1987

A retrospective comparison of tumor recurrence and patient survival after treatment with preoperative radiation therapy and surgery, or surgery and postoperative radiation therapy for squamous cell carcinoma of the pyriform sinus and hypopharynx

Jesse George Wardlow Jr.
Yale University

A RETROSPECTIVE COMPARISON OF TUMOR RECURRENCE AND PATIENT SURVIVAL AFTER TREATMENT WITH PREOPERATIVE RADIATION THERAPY AND SURGERY, OR SURGERY AND POSTOPERATIVE RADIATION THERAPY FOR SQUAMOUS CELL CARCINOMA OF THE PYRIFORM SINUS AND HYPOPHARYNX

Jesse George Wardlow, Jr.

1987

Permission for photocopying or microfilming of

" A Retrospective Comparison of Tumor Recurrence and Patient Survival After Treatment ... for Squamous Cell Carcinoma† of the Pyriform Sinus and " for the Hypopharynx

purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work, or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

Jesse G. Wardlow

(Signature of author)

Jesse G. WARDLOW

(Printed name)

3/13/87

(Date)

A RETROSPECTIVE COMPARISON OF TUMOR RECURRENCE AND PATIENT SURVIVAL AFTER TREATMENT WITH PREOPERATIVE RADIATION THERAPY AND SURGERY, OR SURGERY AND POSTOPERATIVE RADIATION THERAPY FOR SQUAMOUS CELL CARCINOMA OF THE PYRIFORM SINUS AND HYPOPHARYNX

A thesis submitted to the Yale School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine

Jesse George Wardlow, Jr.
1987

TABLE OF CONTENTS

ABSTRACT

Since 1973, patients with advanced tumors (Stage III and IV) of the pyriform sinus and hypopharynx have been consistently treated with surgery and postoperative radiation therapy by the Yale Section of Otolaryngology. This study will investigate whether this form of combined therapy provides more patients with longer disease-free survival than preoperative radiation therapy and surgery which patients received prior to 1973. Charts of 86 patients with advanced tumors of the pyriform sinus and hypopharynx treated by the Yale Section of Otolaryngology with combination therapy between January 1963 and December 1984 were reviewed. Fifty-nine patients were included in the study.

The results of this review showed a 45 percent two-year and a 24 percent five-year disease-free

survival among patients receiving preoperative radiation therapy. In the preoperative radiation therapy group, there were two perioperative deaths due to carotid rupture. Other treatment complications included fistula formation, abscess, and pulmonary infiltrate. In the surgery and postoperative radiation therapy group, there was a 37 percent two-year disease-free survival and a 17 percent five-year disease-free survival.

The difference in survival between the two treatment groups did not achieve significance using the chi-square test. These results agree with the results published in the literature which show no consistent advantage for either mode of combination therapy. These data show postoperative radiation therapy provides little hope for increasing disease-free survival over preoperative radiation therapy, although it is technically more practical providing a better surgical field with fewer perioperative mortalities.

INTRODUCTION

The pyriform sinuses (aka pyriform fossa or recesses) are located adjacent to the glottis and behind the thyroid cartilage ala. They are the recesses through which solids and liquids are channeled into the esophagus. The 1980 American Joint Committee on Cancer (AJC) places the pyriform sinus in the region of the hypopharynx, which includes the pyriform sinus, posterior cricoid area (postcricoid) and posterior hypopharyngeal wall.[1] Each pyriform sinus is shaped like an inverted horn or pyramid, as described in a recent article by T. Sasaki:

> The pyriform sinus or recess (is) defined as the space which extends from the pharyngoepiglottic fold (superiorly), to the entrance of the esophagus (inferiorly). Laterally, the sinus is bounded by the inner aspect of the thyroid cartilage and medially is bounded by the arytenoepiglottic fold and mouth of the esophagus.[2]

Anatomically this is a very confined region which is difficult to assess on physical examination or by

clinical inspection in the clinic. The apex of the pyriform sinus is subject to thorough indirect mirror examination only by the most skillful of examiners. The walls of the pyriform sinus are often only partially open when viewed from above. Direct laryngoscopy performed under general anesthesia could provide information on the horizontal extent of tumor, but is unable to accurately ascertain the extent of submucosal infiltration or soft tissue invasion.

