Chapter 114: Radiation Therapy

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History

After the discovery of x-rays by Roentgen in 1895 and radium by the Curies in 1898, early workers in radiotherapy began to apply ionizing radiation to the treatment of cancer, including cancers of the larynx and hypopharynx. Methods of quantitating dose were crude in comparison to modern dosimetry. Early workers did not know how much radiation to give, nor did they know the optimal time for administration.

Workers in major centers in Europe experimented with several methods of dose delivery: (1) intensive dosages, (2) repeated short courses, (3) many subdivided doses, and (4) the protracted-fractional dosages (Del Regato, 1968). Patients who were given large doses of radiation in a short period often died prematurely. The method of repeated short courses with intervals of 2 weeks or more between treatments over a total period of several months was generally ineffective and resulted in regrowth of the tumor. Repeated intensive courses and several subdivided doses likewise failred to eradicate the tumor and caused some acute normal tissue reactions.

The empiric method developed by Henri Coutard at the Foundation Curie, otherwise known as the protracted-fractional method of irradiating cancer, proved to be the best (Coutard, 1932). Coutard gave small amounts of irradiation daily over several weeks and was able to give higher doses of irradiation to the larynx and hypopharynx than previously thought possible. This method of treatment caused some of the cancers to disappear completely and produced the first reported cures of carcinoma of the larynx and hypopharynx by irradiation (Coutard, 1932). Coutard (1935) also experimented with a concept he termed "periodicity", which was based on the hypothesis that squamous cell carcinomas had periodic heights of greater radiovulnerability and that irradiation during such periods would cure more tumors. The greatest number of cures was recorded between 39 and 52 days, but, of course, this was the period of greatest total dose (Del Regato, 1967).

An important milestone in modern radiotherapy were the animal experiments conducted by Regaud, an early radiobiologist at the Foundation Curie. Regaud experimented with the constantly growing epithelium of the seminal tubules of the ram as a model for a malignant tumor (Del Regato, 1968). He found that several small doses of irradiation sterilized the testis without producing necrosis of the scrotum, whereas the same total dose in a single fraction produced necrosis of the scrotum and failed to sterilize the testis. These experiments provided a rationale for the use of daily fractions of radiation over a longer period.

Early radiotherapy

The use of radiation to treat laryngeal and hypopharyngeal cancers has been documented thoroughly in a series of publications from four major centers in Europe and England: the Foundation Curie in Paris (Baclesse, 1949, 1964; Bataini et al, 1974, 1982; Coutard, 1932), the Radiumhemmet in Stockholm (Ahlbom, 1941; Jacobsson, 1951; Werner and Bäryd, 1970), the Royal Marsden Hospital in London (Lederman, 1953, 1962, 1970), and the Western Infirmary in Edinburgh (Pearson, 1966). Review of these writings is important because they record the trial and error experiences of the early radiotherapists who eventually established the time-dose-fractionation schemata that are currently employed in the irradiation of patients with cancers of the larynx and hypopharynx. Coutard (1932) noted very early that the protracted-fractional method of dose delivery cured more cancers of the upper than the lower hypopharynx. Presumably, cancers of the upper hypopharynx were more responsive to radiation than those in the lower hypopharynx because they were more easily visualized by indirect laryngoscopy and therefore detected at an earlier stage. This classic observation that small cancers of the larynx and hypopharynx are more radiocurable than large cancers remains true today.

In 1949 Baclesse again described four patients with cancer of the hypopharynx that had been irradiated and cured by Coutard between 1932 and 1933. The dose and time in these four patients were 7000 roentgens (R) in 16 days, 7500 R in 28 ays, 8800 R in 34 days, and 9100 R in 45 days. Severe laryngeal edema and possible necrosis of the larynx occurred in all of these patients except the one treated over 45 days. Observations such as these led to the fractionation of the total dose of irradiation over a longer period. Coutard found that he could avoid acute exudative epithelialitis and continue irradiating the cancer without interruption by protracting the time of dose delivery and by progressively reducing the field size (Coutard, 1932). This method also eliminated the late radiation complications so prevalent during early clinical experimentation (1932 to 1933). The next seven patients irradiated and cured of their cancer between 1937 and 1942 received doses ranging from 5200 R in 73 days to 7400 R in 69 days and had no late radiation complications. In summarizing these results, Baclesse declared, "My co-workers and I now attempt to reduce cutaneous reactions by prolonging treatment time and by reducing the size of the fields while increasing the total dose" (Baclesse, 1949).

The technical and clinical evolution of early radiotherapy at the Radiumhemmet in Stockholm was recorded in meticulous detail by Ahlbom (1941). These workers used small teleradium sources to treat small cancers of the larynx and hypopharynx, and kilovoltage beams (170 to 180 kV) to treat larger cancers. The teleradium sources consisted of 3 to 5 g of Radium-226 and had to be placed close to the skin (6 cm) because output was so low that treatment times were otherwise excessive. Roentgen therapy produced higher radiation output (20 to 30 R/min) at longer distances (40 to 50 cm) from the patient's surface. The kilovoltage beams also had greater penetrability than the teleradium sources and could be used to treat larger and more extensive tumors of the larynx and hypopharynx. Dose was occasionally verified by the intrapharyngeal insertion of Sievert's condensor chambers.

Ahlbom, like his fellow workers in Paris, also discovered that the delivery of higher total doses over longer periods resulted in fewer complications and more cures (Ahlbom, 1941). He described three groups of patients with cancers of the larynx and pharynx who were treated by different methods. The first group was irradiated by the intensive method and received large doses of irradiation over short periods. These patients experienced excessive complications, including laryngeal necrosis, aspiration, and airway obstruction. Bronchopneumonia frequently ensued and patients often died several weeks after the completion of irradiation. It seemed to Ahlbom that the tissues around the tumor were unable to repair the defect caused by disintegration of the cancer. A second group receive lower doses of irradiation and experienced temporary relief of signs and symptoms as the tumor shrank. The tumor ultimately regrew in these patients, and no cures were recorded. The best results were achieved in a third group of patients, who received intermediate doses of irradiation over a protracted period. Ahlbom thought the ideal dosage was between 5000 and 6000 R over 20 to 30 days. He observed that the same dose over 40 to 50 days resulted in the regrowth of most cancers and that the same dose in less than 20 days often caused necrotic disintegration of normal tissues. His description of the complications of irradiating the larynx and pharynx to high doses over short periods is classic.

A later publication by Jacobsson from the Radiumhemmet gives insight into technical innovations that would later have significant impact on treatment results for carcinomas of the larynx and hypopharynx. His 1951 publication was the first to show immobilization of a patient in the sitting position during irradiation. It was also the first to describe the use of fluoroscopy for tumor localization and to illustrate the use of a four-field technique for irradiation of a cancer of the larynx. This illustration was very similar to radiotherapy treatment plans that are currently used. It depicted a horizontal cross section of the neck and showed the tumor, the spinal cord, and the direction of the radiation beams and reconstructed the distribution of dose within the tissues. Immobilization of the patient, use of fluroscopy to direct the radiation beam, and treatment planning improved treatment results and reduced complications. More patients with cancers of the hypopharynx were free of signs and symptoms after these technical innovations were introduced in 1943 than before (Fig. 114-1). These workers also observed 13 cases of radiation myelopathy between 1939 and 1942, and none after institution of fluoroscopy in 1943.

Epidemiologic observations

Cancers of the larynx and piriform sinus have been associated with heavy smoking and alcohol intake (Fig. 114-2), whereas those of the lower hypopharynx or postcricoid region have been associated with the nutritional deficiencies of vitamin C and iron (Wynder et al, 1957, 1976). The risk of development of cancer of the larynx increases with increasing amounts smoked (Fig. 114-3) and decreases with time after cessation of smoking (Fig. 114-4). Tuyns and co-workers (1988) report that the carcinogenic effect of alcohol is even present at the lowest levels of tobacco consumption (Fig. 114-5) and that alcohol influences development of epilaryngeal and hypopharyngeal cancers more than development of endolaryngeal cancer. Presumably, alcohol bathes the mucosa of the epilarynx and hypopharynx but does not have access to the mucosa of the endolarynx. So it seems that tobacco and alcohol act both separately and together to increase the risk of cancers of the laryngopharynx.

