# Chapter 105: Malignant Neoplasms of the Hypopharynx

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## Incidence

The American Cancer Society predicts that there will be 12.500 new cases of laryngeal cancer in 1991. Hypopharyngeal tumors have consistently been one third as common as laryngeal tumors; therefore, approximately 4.000 new cases will be diagnosed in 1991. Prognosis has not changed significantly in the past 20 years for patients with advanced disease because of the late presentation, tendency to submucosal extension into the esophagus, and metastatic spread to the mediastinal, tracheoesophageal, and jugular nodes, as well as a higher incidence of distant metastases than that of other head and neck malignancies. Additionally, 20% to 25% of these patients either have or develop a second primary malignancy within 5 years, most often in the head and neck region.

Early recognition and diagnosis of hypopharyngeal tumors remain difficult. The vast majority of patients (70%) still manifest stage III disease. Since virtually all tumors are squamous cell (or epidermoid carcinoma), malignancy of the hypopharynx has become almost synonymous with squamous cell carcinoma. The tumors are initially silent or cause symptoms of chronic sore throat and dysphagia, symptoms often attributed to benign disease processes. The rich lymphatic network in the submucosal tissue surrounding the hypopharynx allows both early spread to regioanl lymph nodes and direct extension into the adjacent soft tissues. In fact, even today, 70% to 80% of patients with hypopharyngeal carcinoma have palpable cervical metastases. Frequently, the presenting symptom is a painless lump in the neck, usually a middle or upper jugular lymph node. Therefore, whenever a patient with a history suggestive of malignancy is found with a mass in the neck and there is no apparent primary lesion, the hypopharynx should be considered. With the exception of postcricoid carcinoma, which was formerly more common in women, all other forms of hypopharyngeal malignancy are far more common in men (80% to 85%), usually those between the ages of 55 and 70. A history of heavy alcohol ingestion, cirrhosis of the liver, and heavy smoking is usual. In women, the reverse ratio of postcricoid carcinoma has been felt to be due to Plummer-Vinson syndrome.

## Anatomy

The hypopharynx (laryngopharynx) is the longest of the three segments of the pharynx. It is wide superiorly and becomes progressively narrower toward the level of the cricopharyngeus, where it merges with the cervical esophagus. Enclosed anterolaterally by the lateral aspects of the thyroid cartilage are two paired recesses that extend inferiorly to about the same level as the laryngeal ventricle. They open posteriorly into the pharynx and are called the piriform (pear-shaped) sinuses (Fig. 105-1).

The hypopharynx does not function solely as a conduit from the oropharynx to the esophagus but has important dynamic actions that allow separation of air and food passage and prevent aspiration. Food enters the hypopharynx during the third stage of swallowing, when the tongue propels it rapidly past the epiglottis. The contraction of the constrictor muscles propels the food toward the region of the cricopharyngeus. The cricopharyngeal

muscle relaxes and the food enters the esophagus, where peristaltic action again transmits the bolus toward the stomach. Innervation of the superior and middle constrictor muscles is through the superior laryngeal nerve and the pharyngeal plexus, which overlies the middle constrictors. It includes the pharyngeal branches of the vagus and glossopharyngeal nerves as well as contributions from the superior cervical ganglion. The inferior constrictor muscle receives branches from both the external and the recurrent laryngeal branches of the vagus nerve. The internal branch of the superior laryngeal nerve passes through the thyroglossal membrane and traverses beneath the mucosa of the anterior piriform sinus. Laryngeal and piriform sinus anesthesia is obtained by application of topical anesthetic to this area. This is helpful when general anesthesia cannot be employed for tumor assessment.

This complex muscular coordination is often not appreciated until after a major surgical resection in this area. Then the replacement with an adynamic muscle flap or a tight pharyngeal closure often can result in aspiration, even when an intact laryngeal sphincter mechanism is preserved. It is often necessary to resect the cancer-free larynx of patients whose tumor could otherwise be resected without laryngectomy were it not for the concern about chronic aspiration.

The mucosal lining of the hypopharynx is stratified squamous epithelium. It is associated with a rich submucosal lymphatic network that exists through the thyrohyoid membrane and leads to the superior and middle jugular lymph nodes. Inferiorly, the passage is directly through the hypopharynx to the paratracheal lymph nodes and low jugular nodes (Fig. 105-2).

The tumor-node-metastasis (TNM) staging system divides the hypopharynx into three distinct regions (see box). The first is the piriform sinus. This lateral pear-shaped funnel with its apex at the cricopharyngeus muscle is bounded laterally by the medial aspect of the thyroid lamina and posteriorly by the lateral wall of the hypopharynx. It begins superiorly at the glossoepiglottic fold and medially is adjacent to the lateral surface of the arytenoid cartilage.

**TNM staging**

***Tumor size (TP)***

Tis Carcinoma in situ
T1 Tumor confined to one site
T2 Extension of tumor to adjacent region
T3 Extension of tumor to adjacent region or site with fixation of hemilarynx
T4 Massive tumor in invading bone or soft tissues of neck.

***Nodal involvement (N)***

Nx Minimum requirements to assess regional nodes cannot be met
N0 No clinically positive node
N1 Single clinically positive homolateral node 3 cm or less in diameter
N2 Sincle clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter or many clinically positive homolateral nodes, none more than 6 cm in diameter

N2a Single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter
N2b Multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N3 Massive homolateral node(s), bilateral nodes, or contralateral node(s)
N3a Clinically positive homolateral node(s), one more than 6 cm in diameter
N3b Bilateral clinically positive nodes (in this situation, each side of the neck should be staged separately; ie, N3b: right, N2a; left, N1)
N3c Contralateral clinically positive node(s) only.

***Distant metastasis (M)***

Mx Minimum requirements to assess presence of distant metastasis cannot be met
M0 No known metastasis
M1 Distant metastasis present. Specify.

The second region is the posterior pharyngeal wall, which extends from a plane drawn at the level of the tip of the epiglottis to a plane at the level of the inferior border of the cricoid cartilage. Others describe the superior plane as at the level of the vallecula or hyoid bone. This roughly corresponds to the level of the bodies of the third through sixth cervical vertebrae. The superior and inferior margins of the posterior pharyngeal wall blend with the posterior wall of the oropharynx and the esophagus.

The third area is the postcricoid region. This includes the posterior surface of the aryepiglottic fold and posterior surface of the arytenoid to the inferior border of the cricoid cartilage. This latter area is the most difficult to assess by mirror examination, and even by direct laryngoscopy, as the tip of the blade of the laryngoscope may obscure an early cancer (see box).

## Definitions

*Pharyngoesophageal junction* (postcricoid area) extends from the level of the arytenoid cartilages and connecting folds to the inferior border of the cricoid cartilage.

*Piriform sinus* extends from the pharyngoepiglottic fold to the upper end of the esophagus. It is bounded laterally by the thyroid cartilage and medially by the surface of the arytenoepiglottic fold and the arytenoid and cricoid cartilages.

*Posterior pharyngeal wall* extends from the level of the floor of the vallecula to the level of the cricoarytenoid joints.

## Risk Factors

### Plummer-Vinson or Paterson-Brown syndrome

The combination of dysphagia, hypopharyngeal and esophageal webs, weight loss, and iron deficiency anemia in women ages 30 to 50 was first reported in the USA by Plummer in 1914 (Goldstein, 1974). Vinson elaborated on it further in 1922. Simultaneously in Europe in 1919, Paterson-Brown described a similar entity. In 1938, Waldenstrom in Sweden referred

to this syndrome as sideropenic dysphagia (Wynder et al, 1957). It soon became apparent that this entity was present in most of Europe as well as North and South America, and it is still most common in the USA, Sweden, and Wales. Eighty-five percent of patients are women.

Initially, the dysphagia is intermittent, but it latera becomes constant. For some reason, patients accept it and continue to modify their diet to softer food. This is unfortunate, because when the disorder is recognized early, treatment with bougienage, iron replacement, and vitamin therapy can reverse the disease process. When fibrosis secondary to chronic inflammation develops, webs and irreversible long strictures develop.

Addtional findings include an early loss of teeth, development of chilosis, and glossitis with an atrophic-appearing mucosa of the tongue and pharynx. There may be associated splenomegaly, hepatomegaly, and achlorhydria.

Radiologic examination with a barium swallow demonstrates a hypopharyngeal web, most commonly in the low hypopharynx, or the area between the postcricoid region and the thoracic esophagus. The web is initially anterior but later becomes circumferential.

The association with postcricoid carcinoma was made because of the reverse in the usual ratio of 80% male to 20% female prevalence of cancer in other areas of head and neck. The assessment of women who developed postcricoid carcinoma in a series of 322 patients in Wales revealed that between one third and two thirds had a history of Paterson-Brown syndrome. Malignancies were more common in those patients who never sought treatment. The malignancy began just proximal to the web, possibly because of chronic irritation. In the same study, of 76 patients with Paterson-Brown syndrome followed prospectively, postcricoid carcinoma developed in only one patient (McNab Jones, 1961). In this circumstance, however, most patients had undergone treatment with iron replacement, vitamin B replacement, and dilation. Currently in the USA because of the reduced incidence of this syndrome, postcricoid carcinoma is more common in men.

## Alcohol and tobacco

The relationship of alcohol and cigarette smoking to the development of head and neck cancer of the oral cavity and pharynx has long been clinically recognized. In 1966, Keller compared 408 cases of head and neck malignancies in the New York City Veterans Administrations Hospitals with age-matched controls (Keller, 1967). He found an excess level of cirrhosis of the liver in patients who had floor-of-mouth, oropharyngeal, and hypopharyngeal malignancies. Additionally, patients who were heavy cigarette smokers (more than 40 per day) had a higher incidence of malignancies, especially floor-of-mouth and tongue malignancies. He concluded that cancer of the pharynx was significantly higher in patients who had a history of heavy alcohol ingestion, heavy smoking, and liver cirrhosis.

## Second primary malignancies

Coexisting second primary malignancies are found in 4% to 8% of patients who have one head and neck primary cancer. For this reason, preoperative assessment includes chest radiograph, endoscopic assessment, and careful evaluation of any other findings or symptoms the patient might have (for example, blood in urine, gastrointestinal symptoms, positive stool

guaiac finding). Additionally, 20% to 25% of patients with head and neck primary malignancies develop a second cancer within 5 years. Evaluation of patients treated at the Minneapolis VA Medical Center revealed 207 patients with second primary malignancies within 5 years of their primary or index tumor in a study of 875 patients with epidermoid carcinoma of the head and neck (Larson et al, 1990). Sixty-four of these patients, or 30.9%, went on to develop a third primary malignancy, and 10%, or 21, developed a fourth primary malignancy. Virtually all patients in this study had a history of more than 50 pack-years of smoking (203 of 207). Three of the remaining 4 patients had a history of alcohol abuse.

The hypopharyngeal area was the third most common site for patients with floor-of-mouth cancers to develop a second primary malignancy. The mean time for development between first and second primary malignancies was 1.5 years; tumors in the hypopharyngeal area tended to occur sooner than in other sites.

## Diagnosis

The diagnosis of a hypopharyngeal malignancy is suspected in an individual who has the appropriate history of heavy alcohol ingestion, heavy smoking, and any of the following signs or symptoms: persistent dysphagia, persistent sore throat, or a foreign body sensation in the throat. The average duration of symptoms before presentation is 2 to 4 months. A later symptom is pain referred to the ear by Arnold's nerve, a division of the tenth nerve. Referred otalgia suggests a malignancy in the region of the hypopharynx, base of tongue, or supraglottic larynx.

Twenty percent of patients have an asymptomatic mass in the neck, usually a jugulodigastric or midjugular lymph node. Associated symptoms include weight loss, and, in most advanced stage disease, hemoptysis and hoarseness when the vocal cord becomes fixed by direct extension to the arytenoid cartilage or muscles.

Indirect laryngoscopy examination includes observation of vocal cord function. An ipsilateral fixed cord suggests a more advanced hypopharyngeal lesion. There may be pooling of secretions on one side of the piriform sinus obstructing adequate visualization of an area. There may be asymmetry of the laryngeal structure and edema in the region of the arytenoid. Lesions in the superior portion of the posterior hypopharynx show ulceration. The edges may be raised or an ulceration may be identified. Flexible fiber-optic laryngoscopy may be necessary to assessment when mirror examination is not adequate.

## Radiologic assessment

Whenever a malignancy of the hypopharynx is strongly suspected, it is preferable to obtain either a computed tomography (CT) scan or magnetic resonance imaging (MRI) before endoscopic evaluation and biopsy. Thus, the findings of edema on CT scan are more suggestive of submucosal infiltration than a result of the biopsy. Further, the CT scan may draw attention to additional areas that may need to be carefully assessed and undergo biopsy at the time of endoscopy. It is not unusual for the CT scan to demonstrate more extensive disease than is appreciated by either indirect or direct endoscopy (Fig. 105-3).

CT scan is essential to determine the full extent of the lesion. It adds to the capability to stage the lesion and to determine cartilage, pharyngeal, and epiglottic space invasion. It is of value in measuring extent of lesions outside the laryngopharynx where direct invasion can be lateral into surrounding soft tissues. Tumors tend to extend vertically in the space between the middle and inferior constrictors. Direct tumor extension can be distinguished from metastatic adenopathy (Fig. 105-4).

A prospective multi-institutional study by the New York Head and Neck Group used CT scans in N0 necks to determine the accuracy of CT scan versus clinical palpation (Stern et al, 1990). Positive indications of adenopathy revealed on scan included 1.5-cm nodal enlargement, enhancement, central lucency, and confluency of nodes. The CT scan correctly predicted the absence of cervical adenopathy in 35 of 43 patients, or 81% of cases. It was determined that an enhancing node was not a reliable indicator of malignancy. Administration of contrast material did not help in determining the presence or absence of cervical adenopathy, but it was helpful in delineating vascular structures. As in other studies of hypopharyngeal malignancies, the high incidence of positive cervical adenopathy results in advanced T3 and T4 lesions made the additional findings obtained on CT scan of no value in determining clinical management.

In most cases, CT scan does not provide information that affects the management of patients with N0 necks, since 30% to 44% of patients who have hypopharyngeal cancer have pathologically positive cervical adenopathy results. However, in patients with fat or thick necks or in those who have previously undergone irradiation therapy, the CT scan is more accurate than clinical palpation in determining the presence of cervical adenopathy for staging (Moreau et al, 1990).

A more important role for the CT scan is evaluation of the contralateral neck when the ipsilateral neck has palpable disease. This may demonstrate the need for a bilateral neck dissection. MRI and ultrasound have been found more valuable in determining presence of carotid involvement than CT scan. However, both MRI and ultrasound may show false-positive involvement of the artery, particularly in patients who have had previous irradiation therapy or previous carotid endarterectomy (Langman et al, 1989). In these incidences, the plane of fibrosis in the area cannot be distinguished from tumor invasion. Although the CT scan has not been valuable in providing early evidence of carotid artery involvement, it can demonstrate whether the carotid artery is totally encased in tumor and whether it is unlikely that resectin will be feasible.

A barium swallow is also performed before endoscopy. This allows assessment of the inferior extent of the tumor as well as being helpful in determining the possibility of a second primary esophageal malignancy. Various positional maneuvers allow the contrast material to pass when the hypopharynx is nearly obstructed.

Chest radiography is performed to evaluate the possibility of metastatic disease as well as a secondary primary malignancy in the lung.

## Endoscopic evaluation

Direct laryngoscopy permits biopsy of the tumor as well as determination of tumor extent. A careful drawing should be made and the lesion fully mapped. It is particularly important to determine whether the cord is mobile or fixed, whether tumor is on the medial or lateral aspect of the piriform sinus, whether there is extension to the apex of the piriform sinus or into the esophageal inlet, or whether the tumor extends across the midline or involves the posterior pharyngeal wall. Tumor extension onto the posterior arytenoid surface must also be assessed.

Endoscopy is also important in ruling out the existence of a second or concurrent malignancy. For that reason, esophagoscopy is performed not only to determine the inferior extent of the tumor but also to make certain that no skip lesions exist. Palpation of the base of tongue and pharyngeal walls is important. It is particularly important to palpate the extent of the lesion on the posterior pharyngeal wall. To be considered resectable, a tumor of the posterior hypopharyngeal wall should be freely mobile over the cervical vertebrae.

Bronchoscopy is not performed in the case of a completely normal chest radiograph result but is indicated, as is a whole-lung CT scan, if chest radiograph suggests any abnormality (Maisel and Vermeersch, 1981).

## Surgical pathology

Characteristics of tumor extension and pathways of spread of malignancy are essential in determining the extent of surgical resection or irradiation ports (Lindberg, 1977).

Submucosal extension has been a major cause of treatment failure. In Harrison's study of whole-organ serial section, recurrent disease after laryngopharyngectomy was primarily due to submucosal extension inferiorly (Harrison, 1973). Murakami et al (1985) found that submucosal extension was both superior and inferior. They recommended extending the superior limit of resection to the base of the palatine tonsil.

Kirchner (1975) and Harrison (1970) both found that tumors of the lateral wall extend into the thyroid cartilage and directly into the overlying thyroid gland. Because of these findings, all authors recommended resection of the ipsilateral hemithyroid and isthmus, even if they are not clinically involved and even if there is no clinical evidence of thyroid cartilage invasion. Kirchner's study confirmed Ogura's recommendation that no patient with involvement of the piriform apex or thyroid cartilage be considered a candidate for partial laryngopharyngectomy (Ogura et al, 1960).

Sessions (1976) reviewed 195 pathologic specimens from patients with tumors of the hypopharynx. This represented 21% of all their laryngopharyngeal malignancies. He correlated pathologic findings with 3-year survival. Factors evaluated included location of tumor, margins, differentiation of tumor, and lymph node involvement. A significant number of this group treated between 1955 and 1971 underwent preoperative irradiation therapy. Thirty-eight percent of patients with tumors in the inferior hypopharynx who had no tumor in the surgical specimen after preoperative irradiation eventually experienced treatment failure. When margins were reported as positive in the inferior hypopharynx, only 5% of patients survived.

This was in direct contrast to patients with supraglottic tumor, for whom close or involved margins did not always affect survival. The presence of pathologically positive cervical adenopathy was related to tumor size, as patients whose tumors were less than 4 cm in size had a 50% incidence of positive cervical lymph node results and those with tumors larger than 4 cm had an 85% incidence of positive node findings. The incidence of positive cervical metastasis results did not correlate with tumor differentiation. However, tumor differentiation at the primary site had a direct correlation with survival.

Invasion of thyroid cartilage, muscle, or nerve was directly related to cervical adenopathy. There were no survivors in the group of patients who had contralateral cervical metastases. The most common lymph node to be involved was the upper jugular node, even for inferior hypopharyngeal tumors. When positive nodes were present in the posterior inferior cervical triangle, there were no survivors.

Martin et al (1980) further reviewed pathologic data and correlated it with the tumor-node-metastasis (TNM) system. They found a greater response to preoperative irradiation among patients who had nonkeratinizing carcinoma. The response to preoperative irradiation did not correlate to the degree of differentiation or whether the tumor had a pushing or infiltrating margin. None of these factors had any correlation with the development of cervical metastases. Between 10% and 29% of their patients had extranodal extension of tumor. Poorest survival was associated with tumor in cervical lymph nodes or at the surgical margins. Patients who had extranodal extension of metastases regardless of T or N staging had an increased incidence of distant metastases.

Histologic differentiation of the tumor did correlate with invasion of thyroid cartilage. Tumors of the medial wall of the piriform sinus tended to extend into the region of the supraglottic larynx. Because of these findings, surgical removal of the preepiglottic space is advised when partial pharyngectomy is considered for medial wall tumors.

Kirchner (1975) reviewed whole-organ sections to determine suitability of patients for partial pharyngectomy. He demonstrated that piriform sinus malignancies may infiltrate into the posterior cricoarytenoid muscle and thereby affect cord mobility. Cord mobility can also be affected by invasion of the cricoarytenoid joint or direct invasion of the recurrent laryngeal nerve. Tumors spread medially into the larynx and may invade the thyroarytenoid muscle. Tumors extend upward to invade the base of the tongue or inferiorly into the esophagus. A 1-cm submucosal infiltration is invariably present, requiring minimal surgical margin of at least 2 cm.

Dumuch et al (1984) studied histopathologic specimens to determine whether piriform apex involvement would still permit a near-total laryngopharyngectomy in patients with piriform sinus carcinoma. In review of 20 total laryngectomy/partial pharyngectomy specimens, they found 17 patints who retrospectively could have been considered for a near-total laryngectomy. They believed that the anterior larynx could be preserved to establish a sphincteric tracheoesophageal shunt. Patients would not be considered candidates for this surgery if there was any evidence of involvement of the postcricoid area, bilateral cord fixation, or tumor in the interarytenoid area, as one functioning arytenoid cartilage must be preserved.

## Management

The diversity of treatment recommendations for the management of hypopharyngeal malignancies reflects the fact that uniform treatment guidelines or recommendations are not available. Current treatment modalities include full-course irradiation therapy with surgical salvage; surgery alone; a combination of irradiation therapy with surgery, with irradiation given either preoperatively or postoperatively; and, finally, prospective protocols including chemotherapy, either before surgery or irradiation or in combination with irradiation therapy and surgery. In order to assess the current treatment modalities, it is first necessary to examine treatment trends over the past 30 years. Each of the preceding options will then be discussed separately.

In the early 1960s, surgery was the primary modality for all forms of malignancies of the hypopharynx once it was determined that the patient was able to undergo an operative procedure. Indications for nonresectability were presence of fixed cervical metastases involving the carotid artery, extension onto and fixation of the posterior pharyngeal wall, extension into the cervical esophagus, and any evidence of distant metastatic disease. Patients not considered candidates for surgery were offered full-course irradiation therapy, recognizing that this would only be palliative. With advances in surgical technique, the limits of resectability were extended. Thus, total laryngopharyngectomy was possible with reconstruction using regional flaps (Bakamjian) and colon interposition rather than local flaps (Wookey) (Mustard, 1960). This extended the capability of the surgeon to resect tumors that were recurrent after full-course irradiation therapy and interpose an acceptable pharyngeal reconstruction. At that time, Harrison and others pointed out that a cause of failure of surgery was tumor extension into the thyroid gland, paratracheal nodes, and upper mediastinal lymph nodes, and, most importantly, submucosal extension inferiorly into the cervical esophagus.

Harrison also recognized the possibility of skip lesions within the esophagus and advised total esophagectomy combined with radical total laryngopharyngectomy for postcricoid carcinoma. His later study of 57 patients with postcricoid carcinoma revealed only one concurrent esophageal carcinoma. Total esophagectomy with gastric pull-up was advised to obtain an adequate resection of the cervical esophagus and limit the number of anastomoses.

Partial pharyngectomy was described by Trotter (1932), who used resection and primary closure for limited lesions of the superior lateral hypopharynx and postcricoid area. Orton (1930) reported on his experiences learned from Trotter and described the "transhyoid pharyngotomy". Alonso (1947) in Uruguay described approaches now known as supraglottic laryngectomy and vertical partial laryngectomy for a malignancy of the hypopharynx. In 1960, 1964, and again in 1979, Ogura (Washington University, St. Louis) reported on his extensive experience with partial pharyngectomy, which by 1979 had included 85 patients (Ogura and Mallen, 1965; Ogura et al, 1960; Ogura et al, 1980).

Assessment of survival statistics revealed that even this extended surgery did not greatly affect overall survival for patients with advanced diseases. Simultaneously, Biller, Ogura, Goldman, and others began to administer low-dose preoperative irradiation therapy before surgical resection (Biller et al, 1969; Goldman et al, 1970). Dosages used were in the range of 2000 to 4500 rad delivered over 1 to 4 weeks. The planned surgical resection was

performed 4 weeks later. The initial results, although not randomized, suggested that survival was improved with this combined therapy. Preoperative irradiation therapy combined with surgical resection became the most popular treatment for hypopharyngeal malignancies during the late 1960s and early 1970s.

In the late 1970s, postoperative irradiation therapy, again administered as part of a planned therapy, was considered. It was believed that surgical complications would be lessened if the irradiation were administered postoperatively. Doses up to 6000 rad could be administered safely after the wound has healed and pathologic evaluation of the speciment allowed the establishment of criteria to determine who should receive irradiation therapy. Criticism of this combined technique came from Carpenter and DeSanto, Yates and Crumley, and others (Carpenter et al, 1976; Yates and Crumley, 1984), who believed that combined therapy was not proved in a prospective study to be better than surgery alone. Still, combined therapy with postoperative irradiation therapy for the treatment of advanced hypopharyngeal malignancies became the trend.

Another advance in surgical management was microvascular surgery, which allowed free jejunal autograft reconstruction. A total laryngopharyngectomy with 6 cm of cervical esophagus could be reconstructed by a single-stage procedure. If total esophagectomy was necessary, then gastric pull-up became the preferred method of reconstruction (Harrison, 1979). Reconstruction with colon and local and regional flaps became less popular, as these newer techniques allowed for more rapid reestablishment of normal swallowing and a shorter hospital stay.

Surgery combined with irradiation therapy provided results that were still unsatisfactory, as overall 5-year survival was not significantly improved. What did change was the pattern of recurrence: increased distant metastases and failure in the opposite neck and decreased local and ipsilateral neck recurrences. In an effort to continue to reduce the distant metastases, reduce the extent of surgery required, and improve overall survival statistics, chemotherapy was administered. Prospective studies (NCI-H&N contracts study) were initiated. These studies demonstrated that a partial response in the tumor mass could be obtained by administering one to four courses of chemotherapy before definitive surgical resection. Additionally, studies were undertaken to administer chemotherapy first and, if there was a partial or complete response, the patient would go on to full-course irradiation rather than surgery. Thus, an effort was made for voice preservation. In all such studies, persistence of palpable cervical metastatic disease remained an indication for radical neck dissection. In the 1980s, further changes in management occurred when it was suggested that a comprehensive or radical neck dissection provided no better survival results than modified neck dissection followed by irradiation therapy.

## Irradiation therapy alone

Irradiation therapy is employed for patients present in the following fashion: (1) those who have early malignancies, often confined to the medial wall of the piriform sinus - particularly exophytic tumors without extension into the piriform apex; (2) those who have primary malignancy of the posterior pharyngeal wall; (3) those who refuse surgical resection or are too ill to undergo resection; and (4) those for whom irradiation is used primarily for palliation to reduce the bulk of extensive nonresectable malignancies and alleviate pain.

Million and Cassisi (1981) presented their excellent results with irradiation therapy, followed when necessary with surgical salvage for T1, T2, and T3 malignancies of the hypopharynx. Irradiation alone was used for the primary tumor if there was no evidence of palpable neck disease, but radical neck dissection was performed in patients who had persistent cervical metastases of who initially had nodes 2 to 3 cm in size. They agreed with earlier reports that cervical metastatic disease did not respond adequately to irradiation therapy for hypopharyngeal malignancies. They reported a 79% local control rate for T1 lesions. For T2 and T3 lesions, 56% of the 42 original patients were successfully treated. Four patients required salvage surgery; three had successful surgery. They noted that the successful cases were T1 lesions on the anterior or medial wall, and failures were associated with malignancies on the lateral wall. The best candidates were those whose exophytic lesions confined to the superior hypopharynx. Evidence suggestive of recurrent disease included persistent edema in the region of the arytenoids; pain, especially on swallowing; and development of a fixed cord and hoarse voice. In stage III and IV lesions, irradiation therapy was administered to the primary tumor only with plans for surgical management of the neck. Unfortunately in this series, there was significant morbidity when surgical salvage was attempted. In all patients, both necks were treated.

Wang (1971), presented his results with 42 patients who had primary malignancy of the posterior pharyngeal wall. He noted that this type of lesion had the poorest prognosis of any area in the hypopharynx. Ninety-five percent of his patients were above 50 years in age and 70% above 60. Presenting symptoms, including dysphagia, persistent pharyngeal pain, sensation of foreign body, and referred otalgia, were identical to those of other hypopharyngeal tumors. The majority of lesions were in the midposterior pharyngeal wall, and some lesions could even be seen by simple depression of the posterior tongue. Fifty-five percent of the patients had metastatic cervical adenopathy and four of this group had bilateral adenopathy. Thirty-six patients were eligible for 3-year survival assessment. Survival with irradiation therapy alone was 25% (9 of 36). However, when patients presented with T1, T2, and T3 lesions and no adenopathy, the survival rate at 3 years was 47%. On the other hand, of 17 patients who had clinically evident cervical adenopathy, only 12% were alive at 3 years. Local recurrence along the posterior pharyngeal wall was the primary cause of failure.

## Primary surgical treatment

### *Surgical planning and prevention of complications*

Total laryngopharyngectomy as well as total laryngectomy with partial pharyngectomy have a higher complication risk than laryngectomy alone. Patients now being considered for surgery may represent irradiation failures or may have received planned preoperative irradiation. In such situations, patients who may have already been at risk for poor healing have been further compromised.

Factors that have been associated with increased risk include poor incision planning, poor nutritional status, longer operative procedures, need for flaps for reconstruction, and tight pharyngeal closure. The one factor found most often to correlate with the development of postoperative fistula was the presence of positive surgical margins.

In an effort to prevent postoperative complications, the following recommendations are made:

--> Incisions that never meet at angles less than 90-degree are designed. Vertical limbs are not placed adjacent to the carotid artery. A long transverse limb, with vertical extensions when necessary, frequently provides adequate exposure and least interference with flap blood supply.

--> Carotid artery protection with a levator scapulae muscle flap or dermal graft has not been statistically shown to reduce carotid artery exposure or rupture. However, this form of protection for the carotid artery is still advocated. The pectoralis major myocutaneous flap muscle pedicle can protect the carotid artery.

--> The introduction of continuous suction has allowed reduction of dead space and adhesion of flaps to underlying tissues.

--> Perioperative antibiotics are initiated 1 hour before surgery and continued for 48 hours after surgery. In cases where flaps have been used or patients have generally poor nutritional status, many surgeons advocate longer use of antibiotics. There are several alternative choices for prophylatic antibiotics. Most popular regimens include a cephalosporin with or without added anaerobe coverage. Most infections are still caused by common gram-positive organisms with an associated polymicrobian infection of anaerobic organisms

--> Blood loss is decreased during surgery by careful hemostatic technique and selectively and carefully using electrocautery to perform the neck dissection. As a general rule, elderly and debilitated patients are better served by an operative procedure that involves the simplest reconstruction. Complicated flap reconstructive procedures are fraught with problems in such individuals and are avoided if possible.

The selection of the appropriate operation must depend on the status of the patient and the extent of the tumor, rather than the challenge offered the surgeon to preserve the voice.

**Surgical options and results**

McGavran et al (1963) reported that irradiation therapy alone was insufficient treatment for patients with cervical metastases. The 5-year survival rate was approximately 8% with irradiation therapy alone when nodes were present. As in other large series, 84% of his patients had pathologically positive cervical adenopathy results, primarily in the upper jugular chain. Only 4 of 52 patients had contralateral nodes. When treated by surgery alone, 8 patients died of local disease, 8 of cervical metastases, and 4 of distant metastases. No patients who experienced recurrence were salvaged regardless of secondary therapy. In this group, surgery included partial pharyngectomy, total laryngopharyngectomy, and ipsilateral radical neck dissection in all cases. Overall 5-year survival rate was 31%.

Shah et al (1976) presented results obtained by using primary radical surgical resection in the management of hypopharyngeal carcinoma at the New York Sloan Kettering Memorial Hospital. Their patient group was 81% male and was primarily elderly, in the sixth or seventh decade of life. As in most studies, approximately 60% involved piriform sinus, 35% posterior

pharyngeal wall tumors, and 6% post-cricoid. Their overall 5-year survival was 25%, unchanged from that of studies in the early 1960s. However, the study demonstrated very successful management of patients who had earlier stage tumors. Five-year survival rate for patients with stage I disease was 43%; stage II, 38%; stage III, 19%; and stage IV, 9%. However, even 40% of their T1 lesions were associated with cervical metastases. Sixty-nine percent of patients with T2 lesions had positive neck node findings at the time of presentation. They noted that survival rate was decreased by 50% in the presence of positive node results.

Elective neck dissection was performed for all patients and had a 32% survival rate when micrometastases were found versus only 22% when a later therapeutic neck dissection was performed. Two hundred thirty-four patients were treated by surgery alone. A limited number of patients received preoperative irradiation therapy of 2000 rad over 7 days. They were unable to demonstrate that this combined therapy improved the results of surgery alone and concluded that these results were significantly better than irradiation therapy alone followed by surgical salvage.

Carpenter et al (1976) analyzed the treatment and results in 162 patients at the Mayo Clinic. Surgery was the primary, and often the only, treatment modality used; irradiation was reserved for palliation. Patients who had mobile cervical metastases underwent surgery with possible combined therapy. Those who had large metastatic cervical nodes were given irradiation before attempts at surgical resection.

The characteristics of patients treated by Carpenter et al (1976) were similar to those in the other studies. Eighty-four percent were male; 85% were in the sixth or seventh decade of life. Ninety-three percent had a history of heavy alcohol ingestion, and 67% had cervical adenopathy at the time of presentation, 5% had contralateral disease, and 24% had fixed cervical metastases. Interestingly, patients with postcricoid carcinoma, the smallest group (six patients), had the best 5-year survival (44%), whereas those with tumors of the posterior pharyngeal wall had only a 22% 5-year survival. There was no difference in survival by the grade of the tumor. Stage I tumors had an overall survival rate of 81%. For stage II, 3-year survival was 66%; for stage III, 51%, and for stage IV, 0%. In their series, no difference could be seen in patients receiving preoperative irradiation versus surgery alone. However, complication rate was higher for patients who had preoperative irradiation therapy. Recurrences occurred equally in both the primary tumor and neck; there was a higher recurrence rate in the neck with surgery alone. Six of eight patients had recurrence in the contralateral neck.

Strong et al (1978) reported the results of a Boston University and VA Hospital study of squamous cell carcinoma of the oropharynx and hypopharynx. They reported the results of planned preoperative irradiation therapy of 2000 rad of cobalt-60 delivered in 5 days before surgery. Compared to patients treated by surgery alone, they had no increased incidence of complications (12% for combined therapy versus 20% for surgery only). This study was unable to demonstrate any difference in survival between the two groups. However, there was an increased incidence of distant metastases in the group who received preoperative irradiation.

Razack et al (1978) presented data for the Roswell Park Memorial Institute on 111 patients with squamous cell carcinoma of the piriform sinus treated with surgery alone, irradiation therapy alone, or planned combined modalities. There were 67 patients who underwent surgery as the primary form of treatment; 42 had total laryngectomy and partial pharyngectomy, and 22 had total laryngopharyngectomy with deltopectoral flap reconstruction. Five-year disease-free survival in this group of patients was 25%. The survival rate was 30% for T1 lesions and approximately 20% for patients with T2 and T3 disease. The extent of nodal disease was the greatest factor in survival, with 60% 5-year survival for N0 status patients and only 19% for patients with N1 status. Recurrence generally occurred within 1 year; 28% of patients experienced recurrence both above and below the clavicle. Postoperative irradiation therapy was used in this series only for 4 patients who had positive margin findings at the time of resection. Two of these patients survived 5 years.

Pathologic evaluation demonstrated that patients had a poor prognosis when tumors were located on the lateral wall or into the apex or when the thyroid cartilage was invaded. Recurrent disease after irradiation was not controlled satisfactorily by surgery: four of seven patients died of their disease. They did not believe that a contralateral neck was indicated as part of the initial surgical resection.

Yates and Crumley (1984) performed a retrospective analysis of patients they had treated, including those who had surgery alone and those who had planned combined therapy. They concluded that preoperative irradiation therapy had not provided the increased survival that initial proponents had suggested. Similar to the experience in other institutions across the country from 1959 to 1967, surgery alone was used in this San Francisco series. From 1967 to 1978, preoperative irradiation therapy was administered; and from 1978 to 1983, postoperative irradiation therapy was administered. Twenty-one patients were in the "surgery alone" group and had a 5-year determinate survival rate of 56%. On the other hand, 39 patients who had combined planned irradiation and surgery had a 5-year determinate survival rate of only 33%. There was no difference in survival patterns noted between the preoperative and postoperative group. For more advanced tumors, such as stage III, surgery alone provided a 63% 3-year survival, compared to 64% for the combined group. Interestingly, their study showed poorer survival for women, regardless of stage. Most importantly, the combined therapy group had a higher incidence of distant metastases: 32% (12 of 37) died of distant metastatic disease within 3 years. By 5 years, 15 of 30 determinant patients in the combined therapy group died of distant metastatic disease. They suggested that the combined therapy somehow made the hosts less able to deal with any residual disease.

Pingree et al (1987) presented data by treatment modality on 695 patients with carcinoma of the hypopharynx treated at the University of Utah between 1973 and 1983. Three-year tumor-free survival for the group treated by surgery alone was 59%; for radiation alone, 28%; for surgery plus radiation, 43%. However, 5-year survival for the same groups of patients was as follows: for surgery alone, 41%; for irradiation alone, 21%; and for combined surgery and radiation, 33%. Five-year survival rates for 156 patients with stage I and II hypopharyngeal cancer also showed that the group treated by surgery alone had a survival of 48%; for surgery plus radiation, 40%. A comparison was made, although not randomized, of preoperative versus postoperative irradiation therapy. At 5 years, the survival rate for patients who received planned preoperative irradiation was 29%; for planned postoperative irradiation it was 32.7%. He concluded that his findings were similar to those

of Yates and Crumley, without a demonstrable improvement in survival with combined therapy over surgery alone. Because many patients who received irradiation therapy may not have been eligible for surgery, it would not be fair to make a comparison with irradiation alone in this series.

Similarly, Eisbach and Krause (1977), in reporting the University of Iowa series, could not demonstrate an improvement with preoperative irradiation plus surgery versus surgery alone for hypopharyngeal tumors. In fact, they found a higher local recurrence rate (28%) in the combined therapy group than in the surgery-only group (5%). They attributed this to the inability to determine the resection margins satisfactorily at surgery in patients who had received preoperative radiation. This series did demonstrate that preoperative irradiation therapy significantly reduced the incidence of contralateral neck recurrence in the combined group when compared to the surgery-alone group.

### *Partial laryngopharyngectomy*

Ogura et al (1960) presented a series of 13 patients who had undergone partial pharyngectomy for piriform sinus malignancies. Conservation surgery for pharyngeal cancers had previously been shown by Alonso (1947) and Trotter (1932) to be an effective means of treatment for limited tumors that fulfilled specific requirements (Fig. 105-5). The three most important requirements were the following: (1) there must be no involvement of the true vocal cords and no limitation of motion of the cords; (2) the tumor could not extend into the apex of the piriform sinus; and (3) there must be no evidence of thyroid cartilage invasion. All patients received an ipsilateral neck dissection, as there was pathologic evidence of positive nodes in 90% of the specimens.

In a follow-up study of these patients, the procedure had been extended to include lesions reaching up onto the glossoepiglottic fold and region of the vallecula (Ogura and Mallen, 1965). The most suitable lesions were in the superior hypopharynx. Overall results for the first 28 patients revealed a 5-year absolute survival rate of 43%. Only four of the patients died of persistent disease, and the predicted 3-year cure rate using life expectancy data revealed an overall survival of 48%. Only one patient ever developed contralateral cervical metastases. They concluded that for selected cases, these results were similar to those for total laryngectomy with partial pharyngectomy.

By 1979, the Washington University series had expanded to include 85 patients who had had partial laryngopharyngectomy for piriform sinus carcinomas (Ogura et al, 1980). Approximately one half of the patients seen during this period were eligible for this type of partial pharyngeal surgery. Three-year actuarial survival rate remained at 59%, compared to 36% for 57 patients undergoing total laryngopharyngectomy. Recognizably, those patients who had total laryngopharyngectomy had more extensive tumors.

The most important prognostic factor was the development of palpable cervical disease. Three-year survival of all patients without nodal disease was 53%, compared to 24% for those with palpable nodal metastases. Overall control of the primary tumor for patients with piriform sinus carcinoma was 47%, with a 66% 3-year survival rate for patients who had conservation surgery. As in patients who had total laryngopharyngectomy, recurrences occurred equally at the primary site, in the neck, and distally.

More than 50% of the patients who had undergone conservation pharyngeal surgery were able to retain the voice. Submucosal spread and extensive lymphatic drainage with cervical adenopathy were limiting factors in conservation surgery of the piriform sinus as compared to supraglottic malignancies.

While some surgeons were advocating larger resections for postcricoid carcinoma, Som (1961) proposed a more limitied surgical resection for patients who had early postcricoid carcinoma. By preserving the anterior portion of the larynx and trachea and resecting the posterior aspect, including the arytenoids and common wall, it was possible to use the larynx as an autograft to reconstruct the pharynx. He analyzed 26 patients with postcricoid carcinoma and found that this method was acceptable in patients with limited tumor. Malignancy had to be limited to the postcricoid area and not extend caudally into the cervical esophagus. The procedure could not be used in patients who had previously had irradiation therapy, and the endolaryngeal aspects of the larynx had to be free of tumor.

By 1974, Som had been able to perform 23 partial pharyngolaryngeal resections with reconstruction using a laryngotrachea autograft for 84 surgically treated patients with postcricoid carcinoma. Of the 23 patients suitable for this procedure, 6 have survived free of tumor. Failure was attributed to lymphatic metastases, particularly to lymph nodes in the paratracheal and deep cervical regions. He advised that all patients undergo an ipsilateral neck dissection.

Krespi, Sisson, and Wurster combined the experience of Som's laryngotracheal autograft with a wider surgical resection and gastric pull-up (Krespi et al, 1984; Krespi and Sisson, 1984). A permanent tracheostomy was created in five patients, and the anterior one half of the larynx and trachea was converted into a tracheoesophageal speaking shunt.

### *Surgical reconstruction*

Resection of large or circumferential hypopharyngeal malignancies requires total laryngopharyngectomy. As reported by Gluckman, Harrison, and others, there is a need for a 5- to 6-cm resection inferiorly or into the cervical esophagus (Gluckman et al, 1987; Harrison, 1979; Murakami et al, 1985). Options for reconstruction include local regional flaps, colon interposition, free jejunal interposition, and gastric pull-up.

Colon interposition, although among the first types of reconstructive procedures considered, has become less popular. The colon can be brought up either subcutaneously, overlying the sternum; substernally; or through the posterior mediastinum. The major advantage of the subcutaneous tunnel is safety obtained since the thorax is never entered, and thus mediastinitis is avoided should the anastomosis develop a fistula. The chief disadvantage was swallowing, particularly at the tight angle of reconstruction of the manubrium or clavicle. Solid food would tend to lodge in this area. This procedure is adequate for the handling of saliva and liquids but is not considered a choice for reconstruction at this time except in very restricted cases. Retrosternal colon interposition is the preferred colon interposition.

Gastric pull-up has several advocates (Harrison, 1979; Griffiths and Shaw, 1973). Its major advantage is its shorter period of hospitalization. In fact, patients can usually eat within 2 weeks and, most importantly there is only one anastomosis in the region of the superior

mediastinum. The stomach is drawn up in the posterior mediastinal space by creating a tunnel. It permits total resection of the esophagus when necessary. Its advocates point to the rapid rehabilitation of patients with this operative procedure. Its drawbacks include hemorrhage occurring during the operative procedure, morbidity of 8.5% in the best of hands, possibility of fistulization in the neck, and reflux or regurgitation from the stomach. Also, the large stomach tends to be bulky when placed into the neck.

The jejunal interposition has gained acceptance ni all centers where microvascular surgical techniques are available (Fisher et al, 1985, 1990). The major advantages include the physiologic size of the jejunum when placed in the neck. The jejunum can tolerate postoperative irradiation therapy, should this be indicated. The major disadvantage is the number of anastomoses required, both intraabdominally and cervically (Gluckman et al, 1985). There is a 20% incidence of graft loss secondary to the anastomoses. Unlike colon or stomach, a second section of jejunum could be obtained should the first graft fail. Patients are able to eat in 10 to 14 days, and if no complications develop, they can be discharged from the hospital after 2 weeks. Considering that more that 80% of patients who require this degree of surgery do not survive beyond 2 years and that the procedure, although intended to be curative, is often only palliative, limited hospitalization with immediate reconstruction is preferable.

Reconstruction with a deltopectoral flap is a safe, effective operative procedure. However, it requires staging. In fact, patients may require three stages before reconstruction is complete. Cusumano and Silver (1989) and Schuller (1985) have recommended the tubed pectoralis major myocutaneous flap to reconstruct pharyngoesophageal defects. This flap has a high success rate. Major problems include fistula formation and stricture at the flap/esophageal inlet. Schuller had used a soft stent placement technique to diminish the frequency of stricture at the second or distal anastomosis. Swallowing is delayed with this procedure when compared to gastric-pull or jejunal interposition procedures. The major advantage of the technique is that it is possible in elderly or debilitated patients.

### *Management of the neck*

Once appropriate management of the primary hypopharyngeal malignancy has been determined, the preferred treatment of the neck must be decided. As noted in the preceding series for hypopharyngeal lesions, particularly of the piriform sinus, the incidence of occult neck disease varies from 30% to 40%. Thus, the neck must be addressed and treated, even in the N0 stage.

Medina (1989( has clarified the concept of a modified neck dissection. When the neck is classified into five nodal groups, regions II, III, and IV are the nodes associated with the jugular vein and are the areas that must be cleared in every neck dissection for hypopharyngeal cancer (Fig. 105-6).

Patients who have palpable cervical metastases, N1, N2, and N3 disease, are uniformly treated by comprehensive neck dissection if the nodes are not fixed to the carotid artery and it is not determined that the patient has unresectable disease. Candela et al (1990) reviewed the metastatic patterns of cervical node metastases in patients with hypopharyngeal malignancies. In 222 cases of hypopharyngeal malignancies, 91 patients had piriform sinus

malignancies, 35 had malignancies of the posterior pharyngeal wall, and 4 had postcricoid tumors. By dividing the neck into five zones, it was evidenct that for piriform sinus tumors with N0 necks, levels II and III were the areas primarily involved. However, in cases of N-positive nodes, levels II, III, and occasionally IV were involved but levels I and V also showed substantial involvement. These findings were similar for posterior pharyngeal wall lesions. They concluded that a modified or anterior neck dissection could be considered appropriate in patients with N0 necks but recommended a comprehensive neck dissection in any patient who had an N-positive node.

When disease is more limited, a modification of the standard neck dissection is acceptable if irradiation therapy is to be delivered postoperatively. The issue whether postoperative irradiation therapy should be administered in the patient with palpable nodes who has undergone a neck dissection arises. In the early 1970s a series of reports suggested that cervical metastatic disease is preferably treated by surgery followed by irradiation therapy. This provided better regional control but did not necessarily extend survival.

Ogura et al (1971) reported his experience with 98 cases of piriform sinus cancer. Palpable cervical nodes were present in 52% of the patients, and occult nodes yielded positive findings in 38%. None of the patients who had negative node results at presentation or occult nodes found to be positive at the time of surgery experienced recurrence in the neck. However, in 21% of patients who had palpable nodes neck recurrence developed in spite of radical neck dissection. With the assumption that patients who had recurrence in the neck after radical neck dissection almost uniformly die of disease, he felt that radical neck dissection was indicated.

The experience of the M. D. Anderson Cancer Center was presented by Barkley et al (1972). This study compared 596 patients with neck disease with a control group of patients whose primary tumor was controlled but recurrence developed in the neck. Their main interest was to determine whether postoperative irradiation therapy was of value when given electively after modified or radical neck dissection. Postoperative irradiation therapy was administered if there were (1) positive margin findings, (2) in situ carcinmoa present at the margins, (3) extension of tumor outside the larynx, (4) many positive nodes at many levels, or (5) evidence of extracapsular extension. There were no delayed failures in the neck in patients with N1 and N2 disease treated by surgery followed by radiation, whereas in 12 of 38 patients treated by surgery alone cervical recurrence developed. They concluded that combined surgery and irradiation therapy was the preferred treatment for patients with N1 and N2 disease.

The report by Leemans et al (1990) recommended extension of the indications for postoperative irradiation therapy to include not only positive nodes at many levels or extranodal extension but also presence of only one positive node. The patients in this study had a comprehensive or standard radical neck dissection. They found a direct correlation between the number of positive nodes present in the surgical specimen and the incidence of recurrent disease. The rate of recurrence was 2.6% in N1, 9.1% in N2, and 11.3% in N3 necks. Their analysis concluded that patients with one or two positive nodes, regardless of extranodal extension, had the same rate of recurrence as those who had more extensive neck disease; overall recurrence rate in a surgically treated neck was 7.2%.

Carpenter et al (1986) disputed the need for postoperative irradiation therapy in all patients undergoing neck dissection, considering this treatment redundant. They challenged statistics presented in series in which staging was based on clinical rather than pathologic criteria, noting that approximately 28% of necks were understaged by clinical examination as to the extent of neck disease. They did not believe that the addition of postoperative irradiation therapy had any effect on the later development of distant metastases. The recurrence rate was 7.5% in clinically and pathologically negative necks. Recurrence in the neck was present in 20% of patients with N1 disease and 37% with N2 disease.

Their study brought up the issue that valid comparisons could not currently be made when results were assessed only on the basis of neck disease rather than including all patients with the same stage of disease. The conclusion that irradiation therapy after neck dissection was beneficial was based on inadequate sample size.

Most studies support the use of postoperative irradiation for local control, even though increased survival has not been demonstrated, for patients with N1 and N2 cervical disease (Arriagada et al, 1983; Briant et al, 1978). The issue that then arises is the management of the clinically N0 neck: whether surgery alone, irradiation alone, or a combination is preferred. Often, the decision is based on the management of the primary tumor (Jesse and Lindberg, 1975). For example, if irradiation alone is used for the primary tumor, it then can be extended to manage the clinically N0 neck. To control the N0 neck, a minimum dosage of 5000 rad is required. If irradiation is intended to control and N1 neck, then a minimum dosage of 6500 rad is required. Higher dosages of irradiation therapy do not show any increase in control of metastatic disease and have higher associated incidences of complications. Doses of 7200 rad or higher have not been shown to improve the control rate and have an increased incidence of complications.

Irradiation therapy to the N0 neck is an acceptable option and has been used as a primary treatment for the contralateral neck. In Fletcher's (1972) series, in only 1 of 65 patients who had irradiation to the contralateral side did a tumor develop in that neck, whereas malignancy developed in the contralateral neck in 20% of patients who did not receive irradiation therapy.

The incidence of occult metastases in Marks's series was 38% (Marks et al, 1985). They concluded that elective neck irradiation was justified for cancers of the piriform sinus.

Leemans et al (1990) based the decision about postoperative irradiation therapy in the N0 neck on the presence or absence of nodes found on pathologic investigation of the neck specimen. They noted an overall recurrence rate in the operated neck of only 2.6% when the neck specimen produced histopathologically negative results for tumor.

Spaulding et al (1987) could not demonstrate any advantage to combined therapy for the N0 neck and recommended either surgery or irradiation. They demonstrated no difference between surgery alone or irradiation alone. The N0 neck was successfully controlled in 95% of cases by combined therapy and in 82% by irradiation therapy. They concluded that the single-modality treatment was inadequate for N2 or N3 neck and that the combined modality treatment was superior whenever nodal metastases was present. They preferred combined therapy, a modified neck dissection and irradiation therapy, to the use of high-dose irradiation.

Control with irradiation alone should not be expected in patients with metastatic nodes 3 cm or greater in size.

There is considerable difference in the incidence of reported positive nodes in the contralateral neck. Murakami et al (1985) found an incidence of 30% histologically positive contralateral nodes in their series and advised bilateral neck dissection for hypopharyngeal cancers in all patients except those who had well-differentiated T2 or smaller lesions. They advised ipsilateral neck dissection in all patients with pharyngeal tumors, even N0 lesions. About one third of their patients had contralateral neck disease and required a bilateral neck dissection.

The majority of studies, however, suggest that when postoperative irradiation therapy is to be administered control of the contralateral neck can be obtained with therapy in the range of 6000 rad. Contralateral neck dissection is reserved for patients who have palpable nodal disease or in whom a node later develops on the contralateral side. If the tumor extends across the midline, then a contralateral neck dissection, usually modified, is performed.

## Combined therapy

The concept of combining irradiation therapy with surgical resection in a planned manner began in the early 1960s after initial reports by Goldman, Powers, Ogura, Martin, and others (Goldman et al, 1970; Powers, 1965; Ogura and Mallen, 1865; Kirchner and Owen, 1977; Lord et al, 1973; Martin et al, 1980). These large series compared patients who initially had low doses (2000 rad) of preoperatively administered irradiation therapy delivered at 200 rad/day followed by a short waiting period and then planned surgical resection with historical control patients from the same institution. Changes in surgical technique including careful incision planning, carotid artery protection, and fistula prevention allowed for larger dosages of preoperative irradiation therapy to be administered without increasing the risk of poor surgical healing.

The initial reports demonstrated that when 2000 rad of irradiation therapy were administered preoperatively, there was no significant increase in surgical complications. At the same time, there was also no significant increase in local regional control or survival. Gradually, the dosage of 4000 to 5000 rad administered preoperatively became the standard and met the requirement of control of micrometastases, lymphatic spread, and reduction of tumor bulk without interfering with healing. The primary theoretic advantage of preoperative irradiation therapy was that well-oxygenated nonoperated tissue had a better vascular supply and made the delivery of irradiation therapy more effective than irradiation to an operated field. Also, the field and extent of irradiation therapy would be more limited, as it could be directly applied to the tumor site.

Postoperative irradiation became more popular in the late 1970s (El-Badawi et al, 1982; Van den Bogaert et al, 1985; Razack et al, 1978; Arriagada et al, 1983). The primary advantage of postoperative irradiation therapy was the establishment of the pathologic extent of disease, true status of cervical nodes, and status of the surgical margins. In order to encompass the entire field, irradiation had to be delivered to a larger port, and a total of 6000 rad over 6 weeks was necessary. The major disadvantage was the fact that postoperative irradiation therapy would have to be delayed if there was a delay in wound healing. Vikram

(1979a and b) pointed out the need to deliver postoperative irradiation therapy within 7 weeks of the operative procedure. His study at Sloan Kettering Memorial Cancer Research Center started soon after they began giving planned postoperative irradiation therapy. In the first group of patients to receive this, he observed that no signs of recurrence developed in 7 of 10, or 70%, of the patients who had postoperative irradiation therapy within 7 weeks of surgery. In the group of 11 patients who had a delay in the initiation of postoperative therapy, regional or local recurrent tumor developed in 3. This need to administer postoperative irradiation therapy within 8 weeks of surgery has been a major argument put forth by advocates of preoperative irradiation therapy.

El-Badawi et al (1982) summarized the treatment results for piriform sinus carcinomas at the M. D. Anderson Cancer Center between 1949 and 1976. Limiting the study to hypopharyngeal cancer only revealed 422 patients with piriform sinus cancer - 91 in the posterior pharyngeal wall and 18 in the postcricoid area. In this study, postoperative irradiation therapy was defined as radiation commencing within 12 weeks after surgery and all gross tumor had been resected. Radiation fields were enlarged in the 1960s to include parapharyngeal lymphatics and inferiorly to attempt to reduce stoma recurrence by subglottic extension. Survival curves were then calculated for surgery versus surgery plus planned postoperative irradiation therapy. In the surgery-only group, the survival rate was 25%; in the combined group, it was 40%. The combined group had a slightly higher incidence of pharyngeal stenosis. Significantly fewer recurrences above the clavicle occurred in the group who received postoperative irradiation therapy. On the other hand, recurrences above the clavicle were related to T stage, with a low incidence (18%) for T1 and T2 tumors and a higher incidence (33%) for T3 and T4 tumors. Recurrence above the clavicle for all end stages was approximately 30%. Patients with N2 and N3 stage neck disease had a higher incidence of distant metastases (28%) compared to N0 and N1 stage (16%).

Two major prospective randomized studies were initiated to determine whether preoperative or postoperative irradiation therapy was more advantageous. The largest study was performed between 1973 and 1975 under the direction of the Radiation Therapy Oncology Group (RTOG) (Kramer et al, 1987; Tupchong et al, 1991). Patients with carcinoma of the oral cavity, oropharynx, supraglottic larynx and hypopharynx were randomized to receive preoperative irradiation of 5000 rad or postoperative irradiation in the range of 6000 rad. Three hundred twenty patients were available for analysis, of whom 78 had primary piriform sinus cancers. Thirty-five patients received preoperative irradiation therapy and 38 received postoperative irradiation therapy. In the hypopharynx area, the preoperative group had a 50% local regional control rate, and the postoperative group had a 61% control rate. There was no statistical signficance, in overall survival.

Another group of patients in this study received definitive irradiation therapy; surgery was reserved for individuals who had persistent disease. In this small group of patients there was no significant difference in results between planned combined therapy and surgery reserved for persistent or recurrent disease and no higher incidence of surgical complications.

The second randomized prospective clinical study was directed by Vandenbrouck et al (1977) at the Gustave-Roussy Institute in France. Their initial goal was 260 randomized patients, but the trial was terminated because of a higher incidence of postoperative deaths of patients who had received preoperative irradiation therapy. Thus, 49 of 177 patients seen

with hypopharyngeal tumors were randomized. The higher complication rate in the preoperative irradiation group was also associated with prolonged healing time (148 hospital days versus 91 days). Overall survival for the preoperative irradiation group was 36%; for the group receiving postoperative irradiation therapy it was 56%.

## Multimodality therapy

In the late 1970s a series of institutions began using preoperative chemotherapy, referred to as adjuvant or induction chemotherapy, in an effort to enhance survival rates of patients with advanced head and neck cancer. At most institutions, patients eligible for study had stage III or stage IV disease or had recurrent disease after irradiation, surgery, or both (Marcial et al, 1990). The long-term "gold standard" for head and neck cancer had been methotrexate (Vogl and Kaplan 1979), but with the advent of cisplatin and its analogs, response rates as high as 50% to 70% for combined partial and complete response in previously untreated patients began to be reported. Thus began the concept of treating patients with chemotherapy before definitive surgery or irradiation. Al-Sarraf et al (1985), through the South Western Oncology Group (SWOG) demonstrated a high combined clinical and pathologic response to a combination of cisplatin (100 mg/m$^2$) followed by 5-fluorouracil (5-FU) (1000 mg/m$^2$ for 4 days) in patients with advanced head and neck malignancy.

The advantage of the cisplatin/5-FU combination was that it was better tolerated by patients, since the side effects were usually renal toxicity and nausea with a lessened incidence of stomatitis. This combination has been taken one step further by other physicians and is used simultaneously with irradiation therapy in both preoperative and postoperative settings (Bachaud et al, 1991). Each combination of modalities has contributed further to the morbidity of the associated treatment. Thus, it becomes necessary to establish whether the combined therapy has an improved overall survival rate or a significant lessening of morbidity for the patient before it can become an accepted or recommended procedure. Recognizing this, large cooperative groups have undertaken prospective randomized studies to assess the response rate and effects on survival in patients with head and neck malignancy.

One intergroup study that included the Eastern Cooperative Oncology Group (ECOG), Radiation Therapy Oncology Group (RTOG), South Western Oncology Group (SWOG), and Cancer and Leukemia Group B (CALBG) demonstrated in 360 patients with advanced inoperable head and neck cancer that simultaneous administration of low doses of cisplatin (20 mg/m$^2$) plus full-course irradiation therapy could be administered safely with reasonable patient tolerance (Haselow et al, 1990). Unfortunately, this combination therapy did not have an improved overall survival rate; median survival was 13 months.

Fig. 105-7 explains the way multimodality therapy has been used in prospective studies. Methods 1 through 4 represent the experimental or research arm of the protocol. This is compared with a standard arm: generally irradiation therapy alone for advanced inoperable disease or combined surgery and postoperative irradiation therapy for advanced inoperable patients. To demonstrate a significant difference between the control arm and the research arm, large numbers of patients (generally 350 to 400) are required. To obtain such numbers in a prospectively, large multi-institutional studies or cooperative studies have been necessary.

Of more recent note have been prospective nonrandomized studies demonstrating that preoperative chemotherapy has been useful in identifying patients who could be treated by chemotherapy followed by irradiation therapy and avoiding surgery. Such efforts have been referred to as "organ-sparing" studies. Demard et al (1990) presented the results of three cycles of chemotherapy consisting of cisplatin, cis-DDP 100 mg/$m^2$, and (5-FU) 1000 mg/$m^2$ for 4 days for advanced hypopharyngeal malignancies. Of 31 patients, they were able to obtain 14 complete responses ni T2 and T3 lesions and 7 partial responses in T2 and T3 lesions of the hypopharynx. The overall response rate for hypopharyngeal lesions was 67.7%. Because of the complete response, 10 patients who would have undergone total laryngopharyngectomy were treated by additional irradiation therapy alone. Seven patients died: 3 of local recurrence, 3 of distant metastases, and 1 of a second primary pharyngeal tumor. In this study, multimodality therapy was not proved to be of benefit for hypopharyngeal malignancies.

Baker, et al (1981) reported on the response rate of patients given preoperative cisplatin (100 mg/$m^2$/day) and intravenous bleomycin (15 mg/$m^2$/day in a 24-hour infusion during days 3 to 7) (Baker et al, 1981). Again, a partial response rate of 42% was noted with this single preoperative course of treatment. Overall primary tumor response for piriform sinus cancers was 46% in 24 patients, with a nodal response in the same group of patients of 40%. The majority of these, however, were partial responses. At the completion of this study, the response rate did not necessarily indicate an increase in survival rate. Since there was some criticism that a single course of chemotherapy should not be considered effective, most now recommend at least three cycles of chemotherapy as part of the regimen.

Jacobs et al (1987) used three cycles of cisplatin and 5-fluorouracil in an effort to produce a complete response and avoid laryngopharyngectomy in six patients with hypopharyngeal carcinoma. They achieved a 60% overall complete response rate with this form of induction chemotherapy and a 30% partial response rate at the site of the primary tumor. In their study, 43% of all patients entered (including patients with tumors of the oral cavity, oropharynx, and larynx), there was a complete response at both the site of the primary tumor and at the nodes. The group that had a complete response did not go on to surgical resection. Again, those patients who achieved complete response with the induction chemotherapy had a better overall survival rate than those who did not. They, too, identified a subgroup of patients who benefited from induction chemotherapy. Complete response rate was considerably poorer in patients with hypopharyngeal and laryngeal carcinoma than in patients with malignancies in the oral cavity or oropharynx.

In a prospective multiple VA hospital trial (Wolt, 1991), an effort has been made to select a group of patients who respond to preoperative chemotherapy and may be able to forego surgical resection and undergo irradiation therapy. This concept of organ preservation with high-dose chemotherapy and irradiation therapy has been tested in a selected group of patients and provided encouraging results.

## Summary

In spite of the progress made, carcinoma of the hypopharynx continues to have one of the poorest prognoses of all head neck malignancies, because of the silent nature of the tumor in its early stages. The majority of patients have metastatic disease or tumors too large

for voice-saving operative procedures or primary irradiation alone. Submucosal extension is common, so the actual tumor may be larger than anticipated, and positive margins on the surgical specimen are too often the result. The rich lymphatic network in the area allows early metastatic extension; 20% to 40% of T1 lesions have either clinically or pathologically positive neck findings.

These tumors are most common in elderly individuals, who often have associated liver disease, chronic lung disease, or poor cardiac status. Thus, treatment must be individualized to be appropriate to the general status of each patient. These patients have a high incidence of second primary malignancies as well as synchronous tumors. Thus, thorough preoperative assessment includes endoscopic evaluation of the entire upper aerodigestive tract to make certain that a synchronous tumor is not present. CT scanning of the head and neck permits evaluation of the extent of the tumor and nodal disease and is of particular value in determining direct extension of the tumor mass into the soft tissues. Early extension to paratracheal and mediastinal nodes as well as downward extension toward the cervical esophagus and node fixation to the carotid artery make some tumors nonresectable. In such cases, palliative irradiation therapy is advised.

In the unique situation in which an early tumor is encountered, patients may be suitable candidates for full-course irradiation therapy or voice-conserving limited resection. Even in these cases, the neck must be addressed. For patients with pathologically established cervical adenopathy, tumors cannot be treated satisfactorily by irradiation alone and must receive surgical treatment of the neck, preferably combined with irradiation therapy. The same group of tumors that are suitable for primary irradiation could also be considered suitable for conservation surgery. The status of the cervical nodes as well as evaluation by CT scan and institutional preference may determine which mode of therapy is used for these exceptional early lesions.

Since the vast majority (70%) of patients have pathologically positive nodes and stage III disease, they require as a minimum a total laryngectomy and partial pharyngectomy as well as an ipsilateral neck dissection. For circumferential tumors or when insufficient posterior pharyngeal wall remains for primary closure, or in the cases of postcricoid extension or involvement of the cervical esophagus, total laryngopharyngectomy with total thyroidectomy, bilateral paratracheal node dissection, and ipsilateral neck dissection are necessary. In this situation, one of three reconstructive techniques may be chosen. Gastric pull-up through the posterior mediastinum is preferred by many, as it permits a larger esophageal resection and only one anastomosis is required. On the other hand, many institutions where microvascular surgery is available prefer that a free jejunal interposition graft be placed. In patients who would not be satisfactory candidates for such an extensive operative procedure, the pectoralis major myocutaneous flap can be used. This flap is of greater value when a small segment of normal mucosa can be preserved, as it is prone to stricture formation.

Postoperative irradiation therapy is administered to all patients who have pathologically proven cervical adenopathy. Patients with N0 disease receive postoperative irradiation therapy if the margins of resection of the primary tumor are considered close or inadequate or there is evidence of extension into the adjacent soft tissues. Preoperative irradiation is preferred by many authors when a gastric pull-up or jejunal interposition graft

will be required, thus avoiding irradiation to the graft.

The vast majority of studes have shown improved local regional control when combined therapy with irradiation is used. These results have not necessarily translated into improved survival (Vikram et al, 1984). Overall survival results relate primarily to stage of disease at presentation, particularly to the status of the cervical lymph nodes. Prospective evaluation of the role of chemotherapy is currently under way. It is hoped, but not yet determined, that chemotherapy may reduce the incidence of distant metastatic disease as well as allow for less radical surgical resection. Current chemotherapy trials have not eliminated the need for combined therapy.