Radiologically, contrast laryngography had been the diagnostic procedure of choice in the 1960s. Contrast laryngography was unable to provide information to evaluate the extent of tumor invasion. In the 1970s, Computed Axial Tomography (CT-Scan) was shown to be a superior method of radiologic evaluation, able to accurately determine the vertical extent of tumor and the degree and presence of cervical adenopathy. Cartilagenous invasion can be detected, although it can be difficult to accurately determine due to irregular ossification of the laryngeal framework. Ossification of the cartilagenous framework can be mistaken for tumor invasion of cartilage on CT-Scan. Misleading results have also been found

using the CT-Scan to evaluate soft tissue invasion by tumor specifically, over estimation of tumor size due to associated edematous changes, inflammation, and mass effect of tumor.[4-6] Magnetic Resonance Imaging (MRI) utilizing surface coil technology seems to hold the promise of detailed studies of submucosal tissue and deep tissue planes in this region. MRI may improve the ability of the surgeon, in cooperation with the radiologist, to preoperatively assess the degree of tumor extension and infiltration into the cartilagenous laryngeal framework and tumor invasion of the soft tissues of the neck.[4-6]

On physical exam the loss of thyroid crepitations or fullness behind the thyrohyoid or cricohyoid membrane may be an indication of malignant disease which is already well advanced. Tumors in this region often do not produce symptoms until late in their course. By the time they become clinically apparent, they may have become quite large with extensive invasion and infiltration. One-third of patients initially present with dysphagia secondary to mass obstruction. The ominous appearance of firm cervical nodes unresponsive to antibiotic therapy is the first clinical sign of malignancy in 20-25 percent of patients. Vocal changes such as

hoarseness may occur late or not at all; "hot potatoe voice" may signify infiltration of the base of the tongue. Other late symptoms include weight loss, foul breath, and general disability.[7] Recently the advent of flexible fiberoptic endoscopy of the oropharyngeal region has allowed for improved direct visualization of the region with a permanent record made on video tape. This technological innovation may permit earlier diagnosis of these tumors.

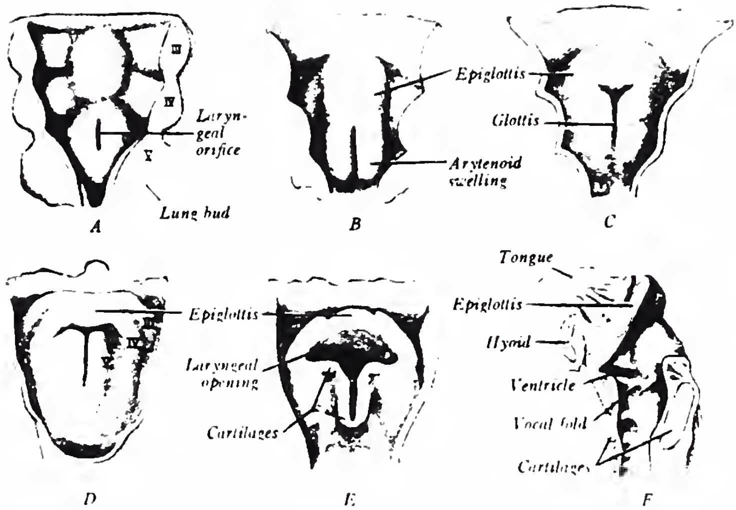
The advanced stage of these tumors at presentation has historically lead to a very dismal prognosis. Mattox (1985) in a review article reported that 60-75% of hypopharyngeal tumors occur in the pyriform sinus and most published series report 20-30 percent five-year survival. Nodal metastases reduce survival by one-half and are present in 50-80 percent of cases of hypopharyngeal carcinoma, although 25 percent of the time they are clinically occult.[7]

Sites of tumor origin in the pyriform sinus include the apex, medial wall, lateral wall and aryepiglottic fold.[8]

EMBRYOLOGY AND ANATOMY OF THE HYPOPHARYNX

The structures of the pharyngeal region arise from the branchial arches and clefts whose most active development takes place between the fourth and twelfth weeks of gestation. The laryngotracheal ridge appears during the fourth week caudal to the fourth pharyngeal pouch. Furrows develop on either side of this ridge which progressively deepen and eventually join to form the laryngotracheal tube. The cranial end of this tube forms the primitive laryngeal aditus (slit) (Figure 1). Hast describes the development of the laryngeal region between the fourth and fifth pharyngeal arches.