Epidemiologic observations have shown a variation in the incidence and type of hypopharyngeal cancer for different countries in Europe and a correlation between sex and location of hypopharyngeal cancer (Ahlbom, 1941; Jacobsson, 1951). Workers appreciated very early that cancers of the lower hypopharynx were particularly common among women from northern latitudes (Ahlbom, 1941). Ahlbom noted a high incidence of postcricoid cancers among the women of northern Sweden, many of whom had subsisted for long periods on diets deficient in fresh meat, fresh-water fish, green vegetables, and fresh fruit. Such a diet was particularly low in vitamin C and iron and was associated with a longstanding history of dysphagia, iron deficiency anemia, atrophic mucosa, and spoon-shaped nails, findings characteristic of Plummer-Vinson syndrome. In 1938, Sweden passed a law requiring that the flour be fortified with iron. This lead to correction of the nutritional deficiencies noted in the women of northern Sweden and ultimately reduced the incidence of both Plummer-Vinson syndrome and hypopharyngeal cancer. Three successive publications from the Radiumhemmet show a dramatic reduction in postcricoid cancers of the upper hypopharynx or pyriform sinus among men (Ahlbom, 1941; Jacobsson, 1951; Werner and Bäryd, 1970).

Megavoltage irradiation

Radiotherapy entered modern megavoltage era with the development of cobalt-60 (60Co) sources, betatrons, and linear accelerators in the late 1940s. These machines produced radiation beams that were more penetrating and therefore capable of irradiating deep-seated tumors. They spared skin, were not preferentially absorbed by bone, and exhibited less scatter to adjacent tissues. These favorable characteristics made it possible for radiotherapists to avoid wet desquamation of skin, to irradiate cancers of the laryunx and hypopharynx in close proximity to the spinal cord safely, and to irradiate cancers of the larynx effectively without shielding of the tumor by ossified thyroid cartilage. An interesting publication by Pearson from the University of Edinburgh (1966) showed an increase in the number of patients irradiated with curative intent after the installation of a 4-megavolt (MV) linear accelerator in 1955. After the installation of this machine, fewer patients were treated with palliative intent and more survived (Table 114-1). The installation of the linear accelerator did not alter the proportion of survivors, but it did increase the total number of survivors because more patients were irradiated with curative intent.

Most patients with cancers of the larynx and pharynx who enter institutions in Europe (Ahlbom, 1941; Baclesse, 1949; Bataini et al, 1974, 1982; Coutard, 1932; Jacobsson, 1951; Werner and Bäryd, 1970), Great Britain (Lederman, 1953, 1962, 1970; Pearson, 1966), and Canada (Harwood et al, 1980, 1981, 1983; Keane et al, 1983) are irradiated with curative intent, whereas many of these same types of patients are treated surgically in the USA (Byhardt and Cox, 1980; Carpenter et al, 1976; Cunningham and Catlin, 1967; Eisbach and Krause, 1977; El Badawi et al, 1982; Marks et al, 1978a, 1978b, 1979; Ogura and Biller, 1970; Shah et al, 1976; Wang, 1971). Surgery has been used for patients with cancers of the larynx and pharynx in the USA because patients primarily consult otolaryngologists and surgeons for diagnosis and treatment recommendations. Radiotherapists have been consulted secondarily about the management of these patients and were not primarily involved until a tendency to use adjuvant irradiation with surgery developed in the mid-1960s (Ogura and Biller, 1970). Since that time radiotherapists and surgeons have worked more closely in the management of these patients and many improvements in surgical and radiotherapy technique have occurred. In particular, improved methods of reconstruction and evolution from preoperative to postoperative radiotherapy have diminished postsurgical complications and made it possible to resect larger tumors safely in a single operative procedure. Also, methods of conservation surgery and radiotherapy that spare anatomy and function without compromising tumor control have been developed. For instance, the ability of irradiation and surgery to control the primary and regional tumor and to save the voice in patients with cancers of the larynx and pharynx has steadily improved over the past 20 years. Little question exists that the results currently achieved by surgery and irradiation are superior to those reported at the end of the early period of radiotherapy.

Anatomy

A fundamental knowledge of laryngeal and hypopharyngeal anatomy is necessary to allow the clinician to understand (1) how a particular cancer affects pharyngeal and laryngeal function to produce signs and symptoms, (2) how patterns of local invasion and lymphatics and distant spread differ for individual cancers of the larynx and hypopharynx, and (3) how the extent of tumor within the larynx and hypopharynx determines treatment selection. The larynx opens into the upper tracheobronchial tree and anatomically separates the functions of respiration and phonation from swallowing. The larynx is surrounded by the hypopharynx laterally and posteriorly and has anatomic boundaries that prevent the aspiration of food during swallowing (Fig. 114-6). The laryngeal vestibule is separated from the piriform sinus laterally by the marginal structures of the larynx (free margin of epiglottis, aryepiglottic fold, and arytenoid), and the glottic and subglottic regions are separated posteriorly from the hypopharynx by a common partition, the cricoid cartilage. Thus food passes laterally into the laryngopharyngeal sulci and then posterior to the cricoid cartilage into the upper cervical esophagus without entering the upper airway.

The larynx is subdivided into glottic, supraglottic, and subglottic regions (Fig. 114-7). The glottic region is formed by the true vocal cords and the anterior commissure and extends 5 mm below the free margin of the true vocal cord. From this point to the inferior border of the cricoid cartilage is the subglottic region of the larynx. The supraglottic region extends from the superior margin of the true vocal cord and includes the ventricle, false vocal cords, epiglottis, aryepiglottic folds, and arytenoids. Cancers that involve the supraglottic region above and the glottic-subglottic region below are called transglottic. Cancers of the free margin of epiglottis, aryepiglottic folds, and arytenoids are frequently referred to as marginal or epilaryngeal cancers, while cancers of the ventricle, false vocal cords, and infrahyoid epiglottis are often referred to as central supraglottic cancers. Cancers of the suprahyoid portion of the epiglottis frequently involve vallecula and base of tongue and are variously referred to as vallecula-base of tongue cancers or glossoepiglottic cancers.

The piriform sinus, or laryngopharyngeal sulcus, is a continuation of the glossopharyngeal sulcus above. It is separated from the laryngeal vestibule by the marginal structures of the larynx, has an ill-defined apex at its inferior extent, and is open posteriorly.

The pharyngeal wall joins the lateral portion of the piriform sinus and forms the posterior part of the hypopharynx. It is in direct continuity with the oropharynx above and the cervical esophagus below. It is formed by the superior, middle, and inferior pharyngeal constrictors and lies in direct contact with prevertebral fascia.

The postcricoid region of the hypopharynx is the large mucosal surface overlying the cricoid cartilage. Postcricoid cancers, because of their close proximity to the piriform sinuses laterally and the cervical esophagus inferiorly, commonly involve these structures and are sometimes termed epiesophageal cancers (Lederman, 1962).

Patterns of Spread

Whole-mount serial section studies after laryngectomy and laryngopharyngectomy for cancers of the larynx and hypopharynx have elucidated patterns of local invasion that explain certain presenting signs and symptoms (Kirchner, 1969, 1975; Kirchner and Som, 1971a, 1971b; Kirchner et al, 1974; Olofsson and van Nostrand, 1973). Glottic cancers commonly invae the underlying thyroarytenoid muscle and inhibit the mobility and vibration of the vocal cords to cause hoarseness. Glottic cancers have a tendency to spread upward and downward in the paraglottic space to become transglottic (Fig. 114-8) (Kirchner et al, 1974). Cancers of the piriform sinus also cause hoarseness by invading the larynx medially to involve the paraglottic space and the thyroarytenoid musculature (Kirchner, 1975). More advanced cancers of the transglottis and piriform sinus frequently invade thyroid cartilage, cricothyroid membrane, and upper cricoid cartilage to involve the extralaryngeal soft tissues (Kirchner et al, 1974; Kirchner, 1975). Cancers of the piriform sinus may also invade the cricoarytenoid joints or involve the recurrent laryngeal nerves just beneath the mucosa of the piriform sinus to fixate the hemilarynx and cause hoarseness (Kirchner, 1975). Hoarseness is also a common presenting symptom for patients with cancers of the supraglottis even though the tumor seldom involves the thyroarytenoid muscle or true vocal cord (Kirchner and Som, 1971a). Presumably, the hoarseness results from the bulk of the tumor, fixation of the false vocal cord, and alteration of the airway.

Cancers of the supraglottis, piriform sinus, and pharyngeal wall frequently ulcerate and cause sore throat and difficulty in swallowing. Sore throat, odynophagia, and hoarseness are, therefore, the cardinal presenting symptoms for the majority of patients with cancers of the larynx and hypopharynx (Marks and Ogura, 1982). Some patients who are otherwise asymptomatic notice an incidental neck mass and seek examination. A few patients develop weight loss and others complain of otalgia caused by pain referre to the ear. The transglottic lesions in particular may narrow the glottic opening to such a degree that stridor and airway obstruction result.

The radiotherapist must become familiar with patterns of local invasion to irradiate the areas at greatest risk for regrowth of tumor effectively. Cancers of the transglottic larynx frequently penetrate thyroid cartilage and cricothyroid membrane to gain access to the lymphatic vessels in the lower neck and parastomal regions (Kirchner et al, 1974). Techniques of irradiation that are effective in these areas are thus needed to prevent regrowth of tumor. Cancers of the piriform sinus also frequently invade thyroid cartilage to involve extralaryngeal soft tissues. The thyroid cartilage is destroyed in approximately half of those with a cancer of the lateral wall and nearly all of those with cancer of the apex of the piriform sinus (Kirchner, 1975). On occasion the cancer spreads posteriorly around the thyroid ala to invade the thyroid gland (Ogura, 1955). Extensive submucosal spread of cancer beyond the visible margins of the lesion is common for cancers of the piriform sinus as wll as those of the pharyngeal walls (Harrison, 1970; Kirchner, 1975; Olofsson and van Nostrand, 1973). Thus it is important to irradiate above and below the lesion adequately to cover for the possibility of submucosal spread.

There are regional variations in the incidence of lymph node metastases that may be explained by lymphatic density, degree of tumor maturation as determined by light microscopy or ploidy, and S-phase analysis as determined by flow cytometry. Aneuploid tumors are more likely to be histologically undifferentiated and to develop lymphatic and distant metastases (Hemmer et al, 1990). The very low incidence of lymphatic metastases from cancers of the true vocal cord is generally ascribed to a paucity of lymphatic vessels in the region of the glottis. The incidence of lymphatic metastases progressively increases as one proceeds above and below the glottis and from the central supraglottis outward. The incidence of palpable cancer in lymph nodes is least for cancers of the glottis; intermediate for cancers of the transglottis, central supraglottis, pharyngeal wall, and postcricoid regions; and greatest for cancers of the marginal supraglottis, glossoepiglottis, and piriform sinus (Fig. 114-9) (Marks et al, 1985).

The incidence of distant metastases varies for individual cancers within the larynx and hypopharynx and correlates fairly well with the incidence of lymphatic metastases (Fig. 114-10) (Marks and Ogura, 1982). Lymphatic and distant metastases also seem to be a function of tumor maturation and differentiation; at least, they are more common in patients who have nonkeratinizing and poorly differentiated cancers of the piriform sinus than in those who have keratinizing and differentiate cancers of the piriform sinus (Martin et al, 1980). The incidence of distant metastases also rises in those subpopulations who live longest, suggesting that time is required for subclinical microscopic deposits of tumor in distant sites to grow to detectable size (Marks et al, 1978a). Clearly, some form of systemic treatment is needed for the relatively high rates of distant metastases seen in patients with cancers of the piriform sinus, pharyngeal wall, and glossoepiglottis (Lee et al, 1980; Merino et al, 1977; Stefani and Eells, 1971).

Technique

The radiotherapist must have an intimate knowledge of the patterns of local and regional tumor spread, the anatomic barriers and relationship between normal structures, and the volume to be irradiated. He or she must then select a field perimeter that adequately encompasses the tumor and its regional lymph nodes as well as a dose distribution that delivers a tumoricidal dose with relative sparing of normal tissues in the irradiated volume. The optimal field perimeter is large enough to prevent regrowth of tumor at the margins of the irradiated volume and yet limited enought to prevent excessive irradiation of critical normal structures. The optimal dose distribution is sufficiently large to prevent tumor recurrence but not so large as to cause late radiation complications. Irradiation of cancers of the larynx and hypopharynx is particularly difficult because of their close proximity to the spinal cord and the fact that the spinal cord will not tolerate doses of irradiation sufficient to eradicate the tumor. It is, therefore, necessary to devise techniques of irradiation that will deliver a large dose to the tumor and satisfactorily limit the dose to the spinal cord. Since the larynx itself has to be irradiated to a high dose, conventional fractions of 1.8 to 2 gray/day (Gy/day) are used. Larger fractions over shorter periods have been associated with laryngeal swelling and cartilage necrosis (Fletcher et al, 1975). Irradiation of the neck often requires irradiation of the parotid glands and results in xerostomia. Once the major salivary glands have been irradiated, the patient's teeth are susceptible to decay. If the teeth can be preserved, they should be periodically cleaned and given fluoride to prevent radiation caries.

Cancers of the larynx and pharynx are easily localized by physical examination and radiographic technique. The field perimeter is then determined and verified radiographically on a simulator. The external contour of the patient and the spatial relationships among tumor, spinal cord, and larynx as determined by computed tomographic (CT) scan are directly transferred or diagrammatically represented in the treatment planning computer. A dose distribution that will satisfactorily irradiate the tumor and regional lymph nodes without excessively irradiating the spinal cord is then planned. A number of irradiation treatment aids are indispensable to the accurate delivery of the prescribed radiation dose. Heavy metal Cerrobend blocks that may be individually shaped to shield the spinal cord and irradiate the tumor are constructed. Patients are immobilized in the supine position with bite blocks and thermoplastic immobilization masks. Verification film can be left in place during irradiation to monitor changes in the volume irradiated, thus assuring reproducible daily delivery of dose to the tumor with sparing of normal tissues. Bolus is placed over scars to eliminate skin sparing and to prevent regrowth of tumor in the skin. Compensating filters and wedges are used to assure homogeneity of dose in regions of variable thickness such as the submaxillary triangles and the neck. Each of these aids is necessary to achieve accurate, homogeneous, and reproducible delivery of radiation dose to the tumor and the structures within the irradiated volume.

Radiation alone

Glottic cancer

Since the incidence of lymphatic metastases is very low, it is necessary to irradiate only the larynx of patients with cancers of the vocal cord. Fields are square and vary in size from 5 by 5 cm to 6 by 6 cm. Beam direction is usually lateral, and the anterior margin falls off the skin, thereby assuring inclusion of the anterior commissure, which is 8 to 10 mm below the skin. For patients who have a short, thick, flat neck it is sometimes necessary to use anterior oblique beam direction to prevent shielding of the larynx by the shoulders. Dose is calculated to the midplane of the larynx using a central axis thickness of 6 to 7 cm. Homogeneous dose distribution is achieved by using open fields for half of the treatments and wedge filters with the thick part anterior for the remaining half. Upright positioning of the patient ni a chair with bite block immobilization is also satisfactory. Doses of 60 to 70 Gy in 6 to 7 weeks are then delivered to the larynx.

Supraglottic, transglottic and piriform sinus cancer

Irradiating the neck as well as the larynx and pharynx of patients with cancer of the supraglottis, transglottis, and piriform sinus is essential since the incidence of lymphatic metastases is significant. Fields extend from the inferior margin of the mandible and mastoid tip to the clavicles and encompass the anterior and posterior cervical triangles as well as the larynx. Laterally directed beams are incapable of irradiating the low neck because of shielding by the shoulders. It is, therefore, advisable to use a three-field technique: two upper-lateral fields that encompass the larynx, pharynx, and upper neck are joined with an anterior low-neck field that encompasses the trachea, cervical esophagus, and lower cervical lymphatic vessels (Fig. 114-11). The spinal cord is shielded at the junction of the three fields to prevent overlap and excessive irradiation of the spinal cord. The spinal cord may be shielded from the lateral direction posterior to the larynx and pharynx at the junction of the three fields or by a midline block for the low-neck field. We routinely shield the cord from the lateral direction and avoid the use of a low-neck midline block since many patients with cancers of the larynx and pharynx are at risk for parastomal recurrence. A beam splitter is placed at the upper margin of the low-neck field to prevent upward divergence of the beam and overlap of the three fields in the region of the spinal cord at the splice. A few lymph nodes in the posterior cervical triangle are shielded, but this shielding is unpreventable if the spinal cord is to be protected.

Full-course irradiation of patients with cancers of the larynx and piriform sinus is accomplished with a series of shrinking fields above the anterior low-neck field. The first upper-lateral neck field encompasses the entire neck and includes the larynx, pharynx, and spinal cord. After a dose of 40 to 44 Gy in 4 to 4.5 weeks, the spinal cord and all of the neck posterior to the cervical vertebrae are shielded. The larynx, pharynx, submaxillary triangle, and that part of the neck anterior to the shield are then irradiated to 60 Gy in 6 weeks before the field is again shrunk to boost the primary lesion to the prescribed dose of 66 to 70 Gy in 6.5 to 7 weeks. That portion of the neck posterior to the cervical vertebra is boosted with an electron beam that penetrates a limited distance and spares the underlying spinal cord. The low-neck field is given 46 Gy in 4.5 weeks to a depth of 3 cm, which is equivalent to a maximum dose of approximately 50 Gy in 4.5 weeks. Areas of the neck that are known to be more heavily infested with cancer may then be boosted to higher doses with electron beam.

Adjuvant irradiation

Irradiating a patient before or after surgery with doses of irradiation that do not exceed the tolerance of the spinal cor is technically easy because splicing of many fields and use of electron beam irradiation can be avoided. The whole neck, larynx, pharynx, and spinal cord are simply irradiated in a singular field with the patient in the lateral oblique "chicken wing" position. Preoperative doses of 40 to 46 Gy in 4 to 4.5 weeks can be given with relative safety by this simple technique.

When the prescribed dose of adjuvant irradiation exceeds spinal cord tolerance, then it is necessary to use several spliced fields and electron beam in the same way described for full-course irradiation. As the tendency to use higher doses of postoperative radiation instead of lower doses of preoperative irradiation developed, the technique of irradiation simultaneously evolved from simple to complex. The use of many shrinking fields and placement of shields to protect the spinal cord require radiographic verification on the simulator and construction of electron beam masks. The logistics of treating the patient with multiple fields and multiple modalities has been simplified by the development of dual-energy linear accelerators that produce high- and low-energy x-rays and variable energies of electron beams.

Patients with large transglottic cancers who require emergency tracheostomy for airway obstruction are at particular risk for parastomal recurrence (Keim et al, 1965). It is essential, therefore, to deliver adequate doses of radiation to the subglottic an parastomal regions. This may be done easily by using anterior-posterior fields to a dose of 40 to 44 Gy in 4 to 4.5 weeks and then using anterior-oblique fields off the spinal cord to deliver the prescribed dose of 66 to 70 Gy in 6.5 to 7 weeks. Compensating filters are used to assure homogeneity of dose, and the tracheostomy tube is left in place to bolus the skin surrounding the tracheostomy opening. We have more recently experimented with a simplified three-field-triangular technique to avoid the difficulties of scheduling patients on several machines and to eliminate the possibility of hot and cold spots at the junctions of several spliced fields (Fig.

114-12) (Fields and Marks, 1986). This techniques uses compensating filters for the anterior oblique beams and a midline shield for the posterior beam. The radiation is distributed in a rind lateral and anterior to the spinal cord, and the distribution is similar in all parts of the neck, high and low. A dose of 50 to 55 Gy can be delivered to the pharynx and neck without exceeding 45 Gy to the spinal cord. Patients can be treated to these doses on a 4- to 6-MV linear accelerator, thus preventing the problems of scheduling the patient on several machines.

Doppke et al (1981) have also developed a method, the minimantle technique, which avoids the use of several fields and gives a homogeneous dose distribution to the tissues lateral and anterior to the spinal cord. Follow-up study of 47 patients treated by this technique has shown it to be safe and effective (Mirananoff et al, 1985). Anteroposterior-posteroanterior (AP-PA) fields are used with a posterior block to reduce the dose to the spinal cord, and the patient hyperextends the neck to prevent shielding of the upper neck by the jaw. The use of 10-MV x-rays for the minimantle technique gives better distribution of dose to the posteriorly located cervical lymph nodes than is possible with cobalt-60 or 4- to 6-MV x-rays. The three-field-triangular and minimantle techniques should improve the dosimetry and simplify the treatment of patients who have advanced cancers of the larynx and hypopharynx.

Factors Influencing Treatment Decisions

Curative versus palliative

Patients with advanced cancers of the larynx and pharynx are frequently nutritionally depleted and suffer from advanced and chronic diseases of the pulmonary, cardiovascular, hepatic, and renal systems. They are sometimes unable to be treated with curative intent because their medical condition is too poor or their tumor too advanced. As methods of anesthesia, surgical reconstruction, and nutritional support during irradiation have improved, it has become possible to treat the majority of these patients with curative intent (Table 114-2) (Marks and Ogura, 1982). This is an improvement of the days of early radiotherapy, when large numbers of patients were treated for palliation or given no treatment other than gastrostomy (Pearson, 1966). Once the patients to be treated with palliative intent are screened, those who have resectable tumors who are in relatively good medical condition remain. Selection of optimal treatment for these patients requires an understanding of the relative risks and benefits of different types of therapy as well as those host and tumor characteristics that predict tumor-node-metastasis (TNM) relapse and survival.

Predictors

Correlation of treatment outcome with the findings of the clinical examiner and surgical pathologist is used to define those patients at highest risk for regrowth of tumor in the larynx, pharynx, or neck. The incidence of occult cancer in lymph nodes, and hence the need for elective treatment of the neck of patients without palpable lymph nodes, is determined by pathologic examination of lymph nodes after elective neck dissection or by N0 to N+ conversion rates in patients without palpable lymph nodes whose neck remains untreated. Dose-response information for tumor and lymph nodes or information relating tumor control to radiation dose is especially important to determine the probability of curing a given tumor with irradiation. Comparative analysis of treatment outcome after radiation alone (RA), surgery alone (SA), and combination of radiation and surgery (R+S) as a function of tumor site and size helps select the best treatment. Knowing the clinical course of patients with cancer of the larynx and pharynx after treatment determines the frequency of follow-up study and defines the period of greatest risk of recurrence. Secondary treatment for salvage of recurrence is most effective if the recurrence can be detected early. Finally, detailed analysis of sites of failure can be used to devise improved treatment strategies. Altogether, a number of clinical and surgical pathologic observations predict patterns of relapse and survival and prove helpful in the management of an individual patient.

Patient characteristics

Age and sex are the two most important prognostic factors for the host who harbors a cancer of the larynx or hypopharynx. Patients who are younger survive longer than those who are older, and women survive longer than men (Fig. 114-13) (Marks and Martin, 1978-1979; Son and Habermaly, 1979). Women tend to present with earlier stage tumors than men, suggesting that they are less likely than males to delay going to a doctor (Marks and Martin, 1978-79). The more favorable prognosis of women is thus explained by more favorable tumor characteristics. Host and tumor characteristics are intimately related and partly dependent variables.

Clinical examination

The most important prognostic factors determined by the clinical examiner are the anatomic location of the tumor, tumor size, fixation of the larynx, and palpable lymph nodes in the neck (Fig. 114-14) (Marks and Ogura, 1982). Patients with cancers of the transglottis less often develop lymph node metastases than those with cancers of the supraglottis and therefore have a better prognosis (Till et al, 1975). Cancers of the piriform sinus are more easily controlled and have a better prognosis than cancers of the pharyngeal wall and postcricoid region because these tumors are more often smaller and surgically resectable. Fixation of the larynx is associated with a poor prognosis because the tumor is deeply invasive and more extensive than one associated with mobile vocal cords (Lederman, 1970). Patients who have palpable lymph nodes are more likely to experience regrowth of tumor in the neck than those without palpable lymph noes (Marks et al, 1985b) and hence have a less favorable prognosis.

Surgical pathology

Pathologic study of surgical specimens is especially important in predicting local or regional recurrence, distant metastases, and survival of patients with cancers of the larynx and hypopharynx. The main factor that predicts regrowth of tumor in the primary site is the presence of cancer in the margins of excision (Table 114-3), whereas the main factor that predicts regrowth of tumor in the neck is the presence of cancer in lymph nodes (Table 114-4) (Marks and Ogura, 1982; Marks et al, 1985b). The incidence of lymph node metastases for cancers of the larynx is a function of the characteristics of the primary tumor as determined by the surgical pathologist. McGavran et al (1961) found an increase in lymphatic metastases in patients with cancers of the larynx whose tumors exhibited size greater than 2 cm, poor cellular differentiation, infiltrating peripheral growth patterns, and nerve sheath invasion. Martin et al (1980) made a detailed analysis of surgical pathologic studies for patients with cancers of the piriform sinus and found that regrowth of tumor in the pharynx or neck was more common for those with keratinizing than nonkeratinizing tumors, for those whose tumor had invasive instead of pushing margins, for those with extension of tumor into soft tissues beyond the capsule of lymph nodes, and for those with tumor in the margins of the surgical excision. They found that the evelopment of distant metastases was more common in patients with nonkeratinizing than keratinizing tumors, in those with poorly differentiated instead of well- or moderately differentiated tumors, and in those with cancer in lymph nodes. Survival was more likely for those factors associated with lower rates of TNM relapse; it was also more likely for those patients with a granulomatous response in the primary tumor but was unaffected by factors suggesting enhanced immune reactivity in lymph nodes such as inflammatory infiltrate, germinal center hyperplasia, and sinus histiocytosis. Quite possibly these cells were depleted by prior irradiation, rendering these parameters of immune reactivity prognostically useless.

In a similar study, Bennett et al (1971) found that evidence of immune reactivity in lymph nodes favorably influenced the survival of patients with cancers of the larynx and piriform sinus. They did not mention whether those patients had been previously irradiated.

Occult lymphatic metastases

Quantitating the incidence of occult lymphatic metastases in the neck of patients without palpable lymph nodes is important to determine the need for elective or prophylactic treatment of the neck by surgery or irradiation. The incidence of occult lymphatic metastases in patients without palpable lymph nodes varies with the location of the tumor. In a study of 253 patients without palpable lymph nodes, we found the highest incidence of occult lymphatic metastases in those with carcinomas of the piriform sinus and marginal supraglottis (Marks et al, 1985b). The lowest incidence of occult lymphatic metastases was in those with cancers of the central supraglottis, transglottis, and glossoepiglottitis (Fig. 114-15). In a separate study of 540 patients with cancers of the larynx and pharynx we determined the risk of nodal recurrence in patients with and without cancer in their lymph nodes: 8% for those without pathologic evidence of cancer in their lymph nodes and 38% for those with occult lymphatic metastases or palpable cancer in lymph nodes (Fig. 114-16) (Marks et al, 1985b). Hence, a subset of patients with cancers of the supraglottis and transglottis exist who have no palpable lymph nodes at presentation and a low risk of occult lymphatic metastases and neck occurrence. A policy of observing the neck in these particular patients without palpable lymph nodes to prevent unnecessary irradiation of eight to benfit two would be reasonable if the outcome of prophylactic irradiation and observation of the N0 neck were similar.

Dose-response information

Information relating tumor control to radiation dose is essential for the radiotherapist, who needs to know whether increasing doses of radiation results in the cure of more tumors. Dose-response information is available for cancers of the glottis, transglottis, supraglottic, piriform sinus, and pharyngeal wall as a function of tumor size. Within the therapeutic range of doses usually employed for cancers of the vocal cord (50 to 70 Gy) no improvement in tumor control occurs with increasing doses (Horiot et al, 1972; Marks et al, 1973). Cancers of the vocal cord are very small compared to other cancers of the larynx and hypopharynx and obviously require lower doses of radiation; cancers in parts of the larynx and pharynx other than the glottis do respond to increasing doses. Generally speaking, tumor control increases with increasing doses for intermediate-size lesions of the transglottis (Harwood et al, 1980, 1981), supraglottis (Harwood et al, 1983; Shukovsky, 1979), piriform sinus (Bataini et al, 1982), and pharyngeal wall (Meoz-Mendez et al, 1978), but does not increase very much for larger lesions (Table 114-5). Larger lesions are less easily controlled by irradiation because they contain more tumor cells and are more often poorly responsive, ulcerating endophytic lesions. The clinical dose-response information available suggests that increasing the dose is advantageous for intermediate-size cancers of the transglottis, supraglottis, piriform sinus, and pharyngeal wall but not for larger ones. Doses greater than 65 to 70 Gy in 6.5 to 7 weeks are unlikely to control more advanced tumors and more likely to produce radiation damage to normal tissues.

Clinical course after treatment

The time required for regrowth of tumor in the larynx, pharynx, or neck varies for individual sites within the larynx and hypopharynx (Fig. 114-17) (Marks and Ogura, 1982). Time to recurrence is probably shorter for sites with the greatest amount of microscopic tumor remaining after the treatment and longer for those with the least amount of tumor. In general, the risk of remaining tumor is greatest for those sites that are not anatomically compartmentalized and have the highest rates of lymphatic metastases. The time to recurrence for cancers of the central supraglottis is greatest because these tumors are anatomically compartmentalized (Kirchner and Som, 1971a), are amenable to surgical compartmentectomy or subtotal supraglottic laryngectomy, and have relatively low rates of palpable and occult lymphatic metastases (Marks et al, 1985b). Time to recurrence for cancers of the glossoepiglottis, marginal supraglottis, and piriform sinus is less because these lesions are less well compartmentalized, more often contain tumor in the margins of excision, and have higher rates of palpable and occult lymphatic metastases than do cancers of the central supraglottis (Marks et al, 1985b). Time to recurrence after full-course irradiation of an intact tumor is a function of tumor size: it is less for large tumors than small tumors because the amount of tumor remaining after a high dose of radiation is greater for the large than the small tumor.

Every effort should be made to detect recurrence at an early stage so that secondary treatment for salvage can be more effective. It is, therefore, important to know when the majority of recurrences are likely to occur and to follow the patient frequently during the period of greatest risk for recurrence: 1 year for those patients with pharyngeal wall cancer who have full-course irradiation; 2 years for those with cancers of the transglottis, marginal supraglottis, glossoepiglottis, and piriform sinus treated by surgery and adjuvant irradiation; 3 years for patients with cancers of the central supraglottis treated by subtotal supraglottic laryngectomy and adjuvant irradiation (Fig. 114-17) (Marks and Ogura, 1982).

Sites of failure differ, depending on the method of treatment, for cancers of the larynx and hypopharynx. The neck is the most common site of regrowth of tumor when the primary method of treatment is surgery, whereas the larynx or pharynx is the most common site of regrowth of tumor after treatment by full-course irradiation. This is illustrated nicely by Venn diagrams showing sites of failure after low-dose preoperative irradiation and conservation surgery for cancers of the supraglottis (Marks et al, 1979; Marks and Ogura, 1982) and after irradiation alone for cancers of the pharyngeal wall (Fig. 114-18) (Marks et al, 1978b, 1985a). Surgery is more effective in controlling the primary tumor than full-course irradiation, and high-dose irradiation is more effective than low-dose adjuvant irradiation in eradicating microscopic tumor in lymph nodes or in tissues of the neck after dissection.

Management

Optimal treatment

The best treatment for cancers of the larynx and hypopharynx is the one that controls the tumor and regional lymph nodes and preserves voice and swallowing with least risk to the host. These tumors are usually treated by surgery or irradiation, alone or in combination. Separating patients with early lesions that are curable by surgery or irradiation alone from those who have more advanced lesions that require combinations of surgery and irradiation is especially important. It is also important to determine whether a particular lesion is amenable to conservation surgery and whether adjuvant irradiation is better given before or after surgery. Quantitation of treatment results for different methods of treatment and interinstitutional comparison of these results is the most practical way, aside from a controlled clinical trial, to determine the best method of treatment. Analysis of sites of failure is also important to determine the major problems that exist with a particular form of treatment and then to devise improved treatment strategies. Retrospective analysis of treatment results not only is necessary if improved strategies are to be devised but is also important preparation for the design of a clinical trial.

The efficacy of chemotherapy for cancers of the larynx and hypopharynx is unproved, but the rationale for its application is supported by the relatively high rates of distant metastases for carcinomas of the glossoepiglottis, piriform sinus, and pharyngeal wall (Fig. 114-10) (Marks and Ogura, 1982; Merino et al, 1977; Stefani and Eells, 1971). Though few trials have specifically targeted this group of cancers, Keane et al (1986) conducted a pilot study using mitomycin C and 6-fluorouracil infusion concomitant with split-course irradiation for advanced cancers of the larynx and hypopharynx. Of 57 patients studied, 90% completed irradiation and 70% completed chemotherapy.

Forms of systemic therapy other than chemotherapy have also been explored. The Institut Gustave-Roussy conducted a randomized trial to determine whether adjuvant nonspecific immunotherapy with Bacille Calmette-Guerin (BCG) would lower the rate of distant metastases in patients with laryngeal and hypopharyngeal carcinomas and found no effect (Cachin et al, 1980). They advised that chemotherapy be given perioperatively instead of after surgery and radiation to treat distant micrometastases more effectively.

Glottic cancer

In situ carcinoma of the vocal cord is often associated with hyperkeratosis, atypia, and dysplasia and is discovered after stripping of the vocal cord for leukoplakia. It may be treated by repeated stripping or full-course irradiation with excellent tumor control and voice preservation (Pene and Fletcher, 1976). We generally favor full-course irradiation in addition to stripping for carcinoma in situ because pathologic study of serial sections often shows invasive as well as in situ carcinoma (Bauer, 1974).

Invasive cancers of the true vocal cord are categorized by their mucosal extent, bulk, and vocal cord mobility and then treated by variable doses of full-course irradiation. Surface lesions confined to the anterior half of one true vocal cord that is mobile are treated with 60 Gy over 6 weeks. Surface lesions that involve an entire true vocal cord or one true vocal cord plus the anterior commissure or surface lesions that involve both true vocal cords and do not inhibit the mobility of the cords are treated with 66 Gy over 6.5 weeks. Nonbulky lesions that inhibit vocal cord mobiity are treated by 70 Gy in 7 weeks, and bulky lesions that partially inhibit the mobility of the vocal cords are generally treated by partial surgical excision and 70 Gy in 7 weeks. Altogether, rates of tumor control and voice preservation are excellent after radiation alone for cancers of the true vocal cord that do not inhibit or only partially inhibit the mobility of the vocal cord (Table 114-6) (Mittal et al, 1983; Wang, 1983). Fairly frequent and long-term follow-up observation is required because regrowth of tumor is often amenable to hemilaryngectomy with preservation of voice (Ballantyne and Fletcher, 1967; Biller et al, 1975). Rates of surgical salvage with preservation of voice progressively decrease as tumors become more extensive.

Small transglottic cancers

The management of the patient whose glottic cancer has invaed underlying thyroarytenoid muscle and fixed the true vocal cord is more controversial. Whether tumor control and voice preservation are greatest after treatment by full-course irradiation of hemilaryngectomy is not clear. Serial section studies have shown that many patients with fixation of the true vocal cord have small transglottic cancers that do not invade perichondrium or cartilage or spread extensively within the paraglottic space (Kirchner and Som, 1971b; Lesinski et al, 1975; Mittal et al, 1984). Other reports, particularly those from the Princess Margaret Hospital in Toronto, indicate favorably results after treatment by full-course irradiation with surgery in reserve for salvage of recurrences (Harwood et al, 1980). A comparative analysis of the two methods of managing patients with small transglottic cancers appears in Table 114-7. A clinical trial is needed to determine which is the best method of treating small transglottic cancers of the larynx.

Experience with hemilaryngectomy for small transglottic lesions that do and do not fix the vocal cord is interesting. Bauer et al (1975) studied 39 patients with involve hemilaryngectomy margins who were not irradiated and found only 7 local recurrences after a minimum follow-up period of 5 years. These patients in general had small cancers of the vocal cord that did not fix the vocal cord. More recently, hemilaryngectomy has been used for more extensive transglottic tumors that invade the ventricle and false vocal cord and fix the hemilarynx. In these cases, tumor in several margins of resection is not unusual and postoperative irradiation is generally given. Irradiation prevents regrowth of tumor in three quarter of those patients whose hemilaryngectomy margins yield positive findings and even eradicates half of those tumors that recur after hemilaryngectomy alone (Lee et al, 1980). Use of adjuvant irradiation after hemilaryngectomy may cause significant edema, further narrow the airway, and necessitate a permanent tracheostomy (Marks and Ogura, 1982).

Our policy has been to maximize the use of conservative surgery for transglottic lesions to preserve voice whenever possible. The problem faced by the surgeon is to separate the small transglottic lesion with a fixed vocal cord that is amenable to hemilaryngectomy from the larger transglottic cancer that requires total laryngectomy. Cartilage destruction can be detected by plain radiographs, xeroradiographs, and computed tomography scans, but the degree of tumor spread within the paraglottic space is often difficult to determine before the specimen is studied in the surgical pathology laboratory. Hemilaryngectomy is sometimes attempted and converted to total laryngectomy when it becomes apparent that the tumor is more extensive than originally thought. In general, hemilaryngectomy is not possible for a tumor that has spread extensively within the paraglottic space, extended more than 7 to 8 mm below the margin of the true vocal cord, crossed the midline more than 1 to 2 mm, or penetrated cartilage.

Large transglottic cancers

Transglottic carcinomas that spread extensively in the paraglottic space, fixate the hemilarynx, and penetrate the cricothyroid membrane or destroy cartilage to involve extralaryngeal soft tissues are treated by full-course irradiation (Harwood et al, 1981) or laryngectomy and adjuvant irradiation (Mittal and Marks, 1984; Mittal et al, 1984). When a patient has an advanced transglottic cancer that is not treatable by hemilaryngectomy, we have favored laryngectomy and adjuvant preoperative or postoperative irradiation to prevent recurrence in the pharynx, neck, or tracheostoma and to eradicate subclinical microscopic lymphatic metastases. The Princess Margaret Hospital, on the other hand, has treated T3N0 and T4N0 cancers of the transglottic larynx by full-course radiotherapy with surgery in reserve for recurrence (Harwood et al, 1980, 1981). A comparison of treatment results for the two approaches is shown in Table 114-8. Laryngectomy with adjuvant irradiation controls tumor and lymph nodes in three quarter of cases but sacrifices voice, whereas irradiation alone controls tumor and lymph nodes and preserves voice in roughly half of cases. The problem with laryngectomy for a large transglottic cancer is that the larynx is sacrificed in some patients whose tumor might have been radioresponsive and cured by irradiation. Hence, the policy of irradiating all large transglottic cancers with surgery reserved for salvage has significant merit. Initial tumor control is not as good as after laryngectomy and adjuvant irradiation, but voice preservation is greater and ultimate tumor and nodal control after surgical salvage is comparable to that achieved by laryngectomy and radiation.

Management of the neck in the patient with a transglottic carcinoma depends on the risk of occult cancer in patients without palpable lymph nodes, the risk of neck recurrence in those with palpable lymph nodes, and the risk of neck or parastomal recurrence in those with advanced primary tumors. The incidence of occult lymphatic metastases, as determined by observation and N0 to N+ conversion rates, increases for larger transglottic cancers (Table 114-9) and was 37% in a group of 16 unirradiated patients undergoing hemilaryngectomy for small transglottic carcinomas of the larynx (McCall et al, 1988). Thus irradiation of the entire neck is probably needed for those with a small transglottic carcinoma and a fixed vocal cord, but its success in eradicating occult lymphatic metastases remains controversial. Some workers have reported that adjuvant irradiation is particularly effective in eradicating subclinical microscopic metastases from carcinomas of the larynx (Fletcher, 1972), but we have continued to see neck recurrences despite increasing doses of adjuvant irradiation (Marks et al, 1986). Others who need adjuvant irradiation are those who require emergency tracheostomy since the incidence of subsequent recurrence in the tracheostoma is significant (Keim et al, 1965). Patients whose tumor penetrates thyroid cartilage to involve extralaryngeal soft tissues also need adjuvant neck irradiation to reduce the risk of neck recurrence (Marcus et al, 1979). High doses of irradiation (60 Gy in 6 weeks) with electron beam boost (10 to 15 Gy) of heavily infested areas of the neck are recommended.

Supraglottic cancer

The management of supraglottic carcinomas of the larynx depends on their size, morphology, and compartmentalization, as well as the presence or absence of lymphatic metastases. Treatment of the regional lymphatics generally depends on the treatment selecte for the primary tumor. The major issue has been determining whether irradiation alone or conservation surgery with adjunctive irradiation will yield the best tumor and nodal control and voice preservation. Comparative analysis of treatment results for small and large cancers of the supraglottic larynx is shown in Table 114-10. Full-course irradiation controls the primary tumor and lymph nodes and preserves voice in three quarters of those with T1-T2 and 40% of those with T3-T4 carcinomas of the supraglottic larynx (Bataini et al, 1974; Fletcher et al, 1975; Fu et al, 1977; Ghossein et al, 1974; Wang, 1974). Irraiation success depends on tumor size and is greater for small than for large tumors. If large tumors are irradiated and subsequently regrow, the patient undergoes laryngectomy with loss of voice. Alternatively, many large cancers of the supraglottis can be managed by conservation surgery because they remain compartmentalized and are amenable to subtotal supraglottic laryngectomy with preservation of voice; the presence of a submucosal lymphatic plexus in the supraglottic compartment prevents the spread of tumor below the inferior margin of the false vocal cord in most cases (Kirchner and Som, 1971a; Pressman et al, 1960; Tucker and Smith, 1962). Thus the majority of cancers of the central supraglottis can undergo subtotal supraglottic laryngectomy with preservation of voice. A few spread downward at the anterior commissure to become transglottic and require total laryngectomy. Altogether, tumor and nodal control and voice preservation are greater for conservation surgery and adjuvant irradiation (Marks et al, 1979) than for irradiation alone for large lesions because compartmentectomy is better able to control the primary tumor than irradiation alone. These results suggest that small lesions of the supraglottis be treated by full-course irradiation and that large lesions be treated by conservation surgery with adjuvant irradiation.

Cancers of the glossoepiglottis and marginal supraglottis frequently spread beyond the supraglottic compartment to involve the base of tongue, piriform sinus, and postcricoid area. Anatomic barriers no longer exist, the chance of successful removal by surgery lessens, and the risk of local recurrence increases (Marks et al, 1979). Therefore, adjuvant preoperative or postoperative irradiation is frequently employed to lessen the risk of local recurrence. Doses of 50 to 60 Gy in 5 to 6 weeks are routine when the margins of excision do not contain tumor, and doses of 66 Gy in 6.5 weeks are used when the margins do contain tumor.

The management of the neck in patients with cancers of the supraglottis depends on the presence or absence of palpable lymph nodes. The incidence of palpable lymph nodes is roughly 25% in patients with cancers of the central supraglottis and 50% for those with cancers of the marginal supraglottis and glossoepiglottis; the incidence of occult lymphatic metastases is 16% for those with cancers of the central supraglottis and 38% for those with cancers of the marginal supraglottis (Marks et al, 1985b). The need for prophylactic or elective treatment of the neck by surgery or irradiation is therefore greater for peripheral than central lesions. Observation of the neck is probably all that is required after treatment of a small cancer of the central supraglottis since the incidence of occult lymphatic metastases and the risk of subsequent neck reccurence are low (Marks et al, 1985b). Elective treatnment of the neck is recommended for large cancers of the central supraglottis as well as cancers of the marginal supraglottis and glossoepiglottis since the incidence of occult lymphatic metastases and the risk of neck recurrence are high. The success of elective irradiation of the neck for cancers of the supraglottic larynx remains controversial. Some have reported that elective irradiation of the neck reduces neck recurrence to a minimum (Lindberg and Fletcher, 1978), whereas others have shown little effect (Goffinet et al, 1975). We have continued to see neck recurrences despite increasing doses of adjuvant irradiation (Table 114-11) (Marks et al, 1986).

Integrated surgical removal of the primary tumor and regional lymphatic vessels is favored in patients with cancers of the supraglottis who have palpable lymph nodes. Some reports indicate, however, that lymph nodes less than 3 cm in diameter can often be controlled by using electron beam to deliver high doses of irradiation to the lymph nodes (Bataini et al, 1974).

Piriform sinus cancer

Cancers of the piriform sinus have been primarily treated by full-course irradiation in the major institutions of Europe (Ahlbom, 1941; Baclesse, 1949; Bataini et al, 1982; Jacobsson, 1951; Werner and Bäryd, 1970), Great Britain (Lederman, 1953, 1962; Pearson, 1966), Canada (Keane et al, 1983), and Japan (Inoue et al, 1973) and treated by surgery and adjunctive irradiation in the USA (Carpenter et al, 1976; Donald et al, 1980; Eisbach and Krause, 1977; El Badawi et al, 1982; Marks et al, 1978a; Shah et al, 1976; Strong et al, 1976; Wang et al, 1970). The decision to use irradiation alone or surgery and irradiation depends on the form, size, and location of the tumor in the piriform sinus. As noted in Coutard's publications, cancers of the upper or membranous piriform sinus are frequently surface or exophytic lesions that are radioresponsive and potentially radiocurable (Coutard, 1932). These must be differentiated from the larger, more infiltrating cancers of the inferior piriform sinus that frequently invade larynx, thyroid, and cartilage and directly infiltrate the soft tissues of the neck. These require total laryngopharyngectomy and neck dissection and frequently receive adjuvant irradiation. The decision to use irradiation or surgery as a primary method of treatment requires direct laryngoscopy and pharyngoscopy or videoendoscopy as mirror examination is inadequate to determine the size and mucosal extent of piriform sinus cancers.

Most institutions have had a general policy of irradiating cancers of the piriform sinus (Ahlbom, 1941; Bataini et al, 1982; Jacobsson, 1951; Keane et al, 1983; Lederman, 1953, 1962; Pearson, 1966) for cure or using surgery as the primary method of treatment with adjunctive irradiation (Briant and Lord, 1973; Carpenter et al, 1976; Donald et al, 1980; Eisbach and Krause, 1977; El Badawi et al, 1982; Marks et al, 1978a; Strong et al, 1976; Wang et al, 1970). The practice of selecting favorable lesions for radiotherapy and unfavorable lesions for surgery has been used by few (Mendenhall et al, 1987; Million and Cassisi, 1981). Several large institutions in this country historically treated cancers of the piriform sinus with surgery alone during the 1950s and moved to the use of surgery and preoperative or postoperative irradiation during the 1960s and 1970s (El Badawi et al, 1982; McGavran et al, 1963; Ogura and Biller, 1970). Comparative analysis of results after differing methods of treatment (RA vs SA vs R+S vs S+R) is shown in Table 114-12 (Bataini et al, 1974; El Badawi et al, 1982; Keane et al, 1983; Marks and Ogura, 1982; Mendenhall et al, 1987). The use of surgery improves tumor and nodal control as well as survival, and the addition of irradiation to surgery has improved results in some series and not in others. In our institution, preoperative irradiation in addition to surgery has been disappointing. Tumor and nodal control has not been improved by the use of low doses of preoperative irraiation (Table 114-13); however, survival of patients treated by R+S was marginally better than the survival of those treated by surgery alone (McGavran et al, 1963; Marks and Ogura, 1982). This observation might well be explained by improvements in surgical reconstruction and supportive care. Review of our patients treated by low-dose preoperative irradiation revealed a number of problems (Marks et al, 1978a). The major problems were regrowth of tumor in the pharynx and neck and inability to salvage these recurrences successfully. Low doses of preoperative irradiation were inadequate for occult lymphatic metastases in the opposite neck and resulted in a high rate of contralateral neck recurrences (25%) in those patients who required total laryngopharyngectomy. Increasing doses of preoperative irradiation from 30 to 40 to 50 Gy and then resorting to higher doses of 60 to 66 Gy postoperatively have failed to improve tumor and nodal control (Marks and Ogura, 1982). Only the M. D. Anderson publication (El Badawi et al, 1982) has shown that high doses of postoperative irradiation effectively reduced the incidence of failures above the clavicle from 39% for a group treated by surgery alone to 11% for a group treated by surgery plus postoperative irradiation (Table 114-12). In addition, they showed improvement in the survival of those patients treated by irradiation in addition to surgery (Fig. 114-19). Their publication suggests that the addition of irradiation to surgery has value for cancers of the piriform sinus, though it is retrospective and may have been biased by the selection of patients for one method of treatment or the other.

One of the major goals in the treatment of cancers of the piriform sinus should be to preserve voice. This may be done by curing the tumor with radiotherapy or by performing partial laryngopharyngectomy or local excision of the marginal structures of the larynx for small lesions of the upper portion of the piriform sinus that do not infiltrate the larynx to fix the vocal cord or destroy thyroid cartilage. In 175 patients treated between 1964 and 1973, 45% had partial laryngopharyngectomy and half of those were cured of the tumor and retained their voice (Freeman et al, 1979). In the series reported by Keane et al (1983) from the Princess Margaret Hospital, voice was preserved in 16% of the total population irradiated with curative intent.

Comparison of preoperative and postoperative irradiation for carcinomas of the piriform sinus has been addressed by two clinical trials, one by the Institut Gustave-Roussy (Vandenbrouck et al, 1977) and the other by the Radiation Therapy Oncology Group (RTOG) (Snow et al, 1981). The RTOG trial gave 50 Gy in 5 weeks preoperatively and 60 Gy in 2 weeks postoperatively. Tumor and nodal control and 2-year survival were similar for each type of adjunctive irradiation. The value of adjuvant preoperative or postoperative irradiation could not be determined as no control group of patients was treated by surgery alone. The Gustave-Roussy trial used 55 Gy in 5.5 weeks preoperatively and postoperatively. The trial excluded a large number of patients (129), selected a more favorable group for radnomization (49), and performed major pharyngectomies on patients within 2 weeks of preoperative irradiation. The trial had to be terminated prematurely because of the severity and magnitude of complications after the short delay after high-dose preoperatve irradiation. Obviously, the time betweem completion of irradiation and surgery was inadequate for repopulation of the tissues by fibroblasts necessary for the formation of scar. Survival was significantly better for the postoperative group than the preoperative group even after exclusion of those patients who died of the complications of pharyngocutaneous fistula and carotid artery hemorrhage (Fig. 114-20). The incidence of complications after preoperative irradiation was not excessive in the RTOG trial because the delay of 4 to 6 weeks between irradiation and surgery was aequate (Marcial et al, 1982).

In a quarter of patients with carcinomas of the piriform sinus distant metastases develop and need effective systemic therapy (Merino et al, 1977; Stefani and Eells, 1971). A number of clinical trials that test the value of chemotherapy in addition to surgery and irradiation for carcinomas of the piriform sinus are in progress, but thus far none is conclusive.

Pharyngeal wall cancer

Pharyngeal wall cancers are more difficult to resect than cancers of the piriform sinus because of their more posterior location next to prevertebral fascia and their propensity to spread submucosally (Harrison, 1970; Olofsson and van Nostrand, 1973). Margins of excision frequently contain cancer and adjuvant irradiation is needed. These silent tumors often grow quite large before detection, thus limiting the ability of irradiation to control them. Postsurgical complications have proved significant (Cunningham and Catlin, 1967; Marks et al, 1978b) because the surgical defect has been difficult to close satisfactorily before the advent of the myocutaneous flap. High doses of irradiation cause fibrosis of the pharyngeal constrictors, making it difficult to swallow, and in some patients edema of the larynx develops and necessitates tracheostomy (Marks et al, 1978b). No tumor of the head and neck requires a more careful balancing of risk and benefit after various methods of treatment than does pharyngeal wall cancer.

Analysis of our patients treated by low-dose preoperative irradiation and pharyngectomy during the 1960s and early 1970s showed an excessive rate of postsurgical complications, surgical mortality of 14% (Table 114-14), mediocre tumor control, and poor survival (Table 114-15). After analysis of these results in 1978 and the appearance of several papers that showed good results after irradiation alone (Meoz-Mendez et al, 1978; Wang, 1973; Wang et al, 1970), it was decided to irradiate most patients with pharyngeal wall cancer for cure. Subsequent analysis and comparison of the patients treated by RA to those treated earlier by R+S showed several interesting results (Marks et al, 1985a). Patients treated by preoperative irradiation and surgery had tumors that were comparable in size to those treated by irradiation alone but survived significantly longer than those treated by radiation alone. The major site of regrowth of tumor after irradiation alone was the pharynx, compared to fewer pharyngeal recurrences in the patients treated by surgery and adjunctive irradiation. The second finding of major clinical importance was the significant reduction in postoperative complications and mortality in the later study that resulted from improved methods of surgical reconstruction with myocutaneous and free flaps. Thin myocutaneous flaps that are now available are particularly suitable for reconstructing the pharynx in a single operative procedure (Smith and Collins, 1984). Once the pharyngeal and cutaneous suture lines have healed, high doses of postoperative irradiation can be given without fear of major complications. High doses of irradiation are more effective than low doses in controlling tumor in lymph nodes and are necessary in addition to surgery to reduce regrowth of tumor in the pharynx (Marks et al, 1985a). It is hoped that our present policy of resection and high doses of adjuvant irradiation will improve treatment results for patients with cancers of the pharyngeal wall.