joule of energy per kilogram of tissue. It must be emphasized that dose itself gives no information on how much of that deposited energy has been translated into actual irreversible cellular damage. This latter biologic effect depends on (1) the dose-time-fractionation scheme employed, as mentioned above; and (2) the typpe of radiation delivered. Simply specifying a total rad dose in describing a course of radiation has little meaning unless the dose per fraction and time interval between fractions are known.

An international commission has recommended that the *rad* as a measure of radiation dose be replaced with a new unit called the *gray*: 1 gray equals 1 joule per kilogram; a gray (Gy) thus equals 100 rad; 1 centigray (cGy) is the same as 1 rad. The remainder of this chapter will refer to radiation doses in centigray (cGy).

Conventional Fractionation

For most curative radiation treatments, a standard fractionation scheme has evolved, known as conventional fractionation, which consists of giving 180 to 200 cGy per fraction, five fractions per week, each fraction separated by about 1 day. Radiation doses consequently are sometimes quoted and compared with the presumption that the time-fractionation portion of the prescription is conventional fractionation.

Other Fractionation Schemes

In additional to "conventional fractionation", other fractionation regimens have been used or are under active investigation. A classification of fractionation schemes is given in Table 1.

Schemes in which the dose per fraction is increased are used in palliation of advanced disease in order to either (1) shorten the overall treatment time or (2) decrease the number of trips the patient must make to the radiation therapy department each week. In

hypofractionation, the dose per fraction is increased over the 180 to 200 cGy given with conventional fractionation, and the time between fractionations is the same as in conventional fractionation. This allows a shorter overall time of treatment to achieve a given biologic effect. In rapid fractionation, the dose per fraction is increased, and the time between fractions is also increased. Although the overal length of treatment may be the same as in conventional fractionation, the total number of treatments and trips to the radiation therapy department is increased.

Table 1. Classification of Radiation Time Fractionation Regimens

Classification	**Fraction(s)**			**Time Compared**
	Size (cGy)	**Per Day**	**Per Week**	**"Conventional"**
1. "Conventional"	180-200	1	5	-
2. Hypofractionation	> 250	1	1-4	Varies
3. Rapid fractionation	> 250	1	5	Shorter
4. Hyperfractionation	100-125	2-3*	10-15	Same
5. Accelerated	180-200	2-3*	10-15	Shorter
6. Accelerated hyperfractionation	125-180	2-3*	10-15	Shorter

* Each fraction separated by 4 to 6 hours.

The problem with hypofractionation and rapid fractionation is the increasing evidence that the late or chronic side effects of radiation are proportional to the fraction size employed. Large fraction sizes thus are probably only appropriate in the treatment of patients whose remaining life span is not expected to be long enough to manifest late radiation damage.

The evidence that the size of the daily fraction determines to a significant degree the late or chronic radiation effects has spurred attempts to develop a fractionation scheme using less than the conventional dose per fraction; fractions as low as 100 or 120 cGy have been proposed. Use of such small fractions, with each fraction separated by a day as in conventional fractionation, excessively prolongs treatment and allows unacceptable repopulation of tumor cells; however, the use of such small fractions with multiple fractions given per day separed by 4 to 6 hours is under investigation.

Hyperfractionation refers to the use of small fraction sizes given two to three times daily, with the overall treatment time the same as in conventional radiation therapy. Accelerated hyperfractionation refers to the use of small fraction sizes given two to three times daily, with the overall treatment shortened. To shorten the overall treatment time, the fraction sizes must be a little larger than 100 to 120 cGy; 160 cGy is typical. Accelerated hyperfractionation may be considered a hybrid of hyperfractionation and what is called accelerated fractionation, which is the use of conventional fraction sizes given with a shortened interval between fractions, ie, with multiple fractions per day.

Continuous Low-Dose Rate Radiation

The logical extreme in decreasing the dose per fraction and the time interval between fractions is continuous low-dose rate radiation, as occurs from radioactive implants. Because

of its unique dose-time-fractionation, the dose delivered from a radioactive implant cannot be compared with the same dose delivered externaly using any of the fractionation schemes described above.

In addition, the doses delivered from two radioactive implants are theoretically not biologically equivalent if the implants delivered dose to the tumor at different dose rates. In practice, it is believed that dose rates of 30 to 100 cGy per hour are roughly biologically equivalent. Most radioactive implants are planned so that the tumor dose rate is 40 to 50 cGy per hour.

Clinical Modalities of Radiation

Radiation modalities may be divided, for purposes of discussion, into (1) external radiation, or teletherapy; and (2) mold, interstitial, and intracavitary radiation, or brachytherapy.

Teletherapy

Two types of teletherapy radiation beams are commonly used in clinical radiation therapy: (1) x-rays or photon beams and (2) electron beams.

X-Ray Beams

The most common x-rays or photons used today for therapy are the x-rays of average energy 1.25 million electron volts (MeV) from cobalt-60 machines, and the 4 to 25 million volt (MV)) x-rays or photon beams from linear accelerators, betatrons, or microtrons.

X-rays or photons of these energies are referred to as being in the megavoltage range as opposed to the superficial and orthovoltage x-rays used in earlier eras (Table 2). In addition, when it is clear that only megavoltage beams are being discussed (the usual context in any contemporary discussion), it is informally common to subdivide the megavoltage energy range into three regions, with beams of 1.2 MeV to 6 MV referred to as of low energy and beams of greater than 15 MV as of high energy.

Table 2. Classification of Photon Beams by Energy

Classification	**Energy**
1. Superficial x-rays	0.05-0.15 MeV
2. Orthovoltage x-rays	0.2-0.4 MeV
3. Supervoltage x-rays	0.4-1 MeV
4. Megavoltage x-rays	1-40 MeV

There are two major advantages in using x-ray or photon beams in the megavoltage energy range. The first is the skin-sparing effect of megavoltage beams. The energy deposited per volume (dose) by megavoltage photon beams is not maximal at the surface, but builds up gradually to a maximum below the skin surface. The region from the skin to the depth at which the maximal dose is delivered is known as the buildup region. The dose at the

surface of the skin is usually only 25 to 30 per cent of the maximal dose; thus, the skin is significantly spared the high doses given to the tumor. The old superficial photon beams, in contrast, delivered their maximal dose at the surface, which frequently resulted in severe skin reactions in the attempt to deliver an adequate dose at the tumor's depth.

Second, the amount of energy deposited per unit volume by megavoltate beams i only very weakly related to the meadn atomic number of the tissue. As a result, the dose in a body tissue of relatively high mean atomic number, eg, bone, is not significantly different from the dose in such relatively low mean atomic number tissue as fat and muscle soft tissue. In contrast, the older superficial x-ray beams delivered a higher dose to bone than to soft tissue, resulting in an increased incidence of bone complications.

Figure 1 depicts graphically how the dose of radiation given varies with depth for photon beams of different energies. Three effects should be noted in particular: (1) the skin-sparing effect of all megavoltage beams, (2)) how the deppth of the buildup region increases with the energy of the megavoltage beam, and (3) how the decline in dose with depth or dose fall-off beyond the buildup region is more gradual, the higher the beam energy. The utility of high-energy megavoltage photon beams, because of their greater buildup region and more gradual fall-off, lies in the treatment of relatively deep tumors. Figure 2 shows a profile of the percentage of the tumor dose delivered across a 25-cm diameter patient treated with two opposing photon beams, such as 25 MV, offer a significant reduction in the dose to the superficial tissues over the low-energy megavoltage beams such as cobalt-60 for the same delivered tumor dose.

Figure 1. Profile with depth of the dose delivered from a single photon beam for various energies of the photon beam. The dose is shown as a percentage of the maximal dose given. The curve labeled 3.0 mm CuHVL is a superficial x-ray beam; its lack of any skin-sparing effect should be noted. The remaining photon beams shown are of megavoltage energies. Notice for the megavoltage beams that (1) the size of the buildup region increases as beam energy increases and (2) the rapidity of the decline in dose beyond the buildup region is less as the energy of the beam increases.

Electron Beams

In addition to photon beams, electron beams of energies ranging from 3 to 25 million electron volts (MeV) are now a standard part of the armamentarium in many radiation therapy departments. The major advantage of using electron beams is their limited penetration into tissues. The actual depth of penetration is dependent on the energy of the beam. A typical accelerator is capable of producing electron beams of several different energies. A particular energy may be chosen to treat a desired depth in tissue; beyond the chosen depth the dose given falls off rather abruptly over just a few centimeters to only 5 to 20 per cent of the maximal dose. This is in marked contrast to the penetration of photon beams where the decline in dose is gradual, typically only 3.5 to 5 per cent per centimeter.

Figure 2. Profile with depth of the dose delivered from two opposed photon beams to a 25-cm thick patient for various energies of the photon beams. The dose is shown as a percentage of the tumor dose given. These "low energy" (1 MV to 6 MV) megavoltage beams as opposed to "high energy" (above 15 MV) megavoltage beams requires giving the subcutaneous tissues a much higher dose.

Figure 3 depicts graphically how the dose of radiation given varies with depth for electron beams of different energies. These graphs also show the major potential disadvantage of electrons as sole modality of treatment: there is little skin sparing.

Figure 3. Profile with depth of the dose delivered from a single electron beam for various energies of the electron beam. The dose is shown as a percentage of the maximal dose given. From left to right the electron beam energies shown are 6, 9, 12, 15, and 18 MeV. Notice first that there is very little skin-sparing effect compared with what is seen with photon beams. The little skin-sparing effect that is present is greater for the lower energy electron beams. As the beam energy increases, the degree of skin sparing decreases: exactly the opposite of the trend seen with photon beams! Second, notice that the drop-off in dose after the peak is reached, although dramatic for all the beams, is most dramatic for the lowest energy beam and least dramatic for the highest energy beam.

A major utility of electron beams in the therapy of head and neck cancer is sparing oof the spinal cord during treatment of neck nodes lateral to the cord.

Cobalt Machines

The first machine capable of producing a megavoltage photon beam was the cobalt-60 machine. Cobalt machines are mechanically quite simple and consequently very reliable. They basically consist of a very intense radioactive cobalt-60 source surrounded by shielding. When the machine is "on", the shielding between the source and the patient is removed; when iit is "off", the shielding is restored. When the machine is on, the patient is exposed to the photons that naturally emanate from the radioactive cobalt-60 source. The photons are of two exact energies: 1.17 and 1.33 MeV.

The dose-profile curve with depth for the cobalt-60 beam has advantages for the relativelly thin portions of the body, such as the head, particularly when areas of risk are relatively close to but not at the surface of the skin, such as nodal chains.

Linear Accelerators, Betatrons, and Microtrons

Linear accelerators, betatrons, and microtrons are similar in that they all accelerate electrons to very high energies. They differ only in their method of acceleration. In all machines, the high-energy electrons are then directed onto a metallic target. When the high-energy electrons interact with the atoms of the target, a spectrum of photons of different energies is produced. This photon beam is then in turn directed at the patient after some filtering.

The energies of photons produced by the interaction with the target are less than or equal to, but never greater than, the energy of the electron beam directed at the target. It is this maximal photon energy that is quoted when the energy of the photon beam is described. The 25-MV photon beam of a linear accelerator, for example, consists of a spectrum of photons of maximal energy 25 MeV. The designation MV is used after the 25 rather than MeV to emphasize that this beam is actually a spectrum of different energies, the maximal energy being 25 MeV. A rule of thumb is that the energy of the most frequent or common photon in the spectrum of photons produced is approximately one-third the maximal energy.

The most frequent or common energy photon, for example, in the spectrum of photons in a 4 MV photon beam from a linear accelerator is about 4/3 or 1.33 MeV - nearly identical to the energies of the "pure" photons produced by cobalt-60.

The electron beam produced by linear accelerators, betatrons, and microtrons can also be used directly for therapy by removing the metallic target. Most commonly, the electron beam is instead directed through a very thin metallic foil (scattering foil) to spread it out (transmission electron beam) before directing it at the patient. The scattering foil is too thin to cause significant photon production. Less commonly, some machines directly scan the thin electron beam (scanning electron beam) up and down and across the treatment area on the patient, in a matter analogous to the way phosphors are excited on a cathode-ray tube by an electron beam scanning up and down and across the area of the tube.

Linear accelerators, betatrons, and microtrons are very complex machines that require frequent maintenance and recalibration. Nevertheless, they are indispensable because of their ability to produce electron beams and high-energy megavoltage photon beams with dosimetric advantages over the low-energy megavoltage photons produced by cobalt-60.

When these machines are used to treat cancers of the head and neck, a relatively low-energy megavoltage photon beam is chosen (4 to 6 MV), at least initially, in order to adequately treat nodal chains and well-lateralized primaries that might be undertreated in the buildup region of a high-energy megavoltage photon beam (18 MV and above). A 4-MV photon beam has a dose profile with a depth very similar to that of a cobalt-60 photon beam; a 6-MV photon beam has a dose profile only slightly more penetrating.

There is thus no major advantage in the dose profile with depth of such a low-energy megavoltage photon beam from a linear accelerator (4 to 6 MV) over a cobalt-60. The advantage of using such a low-energy megavoltage photon beam from an accelerator are rather (1) the much improved sharpness at the edges of the accelerator-produced beam and (2) the increased rate of dose delivery from a linear accelerator, allowing shorter treatment times and hence less risk of error from patient movement. The relative fuzziness of the edge of a cobalt-60 beam is a geometric effect due to the finite size of the cobalt-60 source. The cobalt-60 source could be made smaller and more "pointlike", reducing the geometric penumbra, but only at the expense of decreasing the rate of dose delivery and prolonging treatment times.

Brachytherapy

Radiation from radioactive materials has also been used in the treatment of tumors, either (1) as a plaque or mold containing radioactive materials applied directly on top of the tumor, (2) as radioactive needles, wires, or ribbons of radioactive seeds inserted into the substance of the tumor (interstitial implant), or (3) as radioactive sources placed within a hollow body cavity next to the tumor (intracavitary implant). Usually the high-energy photons emitted from the radioactive materials (such photons are often called gamma rays) are what treats the tumor. Less commonly the therapeutic efficacy of the radioactive material is derived from electrons emitted from the material (often referred to as beta rays). Commonly used radioactive materials, and the energies of the photons or electrons they emit, are listed in Table 3.

Table 3. Common Radioactive Materials Used in Radiation Therapy

Materials Used Because of Their Photon Emission (gamma rays)

Atomic Number	Element-Atomic Weight	Half-life	Energy of Emitted Photon
27	Cobalt-60	5.26 yrs	1.17 MeV, 1.33 MeV
53	Iodine-25	60.2 days	0.027-0.035 MeV (0.028)
55	Cesium-137	30 yrs	0.662 MeV
73	Tantalum-182	115 days	0.07-1.2 MeV (0.59)
77	Iridium-192	74.2 days	0.136-1.06 MeV (0.38)
79	Gold-198	2.7 days	0.412 MeV
88	Radium-226	1622 yrs	0.47-2.45 MeV (0.83)

Materials Used Because of Their Electron Emission (beta rays)

15	Phosphorus-32	14.3 days	0.698 MeV
38	Strotium-90	28 yrs	1.10 MeV
53	Iodine-131	8.04 days	0.19 MeV

Sciences Underlying Clinical Radiation Therapy

It is beyond the scope of this chapter to give a complete review of the basic sciences underlying radiation therapy, but some introduction is necessary (1) to understand such currently clinically relevant matters as the reason for the advantages of megavoltage beams, radiation protection measures, and the rationale behind the dose-time-fractionations schemes employed; and (2) to place in perspective other modalities of radiation such as neutrons, protons, negative pi mesons, the new dose-time-fractions, and radiation sensitizers, all currently under investigation.

The ways in which radiation interacts with tumor and normal tissue may be considered on three levels, each corresponding to a separate basic radiation science: (1) the atomic level - radiation physics; (2) the molecular level - radiation chemistry and biochemistry; and (3) the cellular level - radiation biology.

Radiation Physics

Fundamental Particles

At the present time, six fundamental types of particles are thought to exist in the univers: (1) leptons, (2) quarks, (3) gravitons, (4) photons, (5) weakons, and (6) gluons. The first two types are called fermions and are the fundamental constituents of matter. The remaining four are called bosons and respectively mediate the four fundamental forces of nature: (1) gravity, (2) the electromagnetic force, (3) the "weak" force, and (4) the "strong" force.

The term "particles" may be set in quotes because it is a concept based on our experience with the macroscopic world, and these subatomic "particles" frequently have properties not completely consistent with our intuition of how a particle should act. None of these particles have a size, for example; they behave as true geometric points.

Photons are boson particles that mediate the electromagnetic force. In classical physics a beam of photons is called electromagnetic radiation. When the photons in the beam have energies in the range 4×10^{-11} eV to 40 eV, they have properties reminiscent of waves in the macroscopic world, and hence the frequent use of the terms light waves, radio waves, and microwaves to describe the photon beams of such energies. When the photons have energies in the x-ray range (4 keV and above), the properties reminiscent of waves are relatively unimportant and they behave more like classical particles.

The electron is the most common example of a lepton (from the Greek for the "light ones"). An electron is a particle with a mass of 0.000548 atomic mass units and an electric charge of -1. Electrons are the particles composing the atomic shells of atoms and molecules.

Quarks exist only in groups that manifest themselves as larger subatomic particles. A group of three quarks forms a type of subatomic particle called a baryon (from the Greek for "the heavy ones"). The most common examples of baryons are the proton (mass 1.00727 atomic mass units and electric charge +1) and the neutron (mass 1.0086 atomic mass units and electric charge 0), which compose the nuclei of atoms. A group of two quarks forms a type of subatomic particle called a meson (from the Greek for "the intermediate ones").

Radiation beams of present and future clinical interest may be considered in two categories: (1) beams that deposit their dose and hence cause biologic damage via electrons and (2) beams that deposit their dose and hence cause biologic damage via heavier charged particles such as protons and alpha particles (a cluster of two neutrons and two protons) as well as electrons.

This is a clinically significant distinction, because the efficiency of translating the same dose into biologic damage is quite different for each of the two categories. Beams of the second category usually cause much greater biologic damage for the same dose.

Beams That Deposit Dose Via Electrons

All radiation beams used routinely in radiation therapy fall into this category. Electron beams directly deposit dose in tissue through the electrons; photon beams of x-ray energies produce electrons in the tissues, which in turn deposit their dose in the tissue.

Electron Beams

Electrons have a limited range in tissue before they lose their energy and are captured by an atom. This range is dependent on the electron energy. They are also very light and are easily scattered in many directions when they interact in tissue.

The net result of these two effects is that a beam of electrons entering tissue deposits a relatively uniform dose for about two-thirds of a typical electron range; the dose then rapidly decreases. Beyond the maximal depth of electron penetration the dose deposited is due only

to photons contaminating the beam, about 1 to 20 per cent of the maximal dose, depending on the electron energy and machine design.

A useful rule of thumb is that the depth in centimeters at which the dose deposited by an electron beam begins its decline is equal to the energy of the electron beam in MeV divided by three; the depth in centimeters at which the dose has fallen to only 10 to 20 per cent of the maximal dose is equal to the energy of the electron beam in MeV divided by two. Thus, for example, the use of a 9-MeV electron beam (the dose profile with depth starting its rapid decline after nine divided by three, or 3 cm) to treat the lobe of the parotid is obviously inadequate.

Photon Beams

The number of photons in a photon beam declines gradually within tissue by a relatively constant percentage per centimeter. Electrons are produced by the interactions of the photons with the tissue atoms along the way, and these electrons deposit the dose and cause the biologic damage, not the photon itself. Like the electrons in a pure electron beam, the electrons produced have only a very limited range. However, since electrons are produced by photons throughout their path through the tissue in proportion to the number of photons, the total dose profile of a photon beam also appears to decrease gradually by a constant percentage per centimeter.

As previously noted, the portion of the dose profile between the surface of the patient and the depth at which the maximal dose is deposited is called the buildup region. The depth at which the maximal dose is deposited, and hence the size of the buildup region, varies from 0.5 cm for a cobalt-60 beam to 1.5 cm for a 6-MV beam to 3 to 5 cm for 18- to 25-MV beams. The presence of this buildup region with megavoltage beams is what allows the skin and superficial tissues to be relatively spared from the high doses given at the depth of the tumor. The reason for the presence of this buildup region can be considered a side effect of the fundamental atomic mechanisms by which megavoltage energy photons interact with the atoms in the tissues to produce electrons. For megavoltage photons, two such mechanisms are important: (1) Compton scattering and (2) pair production absorption. In both of these mechanisms, most of the electrons produced are ejected in the forward direction, ie, in the same direction that the entering photons are traveling. Most of the dose deposition from the electrons consequently occurs in front or forward of the region where the photons interacted to produce the electrons. At the surface skin, where there have been no previous interactions, the dose is low, and then builds up, sparing the skin surface.

Beams That Deposit Dose Via Heavy Charged Particles

Heavy particle beams (protons, neutrons, negative pi meson beams) are available only at very specialized radiotherapy centers and are still investigational.

Heavy Charged Particle Beams

Like electrons, heavy *charged* particles such as protons or negative pi mesons have a limited range in tissue before they lose their energy and are captured by an atom. Like electrons, these are dependent on their energy. In contrast to electrons, they are quite heavy and are not easily scattered once they are in tissue.

The result of these two effects is that heavy charged particles tend to plow straight ahead through tissue until just the end of their range, when they give up energy in a rapid series of ionizations. This results in a dramatic deposition of dose over a very small range, with little dose deposition either before or after. This dramatic peak of dose deposition is called the Bragg peak and theoretically allows radiation dose to be deposited with nearly pinpoint precision that could potentially rival the precision of a surgeon.

Neutron Beams

Just as the dose from a photon beam is actually deposited by the electrons formed throguh the interaction of the photons with tissue, the dose from a neutron beam is actually deposited by heavy charged particles formed through the interaction of the neutrons with tissue.

Like photons, the number of neutrons in a neutron beam within tissue also declines gradually by a relatively constant percentage per centimeter. Heavy charged particles such as protons, alpha particles as well as electrons, are produced by interactions with atoms along the way, and these charged particles deposit the dose and cause the biologic damage, not the neutron itself.

Like the heavy charged particles in a pure heavy charged particle beam, the heavy charged particles produced have only a very limited range. However, since the heavy charged particles are produced by neutrons throughout their path through the tissue in proportion to the number of neutrons, the total dose profile of a neutron beam also appears to decrease gradually by a relatively constant percentage per centimeter.

Exact details of neutron dose profiles depend on the mechanisms by which neutrons interact with atoms to produce heavy charged particles, a discussion beyond the scope of this chapter.

Potential of Heavy Charged Particle Beams and Neutron Beams

The heavy charged particle beams and neutron beams have two potential advantages over the conventional electron and photon beams: (1) a possible *biologic* advantage due to the fact that the physical mediators of radiation damage are completely different from the mediator of conventional radiation - the electron, and (2) a *dosimetric* advantage from the Bragg peak seen with pure heavy charged particle beams.

While heavy particles beams typically cause three to ten times more biologic damage for the same dose deposited than conventional x-ray or electon beams, the gain in therapeutic ratio between tumor and normal tissue now appears to be minimal. Neutron beam trials continue in an attempt to define subgroups of patients who may be benefited.

The dosimetric advantage is real but remains unexploited oweing to the present high cost of heavy charged particle accelerators and the technical problem of producing beams of one energy. Only two heavy charged particle accelerators are available for clinical use in the USA. Neutron beams, of course, do not manifest a Bragg peak for reasons explained above,

and have no dosimetric advantages; in fact, they usually have dose profiles with depth no better than a cobalt-60 photon beam.

Radiation Chemistry

Radiation can damage molecules of all types within the cell, but damage to the DNA molecule is responsible for the cellular injury that ultimately leads to cell death.

Beams That Deposit Dose Via Electrons

Beams that deposit their dose via electrons tend to do a relatively small amount of *direct* damage to the most sensitive biologic molecule - DNA, and cause most of their damage *indirectly* through the formation of reactive chemical species, which in turn attack the DNA molecule. A second characteristic of such beams is that the damage is relatively sparse and widely spaced, so that the damage done to a given DNA molecule usually consists of only one or two injuries.

These characteristics have two important consequences: (1) because much of the damage is mediated through reactive chemical species (radicals), changes in cellular environment that modify or interfere with the reactivity of these chemical species also modify the degree of radiation damage; (2) because a given DNA molecule often suffers only a single injury, the damage can frequently be repaired by cellular enzymes.

One of the most important changes in the cellular environment of concern is the presence or relative abscence of oxygen. Oxygen is believed to combine with some of the reactive chemical species to form more toxic and longer-lasting species that attack the DNA molecule. Oxygen also combines with the damaged DNA and makes repair of the damage more difficult. The lack of oxygen in irradiated cells consequently results in less toxic chemical species and less damage to the DNA; the DNA that is damaged is more easily repaired. Hypoxic cells are relatively resistant to radiation damage compared with well-oxygenated cells.

Beams That Deposit Dose Via Heavy Charged Particles

In contrast, beams that deposit their dose via heavy charged particles tend to cause most of their damage to the DNA *directly.* A second contracting characteristic is that when a DNA molecule is damaged, the injuries sustained are usually overwhelming. This is because of the high linear energy transfer (high LET) of such radiation alluded to earlier; heavy charged particles tend to rapidly deposit most of their energy at the end of their range over a very small space.

The consequences of these two characteristics are that (1) cellular environmental factors, and lack of oxygen in particular, do not significantly affect the degree of radiation damage produced; and (2) when damage occurs it often is not reparable.

The Problem of Hypoxic Tumor Cells

As noted above, hypoxic cells are relatively resistant to photons and electrons. Unfortunately, tumors tend to have components that are relatively hypoxic, and the presence

of this subpopulation of hypoxic tumor cells has been of great concern in clinical radiation therapy, for it appears to give a preferential advantage to the tumor cell population over normal cell populations in resisting radiation damage.

Fractionation of the radiation may minimize this problem by allowing tumor cells in a hypoxic region of the tumor to become reoxygenated after the preferential killing and removal of oxygenated cells has decreased the distance of the hypoxic cells from the vascular supply (this reoxygenation is discussed further in the next section); however, some advantage for tumor cells to survive radiation may still remain.

Efforts in the past to further minimize this problem have included putting normal and tumor cells on an equal footing by making all cells hypoxic (a tourniquet was applied to the extremity before radiation of an extremity sarcoma), and by trying to directly increase the oxygenation of tumor cells by 100 per cent oxygen breathing during treatment both at normal air pressure and under hyperbaric conditions.

The absence of the problem of relative radioresistance of hypoxic tumor cells when neutrons or heavy particles beams are used was one of the important motivations to pursue research on treatment with these beams.

There are continuing trials of the so-called electron affinic radiation sensitizers such as misonidazole and SR-2508 combined with x-ray or electron radiation. Such electron affinic sensitizers are known to act like oxygen in stabilizing the reactive chemical species that cause the radiation damage to DNA. The major limiting factor with these compounds has been the development of neurotoxicity before a therapeutic concentration of the sensitizer is reached.

Radiation Biology

The explanation of why radiation damages tumors in preference to normal tissues - the favorable therapeutic ratio of radiation - lies not in the radiation physics of dose deposition or the radiation chemistry of DNA damage, but in differences in the biology of irradiated cells and tissues.

The therapeutic ratio in radiation therapy is based on relative differences between normal cells and cancerous cells in the so-called "four R's" following radiation treatment: (1) the ability of a single cell to *repair* radiation damage; (2) the relative proportions of cells within the stages of the cell cycle (M, G1, S, G2): *redistribution;* (3) the absolute number of cells as cells divide to replace cells destroyed by the previous radiation: *repopulation;* and (4) *reoxygenation* of cells previously in hypoxic areas as oxygenated cells are preferentially destroyed, allowing improved oxygen diffusion because of the decreased distance of previously hypoxic cells from capillary beds.

Repair

If a graph is made of the proportion of tumor cells that survive a single dose of x-ray radiation versus the magnitude of the dose given ("cell survival curve"), a curve qualitatively similar to that in the Figure 5 is seen.

Figure 5. Cell survival curve. The curve labeled sparsely ionizing radiation is a curve typical for beams that deposit their dose via electrons, ie, the standard photon and electron beams used in radiation therapy today. The rounded section in the upper left corner of the sparsley ionizing radiation curve is called the shoulder. Two measures of the width or size of the shoulder are shown: the extrapolation number n, and D_q, the quastithreshold dose. The shoulder is believed to be a measure of the ability of a cell to repair some of the "sparsley distributed" radiation damage cause by proton or electron radiation beam. Beyond the shoulder region, the relation between cell death and dose given is linear, and may be measured by D_o as shown on the graph. The curve for densely ionizing radiation is a curve typical for beams that deposit their dose via protons and other heavy charged particles. These beams are clinically used today only in an investigational setting. Notice that this curve lacks a shoulder; the radiation damage done by these beams to a sincle cell is usually too overwhelming to be repaired.

The early part of the curve where the surviving fraction does not seem to vary much with an increase in dose is known as the shoulder, and quantitatively is measured by the D_q as defined on the graph. This shoulder is believed to represent dose levels at which the radiation damage can be considered sublethal and can be repaired if time is allowed.

Tumor cells are thought to have an intrinsically poorer repair capacity than normal tissue cells. In addition, hypoxic cells appear to have a poorer repair capacity than well-oxygenated cells. Fractionated radiation exploits this advantage of normal cells over tumor cells by allowing sufficient time between radiation fractions for normal cells to repair the sublethal radiation damage.

As mentioned under the discussion of radiation chemistry, heavy particle radiation tends to cause radiation damage that cannot be repaired. Survival curves of tumor cells irradiated with heavy particle radiation such as neutrons consequently show little if any shoulder region; the advantage of the normal cell's increased capacity for sublethal damage disappears.

Redistribution

The life of a proliferating cell is described by the cell cycle, which consists of four phases. The S phase refers to the DNA synthetic phase during which the DNA content of a cell doubles in preparation for mitosis. Before and after the S phase are gaps of apparent inactivity denoted G1 and G2 phase, respectively. The time it takes to cycle once through the cell cycle is the cell cycle time.

The relative radiosensitivity of a proliferating cell varies with its position in the cell cycle. Cells in the M, G1, and late G2 phases are relatively radioresistant. After a fraction of radiation, there is preferential killing of cells in the more sensitive phases of the cell cycle, leaving a greater proportion of surviving cells in the resistant phases. After a fraction of radiation, these surviving cells continue cycling through the cell cycle. If the next fraction of radiation could be given so that normal cells had cycled past the sensitive phases of the cell cycle back to the more resistant phases of the cell cycle, whereas the tumor cells had only cycled into the sensitive phases of the cell cycle, the relative differences in radiosensitivity of phases of the cell cycle could be exploited to increase the therapeutic ratio.

In practice, knowledge of the cell cycle times in tumor and normal cells is inadequate to permit such planning. In addition, most tumors appear to consist of several clones of cell lines, each with different cell cycle times.

Repopulation

The damage to cells and subsequent cellular loss caused by radiation is a stimulus to the remaining cells to proliferate. The repopulation occurs mainly through (1) recruitment of nondividing cells into the population of proliferating cells to increase the numbers and proportions of dividing cells and (2) a speeding up of the cell cycle time to shorten the time between cell divisions.

When damage occurs in normal tissues, an accelerated repopulation of surviving cells occurs, probably stimulated by homeostatic mechanisms of the host. On the other hand, tumor cells are not stimulated by such a mechanism, thus normal tissues are healed much more quickly.

Reoxygenation

As discussed in the section on radiation chemistry, the presence of oxygen is important in stablizing reactive chemical species that mediate radiation damage from x-rays or electrons. When oxygen is not present, the radiation damage is less; cells that are relatively hypoxic are thus relatively radioresistant.

This effect would tend to favor tumor cells, since they are more likely to have hypoxic components. However, fractionated radiation attempts to minimize this advantage by allowing reoxygenation of the hypoxic cell fractions to occur between treatments.

Combinations of Radiation and Surgery

Classification

The combination of radiation and surgery will be discussed as (1) preoperative radiation, (2) postoperative radiation, and (3) a special form of preoperative radiation in which response to a radiation "trial" is used to select patients to receive surgery or definitive radiation alone.

Preoperative radiation can be classified on the basis of (1) the total dose of preoperative radiation given and (2) the daily fraction size used (Table 4).

Table 4. Combinations of Planned Radiation Therapy and Surgery

I. Preoperative Radiation Therapy

Description	*Total Dose, No of Rx*	*Surgery*
I.1. Low-dose, short-course course	A. Using conventional fractions, eg, 3000 cGy/15 Rx	Radical
	B. Using large fractions, eg, 2000 cGy/5 Rx	Radical
I.2. "Conventional"	5000 cGy/25 Rx (dose sufficient for subclinical disease)	Radical
O.3. "Radical"	6000-7000 cGy/30-35 Rx	Conservative

II. Postoperative Radiation

II.1. "Conventional"	6000 cGy/30 Rx	Radical
II.2. "Lumpectomy" + postoperative RT	6500-7000 cGy/32-39 Rx	Conservative

III. Radiation "Trial" (Using Initial Radiation Response to Select Patients for Full-Course Radiation)

4500-5000 cGy/25 Rx:

III.1. "Conventional" preoperative RT	if < 50-80% response -->	Radical
III.2. Full-course RT	if > 50-80% response -->	None.

To minimize the delay of surgery, two types of short courses of preoperative radiation have been tried: (1) a low total dose given with conventional-sized daily fractions (180 to 200 cGy) and (2) a low total dose given with high daily fraction sizes (400 cGy). These short treatment schemes are generally thought not to be as effective as the use of 5000 cGy conventionally fractionated preoperative radiation.

The most common form of preoperative radiation is the "conventional" 5000 cGy given in conventional daily fractions. This dose level is believed to be adequate to control most areas of occult disease in areas in which the vascular supply has not been compromised by surgery.

Radical doses of preoperative radiation (6600 to 7000 cGy) followed by surgery are the most common form of management of clinical neck nodes, for which surgical resection of persistent residual is performed after full-course radiation.

Postoperative radiation can be classified on the basis of whether the remaining residual is subclinical, microscopic disease or gross disease. A dose of 6000 cGy conventionally fractionated radiation is necessary to control subclinical disease in an area in which the vascular supply has been violated by major surgery. Higher doses are necessary if gross residual is believed to remain. Traditionally, postoperative radiation has been given after radical surgery. Postoperative radiation following very conservative and deliberately limited surgery consisting of only excision of the gross tumor mass, or "lumpectomy", is

becoming a popular form of treatment for early stage breast cancer. Good results have been reported in cancer of the oral cavity.

The response to radiation after 5000 cGy has been used to try to select patients who may do well with full-course radiation alone in situations ni which the indications for combined modality treatment are marginal, particularly those individuals in whom surgery may result in considerable function loss.

Rationale, Advantages, and Indications for Preoperative Versus Postoperative Radiation Therapy

Rationale

A preoperative dose of radiation is usually inadequate to control the primary tumor. The rationale of preoperative radiation is rather to (1) destroy the occult peripheral projections of tumor, thus preventing marginal recurrences; (2) impair the viability of tumor cells in the primary, to decrease the probability that cells dislodged into the vascular system can cause distant metastases; and (3) in the case of an inoperable tumor, to cause sufficient tumor regression to make the tumor operable.

The rationale of postoperative radiation is (1) to destroy occult peripheral projections of tumor left behind after the surgery, to prevengt marginal recurrences; and (2) to treat residual unresectable gross tumor, if any.

Advantages and Disadvantages

A potentially important advantage of preoperative over postoperative radiation is that the tumor cells are in their maximal state of oxygenation, in contrast to the potentially hypoxic conditions that can result when the vascularity has been disrupted by surgery. Postoperative radiation has the advantage that additional diagnostic and prognostic information is available from pathologic examination of the surgical specimen.

The disadvantages of preoperative radiation compared with postoperative radiation are that (1) the exact tumor extent for the surgeon is obscured owing to shrinkage and destruction of the radiosensitive elements of the lesion before surgery, (2) completion of treatment (surgery) to the primary tumor is delayed, and (3) healing after surgery may be delayed and surgical complications may be greater. The disadvantages of postoperative radiation are that (1) the exact tumor extent is obscured for the radiation therapist unless consultation was obtained before surgery, (2) treatment (radiation) to occult disease is delayed, and (3) radiation side effects may be greater.

Indications

The indications for pre- or postoperative radiation may be divided into two classes: (1) site-specific factors and (2) general indications common to all primary sites. Site-specific factors will be discussed individually for each primary site. General indications for preoperative radiation common to all sites are (1) marginally unresectable tumor and (2) invasion of the dermal lymphatics. General indications for postoperative radiation common to all sigtes include (1) close or positive margins, (2) invasion of bone or cartilage, and (3)

certain nodal disease factors, including (a) involvement of multiple nodes (pathologic stage N2b), (b) extension of disease beyond the lymph node capsule, and (c) a node size of 3 cm or greater (pathologic stage N2a or greater).

Data justifying these indications include (1) documentation of the need for some adjuvant treatment because of a high recurrence rate after surgery alone and (2) documentation of the efficacy of radiation to reduce the recurrence rate (Table 5).

Table 5. Local-Regional (TN) Control in Patients Receiving Postoperative Radiation Versus Radiation Dose and Indications for Postoperative Radiation

Indications for Postoperative RT	**Local-Regional (TN) Control Rate**					
	< 5500		**5500-6000**		**> 6000**	
Positive margins	1/2		3/7	43%	7/7	100%
Questionable margins	1/3	33%	3/4	75%	1/1	
Perinodal extension	1/1		3/4	75%	1/1	
Perineural involvement	-		1/2		1/1	
Thyroid cartilage invasion	3/5	60%	4/4	100%	2/2	
Mandible invasion	-		0/2		1/1	
Multiple lymph nodes	0/1		6/8	75%	-	
Total	6/12	50%	20/31	65%	13/13	100%

Positive or Close Margins

Looser and colleagues reviewed disease control at the primary site in patients with epidermoid carcinoma of the oral cavity, pharynx, and larynx treated with surgery alone at Memorial Sloane-Kettering Cancer Center between 1960 and 1970. In patients with stage III and IV disease, they found a control rate of onloy 27 per cent when the margins were unsatisfactory (less than 5 mm or positive with invasive carcinoma or carcinoma in situ). A review of similar patients treated at the same institution with surgery and 6000 cGy postoperative radiation showed a control rate of 90 per cent in patients.

Mantravadi and colleagues, reported on 72 patients with carcinoma of the head and neck treated with surgery and postoperative radiation, found that at 3 years 71 per cent of those with negative margins, and 73 per cent of those with microscopically positive margins, remained free of recurrence.

Marcus and associates found that doses of 6500 cGy resulted in local-regional control in eight of eight patients with positive or questionable margins, whereas doses of less than 6500 cGy controlled only eight of 16 such patients.

Number and Level of Involved Lymph Nodes

There are conflicting data on the relative need for adjuvant radiation after a neck dissection. DeSanto and colleagues reported an analysis of 1192 patients who underwent neck dissections at the Mayo Clinic. The regional (N) control rate in patients receiving surgery alone was 93 per cent for pathologic stage N0, 80 per cent for pathologic stage N1,

and 70 per cent for pathologic stage N2. These relatively high control rates suggest that there is only a marginal indication for postoperative radiation for pathologic stages N1 and N2.

Memorial Sloane-Kettering Cancer Center conducted a randomized trial of low-dose preoperative irradiation and radical neck dissection versus radical neck dissection alone. In the "surgery alone" group, the regional (N) control rate in the dissected neck was only 46 per cent in patients with one or more metastatic nodes in the surgical specimen. When the metastatic nodes were present at multiple *levels* in the neck, the regional (N) control rate was only 29 per cent.

In their study, De Santo and colleagues also attempted to evaluate the efficacy of adjuvant radiation in improving the regional (N) control rate after neck dissection, and could find no improvement in patients with pathologic stages N0, N1, or N2 who received postoperative radiation therapy. However, only 39 per cent of patients (125 of 155) received greater than 5500 cGy, which is still 500 cGy less than the 6000 cGy considered to be an adequate postoperative dose. In addition, 20 per cent of patients were treated more than 6 weeks after surgery (see the section on Interval Between Surgery and Radiation below).

Marcus and associates achieved local-regional control in 75 per cent of patients (six of eight) with multiple neck nodes who received 5500 cGy or more of postoperative radiation.

Extension Beyond Lymph Node Capsule

Cachin studied prognostic factors in patients who underwent radical neck dissections. The most important prognostic factor for survival at 3 years was the presence or absence of rupture of the node capsule.

Johnson and colleagues reported on the significance of the extracapsular extent in 349 radical neck dissection specimens. Extracapsular spread was present in 59 per cent of all patients with histologically positive nodes. Freedom from recurrence at 2 years was 75 per cent in patients with stage III tumors with histologically involved lymph nodes but no extracapsular extent, as opposed to only 39 per cent of patients with extracapsular spread. In patients with stage IV tumors, 67 per cent of those without extracapsular extent, versus 36 per cent with extracapsular extent, were free from recurrence at 2 years. Average time to recurrence was 7.5 months in patients with extracapsular spread versus 17 months in those without. Postoperative radiation appeared to improve control: in the subgroup of patients with extracapsular extension who had received postoperative radiation, the 2-year freedom from recurrence was noted in 49 per cent.

In their study of plus/minus postoperative radiation after radical neck dissection, Bartelink and colleagues found an increased survival rate and regional control in the subgroup of patients with extranodal cancer who received postoperative radiation.

Results with Preoperative Versus Postoperative Radiation By Primary Tumor Site

Advanced tumors of head and neck sites are often treated with planned pre- or postoperative radiation because of a high probability of occult residual disease after surgery alone.

A randomized study of 5000 cGy conventionally fractionated preoperative radiation versus 6000 cGy conventionally fractionated postoperative radiation was conducted by the Radiation Therapy Oncology Group (RTOG). Patients were stratified by sex and T and N staging. The results are shown in Tables 6 and 7. There was no statistically significant difference among the randomized treatment groups in survival. Local-regional (TN) control was statistically better with postoperative radiation than with preoperative radiation in patients with supraglottic laryngeal cancer: 77 per cent versus 53 per cent. A trend of improved local-regional control with postoperative radiation was also present in oral cavity, oropharyngeal, and hypopharyngeal sites, although the differences did not reach statistical significance. Part of the reason for the improved local-regional control rates with postoperative radiation was that fewer patients in that group refused surgery. Complications were approximately the same in each group 8 per cent versus 6 per cent.

Table 6. Four-Year Actuarial Survival in Patients With Head and Neck Cancer Treated With Preoperative Radiation (5000 cGy) Versus Postoperative Radiation (6000 cGY): Results From RTOG 73-03 Randomized Study***

Table 7. Local-Regional (TN) Control in Patients With Head and Neck Cancer Treated With Preoperative Radiation (5000 cGy) Versus Postoperative Radiation (6000 cGy): Results From RTOG 73-03 Randomized Study***

A retrospective study by Hamberger and associates of 116 patients with advanced carcinomas of the oral cavity and oropharynx found no significant difference in local-regional control between preoperative and postoperative radiation.

A prospective study of patients with hypopharyngeal cancer reported by Vandenbrouck and associates compared 5500 cGy preoperative radiation with 5500 cGy postoperative radiation. Results were significantly improved in the postoperative radiation group. The poor results in the preoperative group were in large part related to an increased incidence of complications in that group, perhaps due to (1) the higher preoperative dose used (5500 cGy) and (2) the short delay between radiation and surgery (only 2 weeks).

Use of Early Response to Radiation to Select Patients for Full-Course Radiation Versus Radiation Plus Surgery

Patients who eventually achieve a complete remission from therapy nearly always do better than those who achieve at best a partial remission from therapy. However, whether the rapidity of response correlates with ultimately achieving a complete remission or with local control remains undemonstrated. There are some data on a slightly different end point: the time to a complete response versus ultimate control, which is summarized in Table 8.

Table 8. Time to Complete Remission Versus Local (T) Control in Patients Treated With Radiation Therapy***

Interval Between Surgery and Radiation

Preoperative Radiation

There are two potentially conflicting concerns in determining the optimal interval between preoperative radiation therapy and surgery: (1) the effect of the acute radiation reactions in the tissues on the morbiditiy of the operation and (2) the effect of any time delay between completion of radiation before surgery and surgery in compromising overall tumor control.

There is no evidence to indicate that there is any difference in tumor control within the range of interval durations between preoperative radiation and surgery usually practiced - 2 to 6 weeks. However, there are some data suggesting that shorter intervals may result in increased postoperative complications. A wait of 2 weeks after delivery of 5500 cGy before operating on piriform sinus cancers resulted in excessive rates of postsurgical complications and operative deaths, whereas intervals of 4 to 6 weeks have not been associated with excessive complications.

Postoperative Radiation

There are also two potentially conflicting concerns in determining the optimal interval between surgery and postoperative radiation: (1) the effect of the radiation in delaying healing after surgery and (2) the effect of any time delay after surgery before starting radiation therapy in compromising overall tumor control.

Vikram and Farr and Mantravadi and colleagues reported that a delay beyond 6 weeks in starting radiation after surgery decreases the likelihood of local tumor control.

Integration of Radiation and Surgery in Management of Primary and Nodal Disease

Optimal integration of radiation and surgery to treat the primary and nodal disease can be a complex decision process for which there may be no single or ideal solution. The decision process must involve (1) determination of treatment options for management of the primary disease, (2) determination of treatment options for occult or clinical ipsilateral nodal disease, (3) determination of treatment options for occult or clinical contralateral nodal disease, and finally (4) reconciliation of individual treatment options for the primary and nodal disease into one treatment plan.

Achieving this reconciliation may involve several levels of analysis. First, some common sense guidelines, which do not however take into account some specific limitations of each modality: (1) if a single modality can be used to treat both the primary tumor and the nodal disease, that is the modality of choice to treat the total disease; and (2) if a single modality can be used to treat one component of the disease (primary versus nodal disease), but combined modalities are necessary to treat the other component, treatment should start to both the primary and the neck with that single modality to be used in both components of the disease.

Second, the ways in which radiation and surgery interact in reference to a given tumor site (ie, the relative efficacy of pre- versus postoperative radiation therapy) must be taken into account.

Third, some fundamental differences in the strengths and weaknesses of surgery and radiation therapy must be appreciated so that each can be used wisely. The great strength of radiation therapy is its ability to treat effectively relatively large areas of subclinical disease with very reasonable morbidity; its great weakness is that it can safely be given only once. A wise use of radiation thus takes advantage of its ability to treat large areas of subclinical disease. The threshold probabilities for subclinical disease involvement that justify treatment for a radiation therapist may be lower than those appropriate for a surgeon.

Management of Patients With Neck Disease

The choice of optimal management and the integration of modalities in patients with head and neck cancer is complicated by the frequent clinical or subclinical presence of metastatic tumor from the primary site in cervical lymph nodes.

Selection of patients with Clinical Adenopathy for Treatment with Radiation Therapy

Selection of patients with palpable adenopathy for radiation management of the nodal disease must be based first on (1) the maximal size of the adenopathy and (2) the number of nodes involved. In general, radiation alone achieves satisfactory control if the maximal nodal diameter is 3 cm or less. Patients with multiple nodes or with any nodes larger than 3 cm should probably receive combined treatment (Table 9).

Table 9. Initial Nodal (N) Control of Metastatic Cervical Lymph Nodes by Maximal Nodal Size and Number and Treatment With Radiation With Or Without Surgery***

In some particular tumor sites, notably the nasopharynx and tonsils, neck adenopathy appears more responsive to radiation, and these guidelines can be liberalized.

Selection of Patients with Potential Subclinical Disease in the Neck for Treatment with Radiation

The selection of patients with a clinical stage N0 neck for radiation therapy of *potential* subclinical disease is a more complex issue. Decisions must be made whether to treat just the ipsilateral side or both ipsilateral and contralateral sides.

These decisions may involve assessment of several factors: (1) the risk of occult disease in the ipsilateral and contralateral sides of the neck, (2) the efficacy of elective radiation in preventing a recurrence of disease, (3) the salvage rate for recurrence in patients who do not receive prophylactic treatment, (4) the relative morbidity of elective radiation, and (5) whether the presence of subclinical disease in the neck increases the chances of failure at sites other than the neck, adding to the risk of distant metastases.

Incidence of Occult Disease in the Neck

The incidence of occult disease in the neck may be found from (1) the incidence of pathologic nodal involvement in patients undergoing elective neck dissectin for N0 neck disease and (2) the incidence of nodal recurrence in N0 patients who receive no elective neck treatment. These incidences are discussed later on a site-by-site basis.

Initial Nodal Control Rate With Elective Neck Irradiation

Elective neck irradiation does appear to increase the initial nodal (N) control rate over that expected if no elective treatment is given. Lindberg and Fletcher noted a 99 per cent (77 of 78) nodal control rate in cancers of the supraglottic region treated with radiation versus a 67 per cent (37 of 55) nodal control rate in patients treated with surgery alone. The contralateral nodal (N) control rate increased from 75 per cent (141 of 187) in patients with primary cancer of the oral cavity, oropharynx, larynx, and hypopharynx who received no elective neck irradiation to 97 per cent (181 of 186) in those who received elective neck irradiation.

The subgroup who appear to benefit are those patients in whom the risk of subclinical disease exceeds 20 per cent. At the University of Florida, for sites and stages with an estimated risk greater than 20 per cent of subclinical disease in the neck, 69 per cent of patients (nine of 13) with no elective neck irradiation had initial (N) control, compared with 97 per cent of patients (71 of 73) receiving elective neck irradiation. In contrast, there was no difference in the nodal (N) control rate in patients whose risk of subclinical disease was less than 20 per cent (Table 10).

Table 10. Initial Nodal (N) Control Rate In Patients With Clinical N0 Necks by Degree of Elective Neck Irradiation (ENI) and Estimated Risk of Subclinical Disease***

Survival With Elective Neck Irradiation

Whether the increase in initial nodal (N) control rate ultimately translates into a survival advantage is still unclear. Mendenhall and Million presumed a 67 per cent salvage rate of recurrence in the neck, and estimated that 10 per cent of patients receiving no elective neck irradiation might die of an isolated neck recurrence, but only 2 per cent of those receiving elective neck irradiation.

There is also evidence that can be interpreted to show that clinically silent untreated lymph node metastasis may act as a source of distant metastasis, and that early treatment and control may reduce this danger. Jesse and colleagues found that only 3 per cent of patients with N0 oral cavity lesions who remained N0 developed distant metastasis, while 11 per cent of those who became N+ developed distant metastasis. Northrop and associates found that N1 and N2 patients with primary cancer of the oral tongue, floor of the mouth, or palatine arch whose neck disease was controlled had a 12 per cent incidence of distant metastases, compared with a 24 per cent incidence in those whose disease recurred in the neck.

Summary

A 20 per cent chance of subclinical disease in the neck is generally considered a sufficient reason to give prophylactic neck irradiation in patients whose primary disease is treated with radiation, and can be justified by the increased nodal control rate with elective treatment. Although data are inadequate to demonstrate an increased survival rate, the (1) relatively low morbidity involved in elective neck irradiation, (2) uncertain ability to salvage a recurrence in the neck, and (3) possibility of increased distant metastases in patients who do experience recurrence usually weight the decision on the side ot treating.

Selection of Patients for Radiation Therapy After a Neck Dissection

If the clinical or potentially subclinical nodal disease is treated with neck dissection only, there are pathologic factors over and above the clinical factors in Table 9 that, if present, indicate a combined modality treatment. Adjuvant radiation has been suggested to be of benefit when (1) there are multiple involved lymph nodes, (2) there is invasion through the lymph node capsule into the soft tissue of the neck, and (3) there is invasion of the jugular vein or muscle. This has been discussed earlier.

Radiation Dose for Treatment of Subclinical Disease in the Neck

A dise if 5000 cGy conventionally fractionated radiation is generally accepted as adequate to control 90 per cent of subclinical disease in the neck that has not undergone surgery. In contrast, the dose required in a violated neck in which the vascular supply has been compromised (eg, after a neck dissection) has been shown to be higher, at least 6000 cGy.

Oral Tongue

Selection of Patients for Treatment with Radiation Therapy

Primary

Patients should be selected for radiation therapy to the primary cancer on the basis of (1) tumor size (T stage), (2) growth pattern (exophytic and superficial versus endophytic and infiltrating), (3) location (lateral versus midline or posterior) and (4) extent (whether or not the floor of the mouth is involved).

Radiation alone can give good local (T) control of T1 and exophytic superficial T2 primary cancers. It should thus be the treatment of choice in such lesions if (1) the location is such that the alternative surgical treatment would involve excision of enough tongue to cause unnecessary functional morbidity, or if (2) there is extension to the floor of the mouth, so that the surgery would involve mandibulectomy.

Patients with endophytic T2 tumors and the more advanced T3 primary tumors obtain optimal local control from a combined modailty treatment of the primary disease.

An alternative to treating a patient with radiation alone, with a combination of external beam and radioactive implant, is to perform a limited tumor excision or "lumpectomy" of the gross tumor, followed by radiation alone.

Nodal Disease

Clinical Adenopathy

About 15 per cent of T1 tumors, 30 per cent of T2, 45 per cent of T3, and 75 per cent of T4 present with clinical adenopathy in the neck. Of the patients with adenopathy, 88 per cent have nodes on the ipsilateral side only; the remaining 12 per cent have contralateral nodes.

The guidelines in Table 9 can be used to select radiation therapy for patients with nodal disease.

Subclinical Adenopathy

The incidence of occult node metastases by T stage in the neck clinically graded N0 was reviewed by Teichgraeber and Clairmont. A nonweighted average of their results and seven additional studies they reviewd gives an incidence of about 25 per cent for T1N0 and 40 to 45 per cent for T2N0 and T3N0. Meoz and colleagues reviewed the clinical appearance of neck nodes in patients whose primary tumor had been controlled after interstitial irradiation alone, and found an incidence of 32 per cent of nodal failures in T1 primaries and 43 per cent in T2; 74 per cent of the recurrences were in the high jugular, 19 per cent in the midjugular, and 7 per cent in the submandibular regions.

The high incidence of occult neck disease justifies prophylactic treatment of the neck with radiation in all T stages in any patient also receiving radiation to the primary cancer.

Results of Treatment

Radiation Therapy Alone

Local (T) control for T1 lesions is between 85 and 90 per cent, for T2 lesions between 80 and 85 per cent, and for T3 lesions between 20 and 70 per cent (Table 11). The variations in reported results for T2 lesions, and in particular for T3 lesions, probably reflect the particular importance of the other selection factors besides T stage in the choice of radiation alone to treat these lesions.

Optimal local control in oral tongue lesions treated with radiation alone requres that the tumor area be boosted either with an interstitial implant or through an intraoral cone with electrons or kilovoltage radiation. The tongue is a richly vascular organ capable of tolerating quite high doses of radiation without morbidity.

Table 11. Local (T) Control in Patients With Oral Tongue Cancer Treated With Radiation Therapy Alone***

Freedom from any (T, N, and/or M) relapse was reported by Wang to be 62 per cent for T1N0 and T1N1 tumors, 40 per cent for T2N0 tumors, 32 per cent for T3N0 tumors 15 per cent for T2N1 tumors, and 13 per cent for T3N1 tumors. A rare T4N+ lesion could be controlled with radiation alone (two of 40 patients).

Five-year survival is about 75 to 80 per cent for T1 tumors, about 50 per cent for T2 tumors, and 25 to 30 per cent for T3 tumors (Table 12). These T-stage results primarily reflect the prognosis of N0 stage cases, which are represented by about two-thirds of the patients.

Table 12. Actuarial Five-year Survival in Patients with Oral Tongue Cancer Treated with Radiation Therapy Alone***

Combined Modality

Advanced Disease

It is generally thought that combined modality therapy for the primary cancer improves the results over radiation therapy alone, surgery being reserved for salvage in the large or endophytic T2 primary tumor and T3 primaries. Marks and colleagues compared 46 patients treated with radiation alone and found an overall 46 per cent incidence (21 of 46) of local (T) failures; in contrast, there was a 32 per cent incidence (nine of 28) of local (T) failures in patients treated with preoperative radiation and surgery. For T3 tumors, Horiuchi and associates found local (T) control to increase from 18 per cent with radiation alone to 42 per cent for radiation plus surgery (Table 13).

Table 13. Combined Modality Therapy in Patients With Oral Tongue Cancer***

Early Disease

In early lesions (T1N0, T2N0) of the oral tongue, a limited excision or "lumpectomy" and planned postoperative radiation have provided excellent local (T) control in patients who might otherwise have been treated with resection alone or external radiation and implant. In such a combined approach, the areas of potentially occult disease, usually within the margins encompassed by the more extensive resection required in a "surgery alone" approach, are effectively treated by radiation; the "lumpectomy" effectively substitutes for the radioactive interstitial implant that would be required in a "radiation alone" approach.

Floor of Mouth

Selection of Patients for Treatment with Radiation Therapy

Primary

Factors for selecting patients for radiation treatment to the primary site include the following: (1) size (T stage); (2) the location and extent of the disease relative to the mandible, in particular the presence or absence of fixation to the gingiva; and (3) the growth pattern.

Exophytic T1 and small T2 tumors not abutting the mandible can be controlled with external radiation and an implant. Small tumors adjacent to the mandible are at increased risk of complications from a radioactive implant. They are probably best managed with surgery, or a combination of a conservative surgical "lumpectomy" and postoperative radiation

therapy. Endophytic tumors, because their extent may easily be underestimated, and more advanced tumors (large T2, T3, and T4 primaries) are probably best treated with planned surgery and radiation therapy.

Nodal

Clinical Adenopathy

About 10 per cent of T1, 30 per cent of T2, 45 per cent of T3, and 50 to 55 per cent of T4 tumors present with clinical adenopathy. Of the patients with adenopathy, 92 per cent have involvement on the ipsilateral side only; the remaining 8 per cent have contralateral involvement.

The data in Table 9 can be used to select radiation therapy for the management of patients with nodal disease.

Subclinical Adenopathy

The incidence of occult disease in the N0 neck by T stage was found by Teichgraeber and Clairmont to be about 25 per cent in T1-T2N0 and 50 per cent in T3N0. McColl and Horwood found an overall incidence of 30 per cent for T1-T2N0 tumors. These figures justify prophylactic treatment of the neck in all T stages in patients receiving radiation to the primary disease.

However, there is some controversy regarding these figures. In a series of 126 T1N0 and T2N0 patients treated with radiation alone at Massachusetts General Hospital, Wang found that the total incidence for N only failures in patients who had survived 3 years or more was only 8 per cent, and he did not recommend elective treatment to the neck. The difference between the above results and Wang's figures may be because (1) some of Wang's patients had received partial neck irradiation and (2) TN or NM failures were not considered.

Results of Treatment

Radiation Alone

Local (T) control is achieved in 80 to 90 per cent of T1, 75 to 80 per cent of T2, 30 to 60 per cent of T3, and 0 to 35 per cent of T4 primary tumors (Table 14). The wide variation in reported results in the T3 and T4 cases reflects the importance of taking into account other prognostic factors in choosing patients for treatment with radiation alone. As in oral tongue lesions, optimal local (T) control is achieved by giving the primary disease an interstitial implant or an intraoral cone boost.

Table 14. Local (T) Control in Patients With Floor of Mouth Cancer Treated With Radiation Therapy Alone***

Freedom from any (T, N, and/or M) relapse as reported by Wang is 88 per cent in T1N0, 64 per cent in T2N0, 46 per cent in T1-T2N1, 30 per cent in T3-T4N0, and only 5 per cent for T3-T4N+ tumors.

Determinate survival has been reported to be about 80 to 100 per cent for stage I, 75 to 85 per cent for stage II, 25 to 80 per cent for stage III, and 15 to 35 per cent for stage IV (Table 15).

Table 15. Survival in Patients With Floor of Mouth Cancer Treated With Radiation Therapy Alone***

Combined Modality

As in oral tongue cancer, it is generally believed that a combined modality approach to the primary site improves local (T) control over radiation therapy alone for the large T2, T3, and, if resectable, T4 primary tumors. Available data are summarized in Table 16.

Tonsil

Selection of Patients for Radiation Therapy

Primary

Selection of radiation treatment of the primary tumor in patients with tonsillar cancer for radiation therapy should be based on the following factors: (1) size, (2) growth pattern, and (3) the presence or absence of base of tongue involvement or involvement of the lateral pharyngeal wall.

T1 and small, exophytic T2 tumors do well on treatment with radiation alone. T2 tumors that are endophytic in character or involve the base of the tongue should be considered for combined modality treatment. There is controversy over whether the larger T2 and T3 tumors that are exophytic in character and have no base of tongue involvement are best treated with radiation alone or with combined modalities. T3 tumors that are endophytic in character or involve the base of the tongue should probably be treated with combined modalities. Suggested guidelines are given in Table 17.

Nodal Disease

Clinical Adenopathy

Approximately 70 per cent of patients with T1, T2, and T3 and 90 per cent of patients with T4 primary tonsillar tumors also have clinically palpable nodal disease. Of the patients with adenopathy, 86 per cent have clinical involvement of the ipsilateral side only; the remaining 14 per cent have contralateral involvement.

The selection of patients for radiation therapy alone of nodal disease from primary tonsillar cancer can follow more liberal guidelines than described in Table 17. The nodal disease from tonsillar cancer appears to be somewhat more radiosensitive than that at most other sites (Table 18).

Subclinical Adenopathy

The incidence of subclinical disease in the exceptional patient with an N0 neck has not been documented by T stage. For all T stages combined, the incidence of occult disease in the N0 neck has reported as 10 to 45 per cent.

In general, there is no situation in which a primary tonsillar cancer is treated without also treating the ipsilateral neck prophylactically.

Results of Treatment

Radiation Alone

Local (T) control with radiation therapy alone is about 85 to 90 per cent for T1, 70 per cent for T2, about 50 per cent for T3, and 10 to 30 per cent for T4 lesions (Table 19).

Nodal control is better than 90 per cent in patients with N0, N1, N2a, and N2b nodal disease.

freedom from any (T, N, and/or M) relapse is not significantly different for N0 or N1 disease. Wang found rates of 100 per cent (15 of 15) in T1N0-N1, about 66 per cent in T2N0-N1 (65 of 99) and T1N2 (four of six), 50 per cent (13 of 26) in T2N2, about 30 per cent (19 of 62) in T3N0-N1, and about 20 per cent (six of 33) in T3N2. Pereze and colleagus found a higher value of 48 per cent for 21 patients with T3N0-N2 lesions treated with radiation alone. The 3-year freedom frmo relapse rate in T4 lesions was only 9 per cent in Wang's series.

Survival reports have usually employed the Roman numeral AJC stage, although this system inappropriately bins TN stages of different prognoses. Results averaged from two series are about 90 per cent for stage T1N0(I), 70 to 75 per cent for stage T2N0(II), 35 to 40 per cent for T1-T3N1(III), and 30 per cent for stage IV (T1-T3N2-3) tumors (Table 20). Vallis and associates reported no difference in survival between UICC N0 and UICC N1 (homolateral nonfixed nodes) staging for T1 and T2 tumors.

Several series have indicated that in patients treated with radiation alone, base of tongue involvement or pharyngeal wall involvement worsens the prognosis. This effect appears to be independent of T stage (Table 21).

Radiation Plus Surgery

A major issue in the treatment of tonsillar cancer is whether planned combined modality therapy does indeed improve on the results with radiation alone in T3 lesions or large T2 lesions.

There are few single institution studies comparing radiation alone and combined modality treatment for the more advanced lesions with equivocal or conflicting results (Table 22). Perez and colleagues compared low-dose conventionally fractionated preoperative radiation therapy and surgery with radiation alone, and found no significant difference in freedom from recurrence or survival between the two groups for T3 tumors. Shrewsbury and associates compared 5000 cGy given in 175-cGy daily fractions in preoperative radiation

therapy and surgery, and found the 2-year crude survival rate significantly improved in the combined modality arm: 15 per cent versus 76 per cent. No attempt was made, however, to take into account differences in N staging between the two groups in the Shrewsbury paper. Other retrospective studies of patients receiving combined radiation and surgery have not shown a definite improvement in published results from radiation therapy alone.

Salvage of Radiation Recurrences

Gelinas and Fletcher reported a 32 per cent surgical salvage rate in 106 patients who failed after definite irradiation for carcinoma of the faucial arch, tonsillar fossa, and base of the tongue.

Base of Tongue

Selection of Patients for Radiation Therapy

Primary

Patients should be chosen for radiation treatment to the primary site on the basis of (1) tumor size, (2) growth pattern, (3) and location with respect to laterality. The rare T1 and small T2 tumors that are superficial and exophytic can be treated with radiation alone. T1 and small T2 tumors with the more common endophytic, infiltrating growth patterns and the larger T2 exophytic tumors should perhaps be considered for a "lumpectomy" if the location is sufficiently lateralized to permit excision without compromising both lingual arteries or the larynx. Otherwise, radiation alone should be used, and the relatively extensive surgery that would be required reserved for salvage.

The treatment of advanced lesions must frequently be approached from the point of view of radical palliation rather than cure.

Nodal Disease

Clinical Adenopathy

About 70 per cent of all T1 and T2, 75 per cent of T3, and 85 per cent of T4 lesions of the base of the tongue present with clinically palpable adenopathy. Of patients with adenopathy, 78 per cent have involvement of the ipsilateral side only; 22 per cent have contralateral involvement.

Selection of patients with nodal disease for treatment with radiation can follow the guidelines in Table 9.

Subclinical Adenopathy

Data on the incidence of subclinical disease in the neck by T stage are not available. In the exceptional patient with an N0 neck, Ogura and colleagues found a 22 per cent incidence of subclinical disease.

In general, because of the increased chance of contralateral nodal metastases, both the ipsilateral and contralateral sides should be irradiated electively in any patient receiving radiation therapy to the primary cancer.

Results of Treatment

Radiation Therapy Alone

Local (T) control is about 85 per cent for T1 and averages 70 per cent for T2 and 65 per cent for T3 lesions. Results for T4 lesions appear to be variable, probably reflecting differences in selection factors used in choosing patients for treatment (Table 23). There is controversy in the literature over whether optimal results can be achieved with external radiation alone, or whether an interstitial implant boost is necessary.

Three-year freedom from any (T, N, and/or M) relapse was 76 per cent for T1N0-N1, 56 per cent for T2N0-N2 and T1N2-N3, 20 per cent for T3N0-N1, 11 per cent for T3N2-N3, and 6 per cent for T4N0-N3 in Wang's series. As in tonsillar cancer, for a given T1 or T2 stage, there was little difference in freedom from recurrence between N0 and N1 nodal stages.

Five-year survival in the series of Parsons and colleagues, using the AJC Roman numeral grouping, was 88 per cent for stages I and II, 44 per cent for stage III, and 17 per cent for stage IV. Stage IV could be subdivided into two distinct groups: "favorable" stage IV - T1-T3 N2-N3a with survival of 39 per cent; and "unfavorable" stage IV - T1-T3 N3b or T4N0-N3 with survival of 9 per cent.

Radiation and Surgery

Thawley and associates reported the results of 2000 to 5000 cGy in 2 to 5 weeks of preoperative radiation followed by surgery. Five-year local-regional (TN) control by AJC Roman numeral stage was 100 per cent in stage I patients, 75 per cent in stage II and III patients, and 53 per cent in stage IV patients. No stage I or II patient developed distant metastases; in contrast, 21 per cent and 23 per cent of stage III and IV patients, respectively, developed distant disease. Five-year survival was 75 per cent in stages I and II, 57 per cent in stage III, and 40 per cent in stage IV disease.

Salvage or Radiation Recurrences

Very few who fail radiation can be salvaged. Weller and associates reported a 25 per cent salvage rate for recurrences. Only 6 per cent (2 of 36) were salvaged in the series of Spanos and colleagues. In Wang's series, 11 of 126 failures (9 per cent) were salvaged.

Soft Palate and Uvula

Selection of Patients for Treatment with Radiation Therapy

Primary

Patients should be selected on the basis of (1) size of lesion, (2) potential for diffuse or multifocal disease, and (3) growth pattern.

Because of the frequency of multifocal disease, only very early, superficial lesions (less than 1 cm in diameter) can be considered for local treatment such as limited surgical excision or interstitial radioactive implant. Larger T1 and T2 tumors, particularly if exophytic in character, can be treated adequately with radiation therapy alone without the functional problems that would result from a large surgical excision. More advanced tumors, particularly those with endophytic growth patterns, should be considered for combined modality treatment.

Nodal Disease

Clinical Adenopathy

About 10 per cent of T1, 35 per cent of T2, and 65 per cent of T3 and T4 lesions present with palpable clinical adenopathy. Of patients with clinical adenopathy, 75 per cent have ipsilateral disease only; the remaining 25 per cent have contralateral disease.

The guidelines in Table 9 may be used to manage patients with clinical neck disease.

Subclinical Adenopathy

Data on the incidence of subclinical disease in the N0 neck by T stage are not available. Lindberg and associates found an overall incidence of 26 per cent (11 of 43).

Results of Treatment

Table 24 gives the results from several series of local (T) control rates for treatment with radiation therapy alone. Control is consistently good for T1 and T2 lesions but inconsistent for advanced tumors.

Wang reported a 3-year freedom from any (T, N, and/or M) relapse of 100 per cent, 76 per cent, 38 per cent, and 0 per cent for T1N0, T2N0, T3N0, and T4N0 soft palate tumors, respectively. The freedom from relapse was 76 per cent for N0 tumors and 33 per cent for N+ tumors.

Amdur and colleagues reported 5-year determinate survival by Roman numeral stage to be 83 per cent in stage III, and 25 per cent in stage IVB. Keus and colleagues reported determinate survival at 5 years to be 65 per cent for T1-T2 tumors and 41 per cent for T3-T4 tumors. Determinate survival at 5 years was 58 per cent in N0 patients and 37 per cent in N+ patients.

Piriform Sinus

Selection of Patients for Radiation Therapy

Primary

Selection of patients with piriform sinus cancer for treatment with radiation should take into account (1) size, (2) growth pattern, and (3) the presence or absence of involvement of the apex.

Disease size or bulk is the most important factor in choosing patients for radiation; the presence AJC staging system does not incorporate direct measures of tumor volume, and thus is by itself inadequate for selecting patients for radiation. Small tumors of 2 cm or less can be considered for radiation alone. Larger tumors, tumors involving the apex (see Table 28), and endophytic, deeply ulcerating tumors show poor results when treated by radiation therapy alone, and should receive combined modality treatment. A suggested outline for patient selection for radiation treatment is given in Table 25.

Nodal Disease

Clinical Adenopathy

Clinically palpable adenopathy in hypopharyngeal cancers is present in 60 to 65 per cent of T1, 70 per cent of T2, and about 75 to 80 per cent of T3 and T4 lesions. Of patients with clinically positive adenopathy, 91 per cent have ipsilateral nodes only; the remainder have contralateral nodes, with or without ipsilateral nodes.

The guidelines in Table 9 may be used in management of the neck disease with radiation.

Subclinical Adenopathy

Data for the incidence of occult nodal disease by T stage are unavailable. Ogura and colleagues found an overall incidence of 33 per cent in six patients.

Results of Radiation Therapy

Radiation Therapy Alone

Local (T) control by the size of the lesion in patients treated with radiation therapy alone at the MD Anderson Hospital in Houston, Texas is given in Table 31. Other "radiation only" series in the literature have analyzed results by AJC T stage, which is only roughly correlated with disease size. Wang, for example, using the 1965 AJC classification, found a 67 per cent local control rate in both T1 and T2 lesions and 23 per cent local control in T3 lesions.

Three-year freedom from any (T, N, and/or M) relapse is 78 per cent for T1N0, 45 per cent for T2N0, 33 per cent for T3N0, and 7 per cent for the combined groups T4N0 and T1-T4N1-N3 in Wang's series.

Crude five-year survival rates for patients treated with radiation therapy alone were reported in a series from the University of Virginia. Forty-three per cent of T1N0 and 50 per cent of T2N0 lesions were alive 5 years after treatment. None of six patients with T3-T4 disease survived, and only one of 11 patients with nodal disease.

Radiation and Surgery

The results from radiation therapy alone for primary tumors more than 4 cm in size, and possibly 2 to 4 cm, may be improved with combined modality therapy. Results from the MD Anderson Hospital series are give in Table 32.

Nasopharynx

Selection of Patients for Radiation Treatment

Primary

The primary treatment for all nasopharyngeal primary cancer is radiation therapy. Because of the proximity of the nasopharynx to the base of the skull, the morbidity involved in the surgical resection that would be required to obtain results equivalent to radiotherapy cannot be justified.

Nodal Disease

Clinical Adenopathy

There is no correlation between AJC T stage and the incidence of clinically palpable nodal disease. Eighty-five to 90 per cent of all T1-T4 nasopharyngeal cancers present with clinical adenopathy.

Radiation is the primary treatment for all clinically palpable nodal disease from nasopharyngeal cancer because of (1) evidence that even large nodal disease from nasopharyngeal cancer is controllable with radiation alone, suggesting greater radiosensitivity than tumors from other sites of the same bulk; and (2) the problems with adequately managing nodal disease with surgery, owing to (a) the frequent incidence of bilateral disease, (b) the frequent involvement of the junctional and retropharyngeal nodes, which are not easily treated with surgery, and (c) the suggestion in the literature that pretreatment neck biopsy or neck dissection may decrease the survival rate (Table 33).

The role of radiation therapy in the management of clinically palpable neck disease in nasopharyngeal cancer is thus a notable exception to the general guidelines given in Table 9. If, after completion of radiation, residual or persistent disease remains, an excision of the residual disease or limited neck dissection can then be planned.

Subclinical Disease

The incidence of subclinical or occult disease in the rare patient with an N0 neck is unclear. Ho reported an overall incidence of 19 per cent and did not advocate elective neck

irradiation. However Moench and Phillips reported an incidence of 50 per cent in T1N0 cases alone. General practice is to give bilateral elective neck irradiation to all patients with nasopharyngeal cancer.

Results of Treatment with Radiation

Local Control by T Stage

Table 34 gives results from several series of local (T) control. For nonlymphoepitheliomas, local control drops from 90 to 95 per cent for T1 to aboue 55 per cent for advanced T3-T4 tumors. In contrast, there is little relationship between local control and T stage for lymphoepitheliomas, with more than 90 per cent of all tumors locally controlled.

Nodal Control By N Stage

Table 35 demonstrates the excellent nodal (N) control achieved with radiation therapy, with 70 per cent of N3 and 85 per cent of N1 and N2 nonlymphoepitheliomas controlled; 90 per cent or more of all N+ lymphoepitheliomas are controlled.

Bedwinek and colleagues noted that N control correlated better with nodal size than with N stage, nodal (N) control being 96 per cent for nodes 3 cm or less, 65 per cent for nodes 3 to 6 cm, and 45 per cent for nodes 6 cm or greater.

Freedom From Relapse

In analyzing the freedom from any (T, N, and/or M) relapse, it should be kept in mind that there is a marked incidence of distant metastases in patients with nasopharyngeal cancer. The degree of these (M failure) is directly correlated with N stage rather than T stage. The incidence is particularly marked in the lymphoepithelioma variant.

Eight per cent of patients with N0 and N1 neck disease failed with distant metastases and 37 per cent of those with N2 and N3 neck disease failed with distant metastases in the MD Anderson series (31 per cent in non-lymphoepitheliomas, 43 per cent in lymphoepitheliomas). Fifty per cent of patients in a Washington University series with N2-N3 neck disease failed with distant metastases. Consideration should be given for systemic treatment in patients with N2 and N3 neck disease, particularly those with the lymphoepithelioma variant.

Bedwinek and colleagues reported five-year freedom from relapse to be 69 per cent for T1-T2N0-N1 tumors, but only about 20 per cent for T1-T2N2-N3, T3-T4N0-N1, T3-T4N2-N3. T failures were a major problem in the T3-T4N0-N1 group, but M failures were the major problem in the N2-N3 groups.

Ho analyzed his series with an N staging based on the level of cervical lymph node involvement: N1 for lymph nodes above the neck crease extending backward from the thyroid notch; N2 for nodes between a line extending backward from the sternoclavicular joint to the superior margin of the trapezius muscle and the above-described neck crease; and

N3 for supraclavicular nodes or skin involvement. Freedom from any (T, N, and/or M) relapse was 48 per cent for N1, 27 per cent for N2, and only 8 per cent for N3 (Table 36).

Survival

Five-year survival by TN stage from Wang's large series is given in Table 37. Survival for T1-T2N0-N1 tumors was 72 per cent, for T1-T2N2-N3 38 per cent, for T3-T4N0-N1 30 per cent, and for T3-T4N2-N3 15 per cent.

Treatment for Recurrences

Small "local only" recurrences after full-course radiation therapy can be salvaged with further radiation using a combination of local external beam and an intracavitary implant.

Glottic Larynx

Selection of Patients for Treatment with Radiation

Primary

Selection of patients for treatment with radiation should be based on the following factors: (1) tumor bulk, (2) mobility of the true vocal cords, (3) growth pattern of the tumor, (4) presence of spread beyond the glottis, and (5) sex of the patient.

In general, large bulky tumors have poorer control with radiation, and combined modality treatment should be considered. In assessing bulk, the possibility of tumor burden in the pre-epiglottic and paraglottic spaces must be considered. Tumors with infiltrative growth patterns and tumors causing impaired mobility of the true vocal cords also frequently have greater tumor burden than is visible on examination. For the same stage, women have a better prognosis with radiation treatment alone than do men.

Suggested first-order guidelines for selection of patients for radiation treatment are given in Table 38.

Nodal Disease

Clinical Adenopathy

Nodal disease is rare at presentation of primary glottic carcinomas because of the paucity of lymphatics in the true vocal cords. Of patients seen at the Princess Margaret Hospital, 0 per cent of T1, 6 per cent of T2, 15 per cent of T3, and 25 per cent of T4 glottic cancers presented with lymph node metastases.

The guidelines in Table 9 may be used to select patients with clinical adenopathy for treatment with radiation.

Subclinical Adenopathy

There are few data on the incidence of occult disease in clinical N0 glottic cancer, but it is generally believed to be quite low. T1N0 lesions require no elective treatment to the neck. Treatment fields for T2a and T2bN0 lesions with supraglottic extent have often included the midjugular and jugulodigastric nodes, although such coverage may not be necessary. In more advanced tumors, the entire anterior jugular chain is treated.

Results of Treatment

Stage T1 Lesions

Results of radiation alone for T1 lesions are excellent. Initial local (T) control rates are about 90 per cent, with ultimate local (T) control of about 95 per cent (Table 39). Freedom from any (T, N, and/or M) relapse is 90 per cent. Actuarial survival at 3 years is 96 per cent and at 5 years 95 per cent.

In the past, slightly inferior results have been reported for lesions involving the posterior commissure, but this is probably related more to a tendency to underdose this area. With proper radiation therapy technique, location of a T1 lesion should have no relation to results.

Results in T1a lesions (one cord only) may be slightly better than those in T1b lesions (both cords / anterior commissure). Freedom from any (T, N, and/or M) relapse was 92 per cent for T1a lesions and 85 per cent for T1b lesions at the Massachusetts General Hospital; 5-year survival was 96 per cent for T1a and 87 per cent for T1b lesions at the Princess Margaret Hospital.

Stage T2 Lesions

Results with radiation treatment alone in several series have shown a difference in prognosis depending on whether the cord mobility was normal or impaired. For this reason, Harwood and colleagues proposed that the staging system divided T2 lesions into T2a (supraglottic and subglottic extension with normal cord mobility) and T2b (impaired cord mobility with or without supraglottic or subglottic extension).

Results for T2a Lesions

Results of radiation for T2a lesions are still excellent, being almost equivalent to those for T1b lesions. Initial local (T) control is 75 to 80 per cent, freedom from any (T, N, and/or M) relapse 75 to 80 per cent, and 5-year survival 85 to 90 per cent.

Results for T2b Lesions

Results of radiation for T2b lesions have been less than satisfactory, with initial local (T) control rates of only about 50 per cent, about the same as those obtained for T3 lesions.

The ideal management of these T2b lesions is controversial and remains undefined. Results with total laryngectomy and postoperative radiation at a single institution have

yielded improved initial local-regional control rates, but whether this has translated into an advantage in ultimate control or survival remains to be established.

In an effort to conserve the voice while improving initial control rates, hemilaryngectomy and pre- or postoperative radiation has also been used in selected patients. This latter treatment options raises the question of the relative morbidity involved in giving radiation with conservative laryngeal surgery. Gall and associates found a 24 per cent (four of 17) incidence of complications when hemilaryngectomy was performed after low-dose preoperative radiation therapy versus 16 per cent incidence (38 of 199) after hemilaryngectomy alone. Thawley reported that nine of 17 patients (53 per cent) treated with conservative surgery and postoperative radiation developed complications. The most common complication after combined modality treatment was glottic insufficiency.

Stage T3 Lesions

Radiation alone with surgical salvage for stage T3 lesions has yielded initial local (T) control rates of about 50 per cent, ultimate local (T) control rates of about 70 per cent, freedom from any (T, N, and/or M) relapse of 32 per cent, and 5-year survival of about 55 per cent. Results for local (T) and/or regional (N) control from several series are given in Table 40. The major advantage of this approach is that about 60 to 65 per cent of survivors have an intact larynx (Table 41). The major controversy surrounding this approach concerns whether these results are truly equivalent to those achievable with total laryngectomy and adjuvant radiation, or whether, in an effort to conserve their larynx, patients have to some degree compromised their survival.

In the absence of any randomized trials, a definitive answer is not forthcoming. Retrospective comparisons of radiation alone versus radiation plus surgery at single institutions have suggested that treatment with radiation alone may indeed compromise survival. Van den Bogaert and colleagues compared 14 patients considered for laryngectomy who refused and received full-course radiation therapy with patients treated with planned combined modality therapy, and found ultimate control superior in the planned combined modality group.

Stage T4 Lesions

Overall local (T) control in patients treated with radiation therapy alone in the Princess Margaret series was 55 per cent for T4N0 lesions. Five-year actuarial survival was 60 per cent.

The cases were subdivided into two separate groups: "T4-cartilage" indicated cases called T4 on the basis of thyroid cartilage destruction, involvement of the trachea or base of tongue, without any involvement of the hypopharynx. "T4-piriform" referred to cases with any involvement of the hypopharynx. Local (T) control was 67 per cent in T4-cartilage patients but only 19 per cent in T4-piriform patients. The difference in 5-year survival was less dramatic: 67 per cent in T4-cartilage and 58 per cent in T4-piriform patients.

Salvage of Radiation Failures

About 90 per cent of T1 and 60 per cent of T2 and T3 recurrences may be salvaged by surgery.

Supraglottic Larynx

Selection of Patients for Treatment with Radiation

Primary

Selection of patients with supraglottic laryngeal cancer for radiation treatment of the primary should take into account the following factors: (1) tumor size, (2) number of involved sites, (3) location within the supraglottis: suprahyoid or infrahyoid, (4) presence or absence of extension to the true cords and mobility of cords (these factors partially amalgamated in the T-stage), and (5) growth pattern of tumor. Table 42 gives suggested options involving radiation therapy in the management of patients on the basis of these factors.

In general, small exophytic tumors of the suprahyoid epiglottis respond well to irradiation. Radiation results for endophytic infiltrating tumors, tumors of the infrahyoid epiglottis, or tumors causing impaired mobility or fixation of the true cord have frequently been unsatisfactory, probably because of the difficulty in ascertaining the true extent of tumor bulk in these situations. However, if the surgical alternative would involve loss of the larynx, consideration may be given to trying to preserve the larynx by treatment with radiation alone and using surgery to salvage recurrences, or alternatively attempting to select patients who will respond well to a trial of radiation.

Nodal Disease
Clinical Adenopathy

About 40 per cent of T1 and T2 lesions and 60 to 65 per cent of T3 and T4 lesions present with clinical adenopathy. Of the patietns with positive adenopathy, 78 per cent have involvement of the ipsilateral side only; the remaining 22 per cent have contralateral involvement. Patients may be selected for radiation therapy of nodal disease on the basis of the guidelines in Table 9.

Subclinical Adenopathy

The incidence of occult nodal disease in the N0 neck has ranged from 16 to 26 to 33 per cent, averaged over all T stages. Incidence figures by T stage are not available. In patients receiving radiation therapy to a T1 or T2 primary tumor, prophylactic radiation is given to the jugulodigastric and midjugular nodal regions bilaterally; for larger lesions the junctional nodes and low anterior jugular nodes are also included.

Results of Treatment

Radiation Alone

Local (T) control is about 80 to 90 per cent for T1, 70 to 80 per cent for T2, 35 to 55 per cent for T3, and 20 to 30 per cent for T4 lesions (Table 43).

In Wang's series the 3-year freedom from any (T, N, and/or M) relapse for TN groupings with comparable rates was 81 per cent for T1N0-N1; 57 per cent for T2-T4N0; 29 per cent for T2-T4N1, T1-T2N2, and T1N3; and 5 per cent for T3-T4N2 and T2-T4N3. T1 lesions of the tip of the epiglottis had a particularly favorable prognosis, with a 3-year freedom from recurrence rate of 100 per cent (12 of 12) versus 70 per cent (43 of 61 for other T1 sites.

The determinate three-year survival reported by Spaulding and associates using the above grouping was 88 per cent for T1N0-N1; 75 per cent T2-T4N0; 56 per cent for T2-T4N1, T1-T2N2, and T1N3; and 7 per cent for T3-T4N2 and T2-T4N3.

Radiation and Surgery Versus Radiation Alone

For advanced supraglottic primary cancers, combination radiation and surgery appears to yield better initial local control, freedom from relapse, and determinate survival than radiation alone (Table 44). However, in addition to the usual selection problems in comparing retrospective treatment groups, the data for determinate survival are based on very small numbers, and the data for local control and freedom from relapse do not take into account surgical salvage. If thus can still be argued that a policy of radiation alone, with surgery reserved for salvage, may yield *ultimate* local control, regional control, and survival equivalent to that from planned radiation and surgery.

The results of radiation alone with surgery for salvage have been reported from the Princess Margaret Hospital. Local (T) control was achieved in about 50 per cent of T3 and T4 primaries. Survival was not reported by T stage, but the authors noted that the survival rates for patients with advanced supraglottic carcinoma were very similar to those in other series using combined treatment with pre- or postoperative radiation. Of survivors at 5 years, 64 per cent still retained the larynx.

Salvage of Radiation Failures

Overall surgical salvage rates of radiation recurrences have been reported to be 13 to 51 per cent.

Maxillary Sinus

Selection of Patients for Treatment

Primary

Patients should be selected for radiation treatment of the primary tumor on the basis of (1) size, (2) extent, (3) degree of bone involvement, and (4) location (infrastructure or suprastructure).

In practice, most patients should undergo radiation and surgery if the condition is medically or technically operable. The only lesions that can be considered for single modality therapy are small lesions of the infrastructure with no or minimal bone destruction. Such patients can be treated with radiation alone or surgery alone. Small lesions of the suprastructures, and more advanced tumors, which represent most patients, probably benefit from combined modality treatment.

Nodal

Clinical Adenopathy

Clinical adenopathy at presentation is unusual, the incidence ranging from 10 to 20 per cent. Gadeberg and colleagues found an incidence of 0 per cent (none of 8) for AJC T2, 15 per cent (three of 20) for T3, and 12 per cent (two of 16) for T4. Using the Japanese joint committee staging (Table 45), Tsujii and associates noted an incidence of 0 per cent (none of five) for JJC T2, 16 per cent (23 of 142) for T3, and 20 per cent (12 of 61) for T4.

Subclinical adenopathy

Prophylactic neck irradiation is not usually recommended because the incidence of occult nodal metastases is low and the rare recurrence that does occur is usually also associated with failure to control the primary disease.

There are two circumstances in which prophylactic nodal irradiation may be indicated: (1) when there is gross invasion of the oral cavity or (2) when the tumor is poorly differentiated or undifferentiated.

Results of Treatment

Radiation Alone Versus Surgery

Numerous retrospective studies at single institutions have documented that, overall, the patient subpopulations treated by surgery and radiation therapy have had a better prognosis than those treated by radiation alone (Table 46). However, there are few data comparing the two treatments among patients with comparable disease characteristics. In Wang's series, patients with AJC T3N0 tumors treated with radiation therapy alone had a 3 year freedom from any (T, N, and/or M) relapse of 24 per cent versus 61 per cent with radiation and surgery.

Preoperative Versus Postoperative Radiation

Ther available data from retrospective comparisons at single institutions suggests that preoperative is superior to postoperative radiation (Table 47). Both Yu-Hua and colleagues and Wang achieved better results in patients of the same stage with preoperative radiation than in postoperative radiation. However, the number of patients in these series is small. Jesse found no difference.

Effect of Residual Disease After Preoperative Radiation

In the study of Gadeberg and colleagues, 20 of 51 (39 per cent) of patients had no residual tumor at the time of operation after 5700 to 6000 cGy preoperative radiation. The 5-year survival of these patients was 70 per cent, as opposed to the 26 per cent 5-year survival in those with residual tumor.

Local-Regional Control, Freedom from Relapse, and Survival After Preoperative Radiation and Surgery

Tsujii and associates reported a local (T) control rate of 59 per cent for T3 and 30 per cent for T4 tumors treated with preoperative radiation and surgery. Eighteen of the patients also received intra-arterial 5-fluorouracil, but the authors found no improvement in results with this adjunctive treatment. Regional (N) control rate was about 75 per cent in both T3 and T4 tumors (Table 48). Wang reported freedom from any (T, N, and/or M) relapse of 67 per cent in T3N0 tumors. Tsujii and associates reported absolute 5-year survival of 50 per cent in T3 and 25 per cent in T4 tumors. There was a significant improvement in survival for tumors of a given stage in the infrastructure compared with those in the suprastructure (Table 49).

Nasal Vestibule

Selection of Patients for Treatment with Radiation Therapy

Primary

Prognosis with radiation treatment is equivalent to surgery alone for early and moderately advanced lesions. Because reconstruction after surgical resection of significant portions of nasal skin and cartilage usually cannot compare with the cosmesis after radiation, radiation therapy is the treatment of choice. It is unknown whether the advanced, bulky lesions (greater than 6 cm in diameter) are best handled by planned combined modality treatment or by radiation alone, with surgery reserved for salvage at time of relapse. The latter approach has the advantage of sparing a portion of the survivors the severe cosmetic loss from surgery.

Nodal Disease

In a series of 66 patients treated predominantly with radiation therapy, none of 31 patients (0 per cent) with T1 tumors (Wang 1976 staging, Table 50), three of 20 (15 per cent) with T2 tumors, and one of eight (13 per cent) with T3 tumors presented with clinical nodal disease.

The incidence of subclinical nodal disease in patients with a clinical N0 neck is unknown. Prophylactic treatment to the draining lymphatics is not recommended unless there has been invasion of the nasal cavity or inflammatory spread into the skin and dermal lymphatics of the upper lip.

Results of Treatment

Haynes and Tapley reported 22 patients with lesions 0.5 to 3 cm in size. All had N0 necks. Local (T) control was obtained in 19 of 22 patients (86 per cent) after radiation therapy alone. One of the three local failures was salvaged, giving an ultimate control rate of 91 per cent. Local control by T stage and size as reported by Johansen and colleagues is given in Table 51.

Wang reported 3-year freedom from any (T, N, and/or M) relapse to be 92 per cent for T1N0, 71 per cent for T2N0, and 43 per cent for T3N0-N1 tumors.

Johansen and colleagues reported a 10-year survival of 92 per cent for T1, 65 per cent for T2, and 44 per cent for T3 tumors treated predominantly with radiation therapy alone (Table 51).

Salvage of Recurrences

In the large series of Johansen and colleagues, 12 of 22 (55 per cent) *local recurrences* after radiation therapy were salvaged with surgery. Of the 22 local recurrences, eight (36 per cent) subsequently developed nodal metastases. Prophylactic treatment of the neck was consequently suggested as part of any salvage surgery.

In Wang's series, two of 12 (17 per cent) of all failures were salvaged.

Salivary Glands

Selection of Patients for Radiation Therapy

Primary

Surgery is the mainstay of treatment for the salivary gland in all presentations. Patients should be selected for adjuvant radiation treatment on the basis of (1) histology and grade, (2) adequacy or resection, (3) tumor size, and (4) degree of local extension. Table 52 summarizes the indications for radiation.

Neck

Clinical Adenopathy

About one-fifth of patients with parotid tumors present with cervical lymph node metastases. The incidence reported by Spiro and colleagues by histology was high-grade mucoepidermoid, 28 per cent; adenocarcinoma, 18 per cent; epidermoid carcinoma, 10 per cent; malignant mixed tumor, 9 per cent; acinic cell carcinoma, 9 per cent; adenoid cystic

carcinoma, 1 per cent; and low-grade mucoepidermoid, 0 per cent. Fu and associates found that 13 per cent of T1 and T2 lesions and 33 per cent of T3 lesions showed adenopathy at presentation. Data on the incidence by stage for each histology are not available.

Table 52. Selection of Patients for Radiation Therapy of Salivary Gland Tumor

1. Close or probably inadequate margins:
    a. Incomplete surgical removal
    b. Facial nerve sparing procedure with close margins
    c. Deep lobe tumors
2. Histologically aggressive or advanced tumors:
    a. Tumor extension beyond capsule
    b. High-grade malignant tumors
    c. Tumors with perineural invasion
    d. Tumors with lymph node metastasis
    e. Large tumors requiring extensive resections
3. Recurrent tumors
4. Inoperable tumors (palliation).

Subclinical Adenopathy

The incidence of occult disease in the clinically N0 neck in patients with parotid carcinoma, as reported by Spiro and colleagues, was epidermoid carcinoma, 67 per cent; high-grade mucoepidermoid carcinoma and adenocarcinoma, 22 per cent each; malignant mixed and acinic cell carcinoma, 13 per cent each; adenoid cystic carcinoma, 5 per cent; low-grade mucoepidermoid carcinoma, 0 per cent. The incidence by stage was 1 per cent in stage I, 10 per cent in II, and 33 per cent in III. Data on these incidences by stage for each condition are not available.

Standard radiation fields for parotid cancer include the first echelon of nodal drainage: preauricular, parotid, submaxillary, upper cervical. Elective treatment to the entire ipsilateral neck is usually given only for those conditions with a high incidence of occult neck disease: epidermoid, high-grade mucoepidermoid, and adenocarcinomas.

Results of Treatment

Postoperative Radiation

Table 53 gives overall local-reginal (TN) control rates by histology for patients treated with surgery alone. There is clearly a need for adjuvant local treatment in the aggressive or advanced stages of disease.

Adjuvant postoperative radiation appears to be effective, with local (T) control increasing from 50 to 75 per cent in the subpopulations of patients treated with surgery to 85 to 95 per cent in those treated with surgery and radiation therapy (Table 54). This difference is most dramatic in patients with positive or close margins, where local (T) control increased from about 45 to 85 per cent in one series.

Freedom from any (T, N, and/or M) relapse in Wang's series of patients treated with surgery and radiation was 60 per cent at 3 years for those with microscopicd disease after surgery and 37 per cent for those with gross disease.

Reinfuss and Korzeniowski reported a 100 per cent 5-year survival in patients with T2 and 47 per cent in T3 primary disease treated with nonradical surgery and postoperative radiation. Shidnia and colleagues reported 100 per cent survival at last follow-up in four of four T1 and T2 patients and 65 per cent survival in 26 T3 and T4 patients.

Radiation Alone

Radiation alone is used only in tumors that are unresectable or medically inoperable. Local (T) control with radiation alone ranges from about 20 to 80 per cent in the literature, reflecting wide differences in disease bulk in the reported populations (Table 55).

Wang reported an 18 per cent 3-year freedom from any (T, N, and/or M) relapse in 11 patients.

Results from some neutron beam trials have suggested improved control rates with neutron beam treatment compared with conventional photon beam treatment.

Unknown Primary Head and Neck Cancer

Selection of Patients for Treatment with Radiation Therapy

Selection of patients for radiation treatment for metastatic epidermoid carcinoma to the cervical lymph nodes from an unknown primary tumor involves three separate decisions: (1) whether to use radiation to treat the clinically involved neck(s), (2) (in the case of ipsilateral clinical involvement) whether to use radiation to treat subclinical disease in the contralateral side, and (3) whether to treat the potential sites of the occult primary tumor, which can be done only with radiation.

These decisions correspond to the three treatment options to decide among: (1) treatment to the involved neck only with neck dissection or excisional biopsy and/or electron irradiation, (2) treatment to both sides of the neck with combined surgery and radiation or radiation alone, or (3) treatment to both sides with surgery and/or radiation plus treatment to the potential sites of the occult primary with radiation.

Clinical Nodal Disease

The guidelines in Table 9 for treatment of any clinical nodal disease to the neck may be used in deciding whether to treat the clinically involved neck with radiation. Radiation alone is adequate if the nodes are 2 to 3 cm in diameter or smaller; combined modalities should be used if there are multiple nodes or nodes larger than 3 cm.

If the primary treatment is a neck dissection alone, postoperative irradiation should be added for those indications discussed earlier in the section on the management of neck disease.

Occult Disease in Contralateral Neck

There are few specific data available to assist the decision whether to treat occult disease in the contralateral side of the neck; neither the primary site nor the degree of laterality of the primary tumor is directly known.

The only clues to the primary site and the degree of laterality are (1) the pattern of involvement of the lymph nodes regions by the clinical adenopathy and (2) the histologic differentiation of the tumor. Whatever the primary site and degree of laterality, the risk of contralateral involvement may be presumed to be increased when multiple nodes are involved, or when there is large, bulky disease. There are, however, no direct data giving the risk for contralateral recurrence with and without efective treatment of the contralateral side versus the pattern, multiplicity, or bulk of initial clinical adenopathy. Anatomic knowledge of lymphatic spread suggests that (1) patterns of involvement indicative of primary sites close to the midline: eg, involvement of the posterior cervical, junctional, or midjugular lymph nodes, and (2) multiple or bulky adenopathy should be considered to carry a significant risk of contralateral neck disease and should dictate treatment to the contralateral side.

Occult Primary

The selection of patients to receive treatment to potential sites of the occult primary tumor is also an area of considerable controversy and few data. Some centers treat nearly all patients with prophylactic irradiation to potential sites of the occult primary tumor.

At centers where only a select subpopulation of patients are chosen for prophylactic treatment to occult primary sites, the selection ideally should be made on the same basis as the selection for treatment for occult disease in the contralateral side of the neck: the pattern, multiplicity, and bulk of nodal involvement, and (to a lesser extent) the differentiation of the tumor. However, there are few data giving the risk for the appearance of an occult primary tumor with and without elective treatment of potential primary sites as a function of these factors.

Elective treatment of potential occult primary sites is often omitted in two situations. At one extreme, patients with small (less than 2 cm), single, jugulodigastric, submandibular, or submental nodes have been treated on the ipsilateral side only with good results. At the other extreme, patients with large, bulky neck adenopathy may be treated in the neck alone with the rationale that few such patients fail at an occult primary site without also failing in the neck or distantly. Between these two extremes, treatment is usually given to sites thought most likely to harbor the occult primary tumor. This usually means irradiation of the entire nasoorohypopharyngeal axis. If a nasopharyngeal site is particularly probable - lymphoepithelioma on histologic appearance or involvement of a single posterior cervical node - treatment of the hypopharynx may be omitted.

Results of Treatment

Ipsilateral Nodal (N) Control Rate

Jesse reported an ipsilateral nodal (N) control rate of 83 per cent (10 of 12) for NX, N1 tumors treated with radiation alone, and 78 per cent (31 of 40) for N2, N3 tumors treated

with radiation alone. The corresponding values for combined surgery and radiation were 100 per cent (six of six) and 82 per cent (18 of 22).

Contralateral Nodal (N) Control Rate

Prophylactic radiation of the contralateral side of the neck increases the contralateral nodal control rate from about 90 to 100 per cent (Table 56).

Occult Primary (T) Control Rate

If all presentations of metastatic lymph nodes from an unknown primary site are pooled, the occult primary site eventually appears clinically in about 20 to 25 per cent of the patients when no prophylactic treatment to the potential primary sites is given. Overall primary (T) "control" rates with and without prophylactic treatment of occult primary sites are shown in Table 57 and suggest a small improvement of 10 to 15 per cent when prophylactic radiation is given.

Although the benefit is small, the appearance of the occult primary tumor is a poor prognostic factor, associated with a 50 per cent reduction in survival.

Data for particular subsets of presentations in which this benefit may be less or more dramatic are not available.

Freedom From Relapse

Freedom from any (T, N, and/or M) relapse is about 80 to 90 per cent for N1, 40 to 60 per cent for N2, and 25 to 35 per cent for N3 presentations (Table 58). Carlson and associates found rates of 67 per cent for patients with N1, N2a disease treated in the neck alone versus 95 per cent for patients with N1, N2a disease treated at the most likely sites of occur primary tumors. Similarly, for patients with N2b, N3a, and N3b neck disease, the freedom from relapse was 65 per cent for those treated in the neck alone versus 90 per cent for those treated at the most likely sites of occult primary tumors.

Survival

Carlson and associates achieved an overall 10-year determinate survival of 70 per cent for treatment with radiation with or without surgery, after excluding patients with bulky disease who were considered incurable. There was no relationship with N stage and survival for the subpopulation of "curable" patients they studied.

Radiation Morbidity

Skin

Acute

During the first few weeks of treatment with conventional fractionation, a faint blush may be noted. This is probably due to capillary dilation and possibly an increase in vascular permeability.

By 3 to 4 weeks (3000 to 400 cGy), a definite area of erythema is visible within the radiation portals.

The erythema phase is followed by dry desquamation, characterized by scaling and dryness of the skin. There may be an increase in melanin pigmentation in the basal layer, causing a clinical impression of "hyperpigmentation".

Dry desquamation may be followed by wet desquamation, characterized by loss of the epidermis and exposure of the underlying dermis.

Management

Topical ointment and creams such as Aquaphor ointment, Acid Mantle Creme, lanolin, Vaseline, baby oil, vitamin E oil, and Eucerin Creme may be used topically three times daily for areas of dry or wet desquamation. If there is significant pruritus in such areas, a steroid cream often provides relief. Hydrocortisone cream 0.5 per cent applied two to four times daily if often sufficient.

Chronic

Chronic radiation dermatitis is characterized by poikiloderma: hyperpigmentation and/or hypopigmentation, atrophy, and telangiectasia. The thin, dry epidermis is semitranslucent and the spidery vessels are seen. The epidermis may be only a few cells thick in some areas.

Management

Patients should be instructed to avoid exposure of irradiated skin to the sun as much as possible, either by covering the area with clothing or by using a high sun protection factor (SPF-15 or greater) sun screen.

Oral Cavity and Pharyngeal Mucosa

Acute

The oral cavity and oropharynx are lined by nonkeratinizing stratified squamous epithelium. The renewal and radiosensitivity of the epithelium is slightly higher than that of skin.

After 2 to 3 weeks (2000 to 3000 cGy) of treatment at conventional fractionation, an erythema of the mucosal surfaces may be noted. After 4 to 5 weeks (4000 to 5000 cGy), superficial ulcerations with pseudomembranes may be seen, owing to the failure of the epithelium lost by desquamation to regenerate. The pseudomembrane consists of caked, dead epithelial cells, fibrin, and neutrophils. The ulcerations and pseudomembranes are usually scattered, producing a clinical picture of patchy mucositis; in severe cases ulceration associated with pseudomembrane covers relatively large areas, producing the clinical picture of confluent mucositis.

By the end of a 6- to 7-week course of radiation, the repopulation of the normal epithelial cells stimulated by the continued cell loss from the radiation is intense, and new cells have begun to replace the previously denuded areas. Clinically, this repopulation sometimes results in a picture of radiation mucositis peaking in intensity during the fifth week of treatment, and then paradoxically seeming to improve near the end of treatment despite the continuation of the radiation.

Mucositis may occur earlier and be more severe in the buccal mucosa along the biteline and lateral border of the oral tongue when they lie adjacent to dental silver amalgam or gold fillings. This occurs secondary to the generation of an excessive number of low-energy electrons when the x-ray therapy beam interacts with the metal filling, causing an increased surface dose along adjacent mucosa of 109 to 170 per cent. Placement of some low-atomic-number material such as the plastic of an athletic mouthguard between the filling and mucosa absorbs the electrons and prevents the excessive dose.

Mucositis heals rapidly, beginning a few days after the completion of radiation, and typically is almost completely resolved in 2 to 3 weeks.

Management of Radiation Mucositis

Pain and discomfort from early mucositis can often be relieved by the use of a liquid antacid such as Maalox, 30 mL before meals, and Aspergum between meals.

Systemic narcotic pain medications such as acetaminophen and codeine may need to be prescribed for pain from more severe mucositis. Topical medications such as Viscous Xylocaine 2 per cent (15 mL q4h), Oxaine M suspension (15 mL q4h), or Dyclone liquid 0.5 per cent (dilute 1:1 with water and take 15 mL of dilution q4h) may also provide temporary relief. They are usually of most benefit when taken just before eating.

Chronic

Areas of mucosa receiving high doses of radiation become atrophic and scarred, with the development of telangiectatic vessels.

Salivary Glands

Acute Radiation Parotitis

Serum amylase levels have shown 10- to 20-fold rises within 24 hours after the atart of radiation to a field including the parotid gland. Rarely, on the same time scale, the patient may develop pain, tenderness, and swelling in the region of the parotid. These acute findings typically resolve even if the radiation is continued.

Acute Changes in Salivary Composition and Secretion

In patients in whom the major salivary glands are being treated, there is a 50 to 75 per cent decline in the salivary flow rate after 1 to 2 weeks of conventionally fractionated radiation.

Saliva sodium concentration rises sharply during the first week of radiation, with minimal changes in the potassium, magnesium, and calcium concentrations. There is also a gradual increase in the number of salivary *Candida albicans* during radiation. The saliva tends to be more mucoid in quality; it is hypothesized thagt the serous acini are affected earlier than the mucous acini.

Management of Salivary Changes During Treatment

Because of the decreased, thickened saliva, patients are instructed to rinse the mouth with a solution of salt and baking soda (1/2 teaspoon of salt plus 1/2 teaspoon of baking soda in 1 quart of water at room temperature) from the start of treatment.

Overgrowth of *Candida* infection results in the appearance of fungal plaques and/or a premature pharyngitis and may be managed with one of the following regimens: (1) nystatin oral suspension, 100.000 units per mL, 5 mL four times daily, retained in the mouth as long as possible before swallowing; (2) Mycostatin pastilles, one dissolved in the mouth four times a day; (3) Mycelex Troche (clotrimazole), 10 mg dissolved in the mouth five times a day; or (4) ketoconazole, 200 mg, one tablet a day.

Chronic Salivary Changes: Xerostomia

The severe reduction in salivary flow is nearly always permanent after a full course of radiation that incluides the major salivary glands. In a Washington University study, only one-fifth of treated patients receiving doses of 4000 to 6000 cGy had measurable parotid flow after salivary stimulation; none of 24 patients receiving doses of more than 6000 cGy had measurable flow.

At least 50 per cent of both parotids must be excluded from the radiation field to prevent the development of severe xerostomia when the sublingual and submaxillary glands are also in the field.

Management of xerostomia is palliative only. Artificial saliva solutions, glycerin, or water may be used by patients as a matter of individual preference to keep the mouth lubricated.

Teeth and Bone

Prophylactic Dental Management

The main goals of an aggressive system of prophylactic dental management before and after radiation are (1) to preserve any remaining teeth, which, because of the reduction in saliva and changes in salivary composition, are prone to radiation caries; and (2) to eliminate any existing, and head off the development of any future, predisposing factors toward osteoradionecrosis.

Dental management of patients must begin before the start of radiation. Daly and colleagues defined four management groups of patients on the basis of their initial preradiation dental evaluation:

Group I. Edentulous patients.

Group II. Poor dental hygiene; severe periodontal disease involving numerous teeth.

Group III. Average dental hygiene; severe periodontal disease or periapical cysts involving only a few teeth.

Group IV. Very good dental hygiene. No significantly diseased teeth.

Group I patients usually require no special care before treatment but may need to adjust to being temporarily unable to wear dentures routinely once radiation has begun. Group II patients require complete extractions of teeth and radical alveolectomy. It is critical that the alveolus be smoothed and that good primary closure be obtained. A minimal of 10 to 14 days must be allowed for healing. Group III patients may need selective extractions of diseased teeth, but usually most of their teeth can be salvaged. Group IV patients require no extractions.

Any remaining teeth in groups III and IV patients should have polishing and smoothing of any irritating spicules, and filling of any cavities.

After completion of radiation therapy, patients with remaining teeth must continue to apply acidulated phosphate fluoride gel for a minimum of 5 to 10 minutes daily, using a custom carrier mold over their teeth. Acidulated phosphate fluoride is also available as a rinse supplement (5 to 10 mL swished vigorously around and between the teeth for 1 minute after brushing, then expectorated), but the gel is the preferred method. Compulsive daily dental hygiene with gentle, thorough brushing is mandatory. A water pik may be used at low-force setting to ensure clearing of food particles. Daily alkalinization (1/2 teaspooon of baking soda plus 1/2 teaspoon of salt in 1 quart of room temperature water, to be used as a mouth rinse at least four times daily) of the oral cavity should also be done, because the acidic pH of saliva after radiation may be an important factor in the development of radiation caries. Dental checkups should be performed on a regular basis.

These measures must be continued for life, and clearly require a highly motivated patient.

Osteoradionecrosis

Pathologically, osteoradionecrosis is characterized by (1) loss of osteoblasts and osteoclasts, in turn causing lack of new osteoid; (2) replacement of marrow by loose connective tissue; and (3) vascular changes, with narrowing of arteriolar lumens and fibrosis and obliteration of the fine vasculature. The consequence of these changes is an increased susceptibility to stress and fracture, and poor healing after infection or trauma.

Radiologically, the most common feature is bone demineralization, sometimes with coarsening or disorganization of the trabecular structure.

Several radiation therapy factors predispose to osteonecrosis. Morrish and colleagues found mandibular bone necrosis in 85 per cent of dentulous patients receiving a mandible dose exceeding 7500 cGy; there were no cases at dosages of less than 6500 cGy. Cheng and

Wang, converting dose-time-fractonation to NSD ret, found a significant risk at 2100 ret (equivalent to about 7800 cGy given in a dosage of 200 cGy per day five days a week). Such doses may easily be exceeded if the patient has had an interstitial implant close to or abutting the bone. Radiation treatment volumes covering more than 75 per cent of the mandible increased the risk.

The most common dental or surgical factors associated with osteoradionecrosis include (1) breakdown of a postradiation extraction wound, (2) spontaneous bone exposures associated with diseased teeth (periodontal disease, or less importantly, caries), (3) breakdown of preradiation extraction sites, (4) subsequent mandible resection for recurrence, and (5) irritation by dentures.

Anatomic and tumor factors increasing the risk include (1) a four times greater incidence in mandibular sites than in maxillary sites and (2) primary tumor involving bone or mucosa over bone.

Beumer and associates considered that the most useful prognostic factor for the ultimate outcome was the nature of the bone exposure at initial evaluation. When the bone necrosis was surrounded by a zone of attached mucosa, 66 per cent of patients responded to conservative treatment. When the bone exposure extended beyond the attached mucosa, only 37 per cent of patients responded to conservative measures.

Management of Osteoradionecrosis

Conservative measures should first be tried to manage areas of osteoradionecrosis. Beumer and associates described the following: (1) several daily saline irrigations, (2) oral antibiotics for acute infections or with significant pain, (3) occasional topical antiseptics or antibiotic packings if anatomically feasible, and (4) removal of any visibly loose bone elements with forceps. These measures should be continued as long as the lesion remains stable or improves.

If the area of involvement increases, a trial of hyperbaric oxygen may be considered, with or withou surgical sequestrectomy.

Management of Postradiation Dental Extractions

Patients who must undergo postradiation dental extractions are potentially at very high risk of developing osteoradionecrosis. Furthermore, once osteoradionecrosis has developed in such a site, it responds poorly to conservative management. Beumer and associates believed that every effort should be made to avoid extraction, and suggested the option of root canal work with subsequent amputation of teeth at the gingival margins to allow good access for cleaning.

Hariot and colleagues described the following procedure for managing the patient who must have a postradiation extraction. Patients are placed on a broad-spectrum antibiotic, typically a cephalosporin, 2 days before the planned extraction. The antibiotic is continued a minimum of 8 days after the extraction, which is performed under general anesthesia using strict aseptic technique. A careful alveolectomy is carried out, with smoothing of the alveolar ridge. The gingiva is closed primarily even if a piece of lingual or buccal mucosa must be

mobilized. Suturing is done without tension. All feedings are through a nasogastric tube for 8 days after surgery to avoid trauma to the extraction site.

Using such a conservative technique, Horiot and colleagues achieved a very low (2 per cent) incidence of osteoradionecrosis in 22 postradiation (16 months or longer) extractions. This percentage is in contrast to the more typical one of 20 to 25 per cent.

Larynx

Subacute Changes: Laryngeal Edema

Edema of the larynx and arytenoids develops in nearly all patients after full-course radiation therapy to the larynx. Radiation-associated edema typically subsides within 3 months after radiation. Persistent smoking, chronic postnasal drip, voice abuse, or overstraining may aggravate and prolong the edema.

Persistence of significant edema beyond 3 months may pose a serious diagnostic dilemma, since it may potentially represent persistent or recurrent submucosal tumor. However, the deep biopsy necessary to rule out this possibility may precipitate a worsening of the edema, chondritis, or chondronecrosis.

Fu and associates reported that 38 of 247 patients (15 per cent) irradiated for carcinoma of the true vocal cord had edema that persisted beyond 3 months. Of these, 17 of 38 (45 per cent) had persistent or recurrent disease associated with the edema. The incidence of persistent edema beyond 3 months significantly increased when the total dose exceeded 7000 cGy given with conventional-sized fractions.

Management of Persistent Edema Beyond Three Months

Conservative measures should be tried first: voice rest, discontinuation of alcoholic beverages and cigarette smoking, and a course of antibiotics and steroids. If despite these measures, (1) the edema does not subside, (2) the edema is asymmetric, (3) the edema reappears or worsens, or (4) fixation of the larynx develops, a biopsy must be performed to rule out a tumor.

Chronic Changes: Chondronecrosis

Necrosis of cartilage in the laryngeal skeleton is a rare complication of conventionally fractionated radiation treatment of larynx cancer; eight of 1077 cases (0.7 per cent) were reported in series from four institutions. Significantly higher incidences have been reported when daily fraction sizes of 300 cGy or more are used. Necrosis is characterized by pain, edema, tenderness, and low-grade fever.

Treatment initially should be conservative with antibiotics and steroids. If this is unsuccessful, a laryngectomy may be necessary.

Thyroid

Laboratory evidence of primary hypothyroidism after irradiation to the thyroid is common. Samaan and colleagues found that 40 of 66 patients (61 per cent) irradiated to the neck with tumoricidal doses (5000 cGy or greater) developed low T3 and T4 hormones in the presence of high serum TSH. Symptomatic hypothyroidism is relatively uncommon, occurring in about 5 per cent of patients.

Management

Symptomatic primary hypothyroidism is easily treated with thyroid hormone replacement. Hormone supplements should probably also be given in asymptomatic patients, particularly in younger individuals, since it has been suggested that chronic stimulation of the thyroid gland with high levels of TSH may play a role in the genesis of thyroid cancer. Thyroid function should be checked at follow-up at 6- to 12-month intervals.

Ear

Middle Ear

Obstruction of the eustachian tube with conductive hearing loss may occur as a result of the hyperemia and edema caused by radiation after about 5 weeks of conventionally fractionated radiation. Oxygen and later nitrogen is absorbed from the closed middle ear cavity, producing negative pressure and transudation of serous fluid. This is enhanced by the vascular dilatation and edema caused by the radiation. The fluid is sterile and is usually absorbed within a few weeks after completion of therapy.

Active treatment with myringotomy and the insertion of ventilation tubes to remove fluid should be carried out if the fluid persists after treatment.

Inner Ear

Direct damage to the inner ear structures has rarely been reported with cancericidal levels of radiation. Indirect damage due to an untreated radiation-associated chronic serous otitis is the more common concern.

Eye

The eye or the optic nerve is commonly within the radiation field only in the treatment of tumors of the paranasal sinuses, nasal cavity, or nasopharynx.

Lens

The lens is exquisitely sensitive to radiation. Single doses of 400 to 500 cGy and conventionally fractionated doses of 1000 to 1200 cGy are sufficient to cause a significant incidence of cataract formation. Radiation cataracts usually are first visible in the posterior subcapsular zone. They may arrest at any stage of their development.

The time before development of a radiation cataract depends on the dose given: the higher the dose, the more quickly a cataract may develop. The latent period is usually several

years after low doses of fractionated radiation or may occur within months after very high doses (greater than 6000 cGy).

Management of Radiation-Induced Cataracts

Cataract extractions with placement of a contact lens or an intraocular lens implant are common surgical procedures, but there is little published experience in their use in patients who have received high doses of radiation. Patients who also have a dry eye syndrome may not tolerate a contact lens. It has been suggested that there may be an increased incidence of complications if an intraocular lens implant is attempted in an irradiated eye.

Lacrimal Glands

Loss of adequate lubrication to the eye because of damage to the lacrimal glands may result in a dry eye syndrome characterized by a foreign body sensation in the eye, pain, and photophobia. Loss of vision may result from corneal ulceration and scarring.

Most of the basal secretion of tears is from the accessory lacrimal glands rather than the major lacrimal gland. In general, the sensitivity of the lacrimal glands to radiation approximates the sensitivity of the salivary glands. Most patients can receive 3000 to 4000 cGy to the entire orbit without developing symptoms of a dry eye. If higher doses than this are given, the major lacrimal gland and a portion of the lateral upper lid (to spare accessory lacrimal tissue) should be spared. If this cannot be done, the prospects of maintaining vision are small if the dose to the orbit exceeds 5000 cGy.

Management of Dry Eye Syndrome

Frequent and compulsive use of lubricating eye drops during the day and an ophthalmic lubricating ointment at night (Lacri-Lube), along with the use of protective glasses to spare the eye from winds, may help to prevent the development of corneal ulcers. If such an ulcer does develop, a hydrophilic soft contact lens may be tried as a "bandage".

Optic Nerve

For conventionally fractionated radiation, injury to the optic nerve causing visual loss is rare when the total dose is less than 6000 cGy. Damage may appear at lower doses when higher daily fraction sizes (250 cGy or greater) are used.

Injury has been classified into two types. Ischemic optic neuropathy is due to injury at the distal end of the optic nerve. Ophthalmoscopic examination reveals edema and pallor of the disc and splinter hemorrhages on or around the disc. Retrobulbar optic neuropathy is due to injury to the proximal portion of the nerve. There often are no signs on ophthalmoscopic examination.

The injury typically develops 2 to 5 years after radiation treatment.

Retina

Injury to the retina probably begins to appear with a significant incidence after doses of 5000 and 6000 cGy. Visual acuity is typically normal until 9 to 18 months after the radiation, when gradual, progressive visual loss begins. The pathologic characteristic of radiation injury to the retina is (1) hyalinization of the walls of the arteries and arterioles with myointimal proliferation and (2) capillary obliteration. The ophthalmoscopic examination shows signs very similar to those seen in diabetic retinopathy: capillary microaneurysms, cotton-wool patches, retinal hemorrhage, vessel sheathing, and neovascularization.

Management of Radiation Retinopathy

Panretinal laser photocoagulation has been useful in the treatment of diabetic proliferative retinopathy. There are anecdotal reports that this technique may be effective to treat the neovascularization associated with radiation retinopathy.

Pituitary and Hypothalamus

The pituitary and hypothalamus are rarely in the radiation portal for head and neck tumor. The common exceptions are tumors of the paranasal sinuses and the nasopharynx.

Samaan and colleagues studied hypothalamic-pituitary dysfunction in 110 patients who received a median dose of 5600 cGy to the anterior pituitary gland and 500 cGy to the hypothalamus during radiation treatment of carcinoma of the nasopharynx and paranasal sinus. Of these, 76 of 110 (69 per cent) showed some evidence of hypothalamic dysfunction. The most common hypothalamic deficit resulted in decreased growth hormone levels to insulin hypoglycemic challenge in 56 of 110 (51 per cent). The next most common deficit was high basal serum prolactin due to loss of the hypothalamic-produced prolactin inhibitory factor in 43 of 110 (39 per cent). Next was decreased cortisol levels to hypoglycemic challenge in 30 of 110 (27 per cent). Eight of 30 (27 per cent) of these patients had symptoms of severe cortisol deficiency. Lastly, nine of 110 (8 per cent) showed subnormal thyroid function, thought to be secondary to a hypothalamic lesion.

Forty-three of 110 patients (39 per cent) showed some evidence of pituitary dysfunction. The most common pituitary defect was decreased LH and FSH levels in 33 of 110 (30 per cent). The next most common deficit was secondary hypothyroidism with inadequate TSH secretion in response to administration of thyroid releasing hormone in 22 of 110 (20 per cent).

Samaan and colleagues suggested that there is a progressive increase in the percentage of endocrine abnormalities with time, most of the endocrine deficiencies appearing more than 2 years after radiation.

Management of Hypothalamic or Pituitary Dysfunction

The hypothalamic-pituitary axis should probably be evaluated every 6 to 12 months in patients receiving tumoricidal doses of radiation to these areas, and appropriate replacement therapy initiated when the endocrine dysfunction is first noted.

Brain

Acute Radiation Injury of the Brain

It was once thought that beginning a course of radiation therapy to large areas of the brain with doses of 200 cGy or more might cause cerebral edema, and it was common practice to initiate brain irradiation with doses as low as 50 cGy and then gradually increment the daily dose until 200 cGy per day was reached. Today the use of dexamethasone (4 mg q6h) before the start of brain radiation has minimized the concern over cerebral edema when daily dose fractions of 200 to 300 cGy are being used.

Typical head and neck radiation fields include only small areas of the brain, with the exception of fields for advanced nasopharyngeal cancer, paranasal sinus cancer, and temporal bone tumors. Even in these latter cases, it is not standard practice to start patients on steroids before the initiation of radiation. However, such patients should be followed carefully during treatment for signs of increased intracranial pressure.

Subacute Radiation Injury of the Brain

Two syndromes of subacute radiation injury of the brain have been described: (1) somnolence syndrome and (2) early demyelination syndrome. The pathogenesis of each is believed to be a transient disturbance in myelination, analogous to Lhermitte's syndrome of the spinal cord.

Somnolence syndrome occurs most frequently in children who receive prophylactic cranial irradiation in association with intrathecal methotrexate for acute leukemia. It is characterized by drowsiness, lethargy, anorexia, and irritability beginning about 6 weeks after radiation and lasting about 3 weeks. It resolves spontaneously without sequelae.

Early demyelination syndrome is an extremely rare clinical syndrome characterized by nausea and vomiting, followed by ataxia, dysarthria, dysphagia, nystagmus, and a positive Romberg sign beginning about 10 weeks after completion of 5500 cGy or more in or about the middle ear. Two out of three patients in the report that first described the syndrome recovered completely in 8 weeks; the third patient died.

Chronic Radiation Injury of the Brain

Late radiation necrosis of the brain is characterized by a progressive and chronic neurologic deficit originating in the volume of brain previously irradiated. The onset is typically 3 months to 5 years after the completion of radiation.

Pathologically, the lesion is confined to the white matter of the brain. Microscopic examination shows extensive areas of demyelination and large areas of coagulation necrosis in the white matter within or adjacent to the areas of demyelination.

The typical appearance on CT scans depends on the dose received. In patients receiving 5000 to 5500 cGy of conventionally fractionated radiation, radiation necrosis appears as diffuse, low-density lesions in a white matter area that received greater than 4500 cGy, with no mass effect or enhancement after contrast administration. In patients receiving

6000 to 7000 cGy, two patterns are seen: (1) a localized mass in an area that received greater than 6000 cGy that enhances irregularly after contrast, and (2) diffuse low-density, isodensity, or high-density lesions affecting a white matter area that received 5500 cGy or greater; some of the lesions may show enhancement with contrast.

Sheline and associates estimated the risk of brain necrosis to be 0.04 to 0.4 per cent with a dose of 5200 cGy of conventionally fractionated radiation; Rubin and colleagues estimated an incidence of 50 per cent when the whole brain receives 6000 cGy.

The pathogenesis is uncertain. Three hypotheses have been proposed. The vascular hypothesis (the most widely favored) is that progressive radiation damage to small and medium-sized blood vessels causes tissue necrosis from ischemia. In the glial hypothesis, radiation-induced injury to glial cells, particularly oligodendroglial cells, is believed to lead to demyelination and white-matter cavitation. In the immunologic hypothesis, the pathologic lesions are thought to result from an allergic response to antigens released from damaged cells.

Spinal Cord

Subacute Radiation Injury to the Spinal Cord

Lhermitte's syndrome or transient radiation myelopathy is a subacute, radiation-associated injury to the spinal cord characterized by an abnormal sensation of electric discharge down the spine and limbs on flexion of the neck. It typically occurs 2 weeks to 7 months after irradiation to the spine. This clinical latent period is thought to correspond to the survival of myelin that was laid down before irradiation. When replacement is finally needed, the irradiated oligodendroglial cells do not lay down new myelin properly. Some of the axons remain denuded and sensitive to physical distortion until the oligodendroglial cells recover.

This condition is more common with higher radiation doses but can be seen with doses as low as 200 cGy. Symptoms are transient and abate spontaneously. There is no relationship between the occurrence of Lhermitte's syndrome and the later development of chronic progressive radiation myelopathy.

Late or Chronic Radiation Injury of the Spinal Cord

Acute Paraplegia or Quadriplegia Syndrome

This exceedingly rare syndrome is characterized by a rapid progression to completion of the neurologic deficit over a period of just a few hours to days. It occurs after a typical latent period of about 6 years after radiation, and is presumably the result of sudden spinal cord infarction caused by radiation-related vascular changes.

Motor Neuron Disorder Syndrome

This exceedingly rare syndrome is characterized by a flaccid paralysis of the legs or rarely the arms without sensory loss, the onset being 5 months to 5 years after irradiation. It is due to selective radiation-associated damage to the anterior horn cells.

Chronic Progressive Radiation Myelopathy

This is the most common manifestation of chronic or late radiation spinal cord injury. It is characterized by a progressive spinal cord lesion affecting particularly the lateral columns. The first symptoms are numbness and paresthesias of the lower limbs, often initially unilateral, followed by weakness and loss of sphincter control. Some patients present with Brown-Séquard syndrome. Myelography usually shows an atrophic segment of cord but sometimes may show cord swelling simulating an intramedullary tumor. The onset is 5 months to 5 years after radiation. The latent period tends to be shorter, the higher the dose of radiation. The disability typically progresses over a period of months to a spastic paraparesis, which in half the patients is fatal within 2 years. Pathogenesis is similar to that of radiation necrosis of the brain.

Rubin colleagues estimated that the incidence of radiation myelopathy is 5 per cent at 4500 cGy and 50 per cent at 5500 cGy when a 10-cm length of spine is being irradiated. Wara and associates noted that in their experience, 5000 cGy of conventionally fractionated radiation appeared relatively safe. Abbatucci and colleagues, specifically studying myelopathy in the cervical spinal cord, suggested that there is little risk up to 5500 cGy, but that myelopathy is inevitable at 7000 cGy. Head and neck radiation treatment usually attempts to limit the spinal cord dose to between 4000 and 4500 cGy.