> The vocal folds and thyroarytenoid muscle are not differentiated until the mesenchymal mass of cells that forms the future glottis has split and the ventrodorsal depth of the thyroid cartilage has increased. With the development of the thyroid cartilage during the second month, the vocal folds are drawn out between the intra thyroid lamina and the arytenoid cartilages. The normal formation of the vocal folds, however, is intimately related to the development of the sinus of the larynx and the vestibular folds. During



Development of the embryonic larynx and at birth: (*A*) 4 weeks (5 mm); (*B*) 5 weeks (9 mm); (*C*) 6 weeks (12 mm); (*D*) 7 weeks (16 mm); (*E*) 10 weeks (40 mm); (*F*) at birth. (From Arey, 1965.)

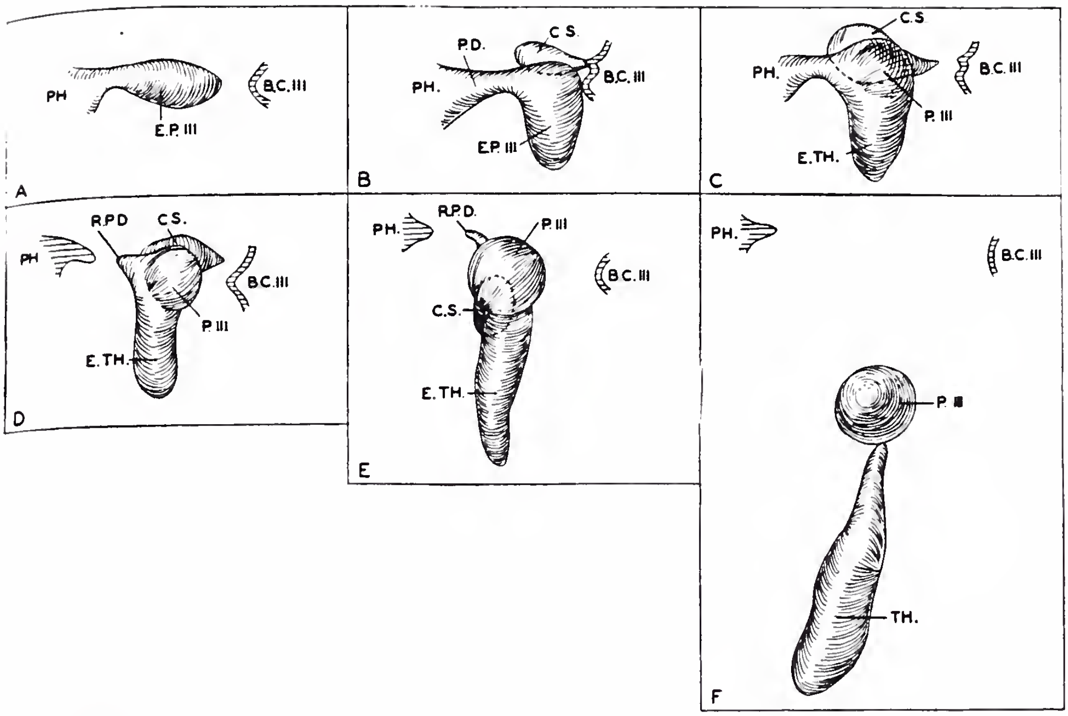
Figure 1, From Hinchliffe, Ronald ands Harrison, Donald (eds.) Scientific Foundations of Otolaryngology, William Heinemann Medical Books, 1976 p.531

> this period there is an outpouching of the lateral and inferior portion of the laryngeal cavity, extending from the eminence of the arytenoid anteriorly to the floor of the primitive vestibule. The apex of this evagination forms the saccule of the larynx and the proximal and wider portion of the sinus of the larynx. With the development of the sinuses (between the fourth and fifth arches), the vocal and vestibular folds are separated, the mass splitting during the third month (Hinchcliffe and Harrison).[9]

Krahl (1950) described the development of the branchial arches and pouches. He illustrates the interaction of the third branchial arch with its branchial cleft and the formation of the parathyroid gland (P III) with its subsequent separation and migration from its pharyngeal opening (Figure 2). "The pyriform fossa at either side of the laryngeal opening marks the original location of the third pouch. The site of the fourth pharyngeal pouch is less distinct . . . it is at the lower end of the pharynx . . . somewhat dorsal to the third pouch, being separated from the latter by the fold of the laryngeal nerve."[10]

In the adult, this region is called the hypopharynx. Donald (1984) describes the pyriform sinus of the hypopharynx in detail:

> The hypopharynx includes both pyriform fossae and an intervening area of the pharynx directly posterior to the larynx; the anteror wall of this area is called the postcricoid area. Each pyriform fossa is



Schema of the morphogenesis of the third branchial pouch and its derivatives, seen from ventral.

A. Third branchial pouch approaching the floor of branchial cleft III.

B. Elongation of third pouch into the primordium of the thymus. Early association of the cervical sinus with the thymus.

C. Appearance of the primordium of parathyroid III at the cephalic end of the pharyngeal pouch. Separation of ectodermal sinus; its dorsal relationship to the upper end of the thymus.

D. Complete separation of third pouch derivatives from the pharynx.

E. Growth of parathyroid III, and elongation of the thymus; beginning of isolation of third branchial complex components.

F. Caudal migration of thymus. B.C., III, Branchial cleft III. C.S., Cervical sinus. E.P. III, Third entodermal pharyngeal pouch. E.Th., Entodermal thymus. P. III, Parathyroid III. P.D., Pharyngo-branchial duct. Ph., Pharynx. R.P.D., Remnant of pharyngo-branchial duct. Th., Thymus. (Redrawn from illustrations by E. Erickson n article by Norris, '37. Courtesy, Carnegie Institution of Washington.)

Figure 2, Ward, Grant and Hendrick, James
<u>Diagnosis and Treatment of Tumors fo the Head and Neck</u>, Williams and Wilkins, 1950 p.59

rimmed by the aryepiglottic fold medially, the lateral pharyngoepiglottic fold anterolaterally, and the lateral hypopharyngeal wall lateroposteriorly. The aryepiglottic fold is considered to be the medial wall of the pyriform sinus. This fold is actually part of the larynx, but the medial wall of the pyriform sinus begins 1 cm below the fold's superior most extremity. This medial wall pyriform mucosa is in continuity with that of its opposing side through the aforementioned postcricoid area. The cricoid cartilage is the principal skeletal component supporting this latter region. The posterior cricoarytenoid muscles and a portion of the interarytenoid muscles intervene between the mucosa and the cartilage. At the inferior border of the cricoid, the hypopharynx becomes the cervical esophagus.

The posterior wall of the pharyngeal area is continuous with that of the oropharynx above and the cervical esophagus below.

The pyriform fossae, except at their posterior extremities, are contained within the alae of the thyroid cartilage: Superiorly, the aryepiglottic and, slightly more inferiorly, the lateral cricoarytenoid muscles separate the fossae from the laryngeal lumen. The arytenoid cartilage composes part of this medial wall posteriorly. Inferiorly, the cricoid cartilage makes up this wall as the pyriform progressed toward the cervical esophagus (Donald, p. 63-64, Figure 3).[11]

From this description the intimate relationship of the pyriform sinus and hypopharynx to several important structures in the neck can be seen. These are the cervical opening of the esophagus, the laryngeal opening of the trachea, and the recurrent laryngeal branch of the vagus nerve.

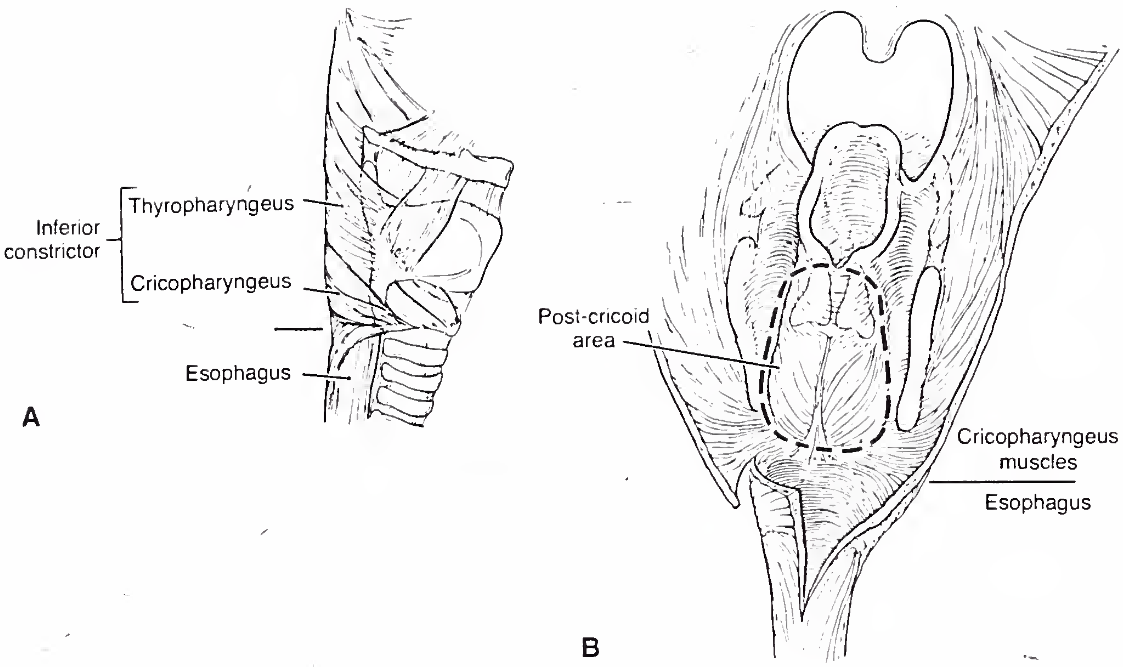


Figure 3– Anatomic boundaries of the hypopharynx. *A*, External view. *B*, Internal view.

Figure 3, Donald, Paul J. Head and Neck Cancer Management of Difficult Cases, W.B. Saunders, 1984 p. 63

> An important structure related to the pharyngeal wall in this region is the recurrent laryngeal nerve, which lies between the cricopharyngeus fibers of the inferior constrictor muscle of the pharynx and the posterior cricoarytenoid muscle of the larynx (MacComb and Fletcher).[12]

Late stage tumors often involve adjoining structures. Involvement of the cervical chain of sympathetic nerves may produce a Horner's syndrome. The carotid sheaths which pass immediately outside the layer of constrictor muscles on either side of the neck may also be involved. Lesions in the hypopharynx may impinge on the internal branch of the superior laryngeal nerve leading to the symptom of ear pain.

The muscle layers which surround the structures of the hypopharynx are continuous with those of the oropharynx above:

> The hypopharynx is composed of the middle and inferior constrictor muscles of the pharynx and their investing fascial layers. The loose areolar fascia between the buccopharyngeal fascia investing the muscular coats and the stout fascia of the prevertebral area exists in the same way that it does in the oropharynx . . . (Donald).[11]

The aggressive spread of carcinoma in this region is due, in part, to the lack of restricting anatomic barriers. Muscle tissue is relatively resistant to invasion. When tumor extends into the cartilagenous

framework of the larynx, it usually begins in the thyroid cartilage. Thyroid cartilage invasion usually begins at the lateral border.[13]

The lymphatic network which drains the hypopharynx is extensive. The lymph nodes are intimately associated with the glandular, vascular and neural structures which pass through the region, and carry the same names. Specifically, lymph node chains are associated with the internal jugular vein, the spinal accessory nerve, the transverse cervical nerve, the parotid gland, the submaxillary gland, and the submandibular gland.

The deep cervical lymph nodes are clinically important, they receive the lymph from the mucous membranes which line the region. Their lymphatic channels have a larger caliber than superficial vessels which increases the rate and probability of metastatic tumor seeding.

The most important of the deep cervical nodes are those which lie along the internal jugular vein. The most superior group are the primary echelon nodes. They lie just below the posterior belly of the digastric muscle. The most inferior group of jugular nodes lies just above the clavicle.[11] This provides the anatomic basis for ligation and removal

of the internal jugular vein and its associated nodes in the standard radical neck dissection.

Lymphatic chains also follow the course of the spinal accessory nerve beneath the upper end of the sternocleidomastoid muscle, running posteriorly and inferiorly into the posterior triangle. These nodes primarily drain the nasopharynx, but they communicate with the internal jugular chain.[14] Cervical lymphatics contain valves. Retrograde flow to collateral lymphatic vessels occurs after obstruction of main lymphatic channels by tumor. Involvement of spinal accessory nodes of the posterior triangle occurs when tumor cells are carried retrograde due to blockage of the jugular chain.[15] The spinal accessory nerve may itself be involved with tumor and is sacrificed in the standard radical neck. Preservation of this nerve and the ipsilateral function of the trapezius muscle is a feature of the modified neck dissections discussed elsewhere in this paper.

Tumors of the pyriform sinus and hypopharynx are often clinically silent in the early stages. The cancer spreads from the primary site along the pharyngeal mucosa, or submucosally via infiltration of soft tissue planes. Lesions which arise "on the

lateral walls spread upward and downward in the pharyngeal mucosa then laterally to invade the thyroid cartilage, the thyroid gland, and the cartilagenous structures of the neck. When the original site is on the medial wall, the growth extends upward and medially to invade the arytenoid and the aryepiglottic fold and eventually encroaches upon the vestibule of the larynx."[12]

Primary tumor spreads along the path of least resistance (fascial planes). Muscle tissue itself is relatively resistant to tumor invasion, as are bone and the cartilagenous framework of the larynx. Involvement of these structures indicates advanced disease.[13]

Perineural spread occurs along nerve bundles and should be suspected when patients complain of ear pain, localized burning, stinging, or shooting pain.[15]

Clinically, the symptoms associated with a mass obstruction in the hypopharynx includes obstruction of the airway (dyspnea), delay or obstruction of the passage of food in the esophagus (dysphagia), pain upon swallowing (odynophagia) and ear pain due to laryngeal nerve involvement (otalgia). Behavioral adaptation to these symptoms, especially decreased

appetite and food intake secondary to difficult or painful swallowing leads to the dramatic weight losses often seen at presentation.

Other symptoms at presentation are caused by metastatic involvement of cervical lymph nodes of the neck ("mass in the neck"). Direct infiltration and extension along soft tissue planes can lead to "hoarseness" secondary to involvement of vocal cords or cricoarytenoid muscle.

The superior laryngeal branch of the vagus nerve (cranial nerve 10), develops with the fourth pharyngeal arch. The internal branch of the superior laryngeal nerve supplies sensory innervation to the mucosa of the laryngopharynx and larynx down to the level of the true vocal cord. The external branch of the superior laryngeal nerve provides motor innervation to the cricothyroid muscle.

The inferior laryngeal branch of the vagus nerve is called the recurrent nerve. It supplies all the intrinsic muscles of the larynx, the inferior constrictor muscle, the upper fibers of the esophagus, and the mucous membrane of the larynx, below the level of the true cord. In the adult, the internal branch of the superior laryngeal nerves (4th pharyngeal arch) lies on the thyrohyoid membrane

between the greater cornu of the hyoid bone and the upper margin of the thyroid cartilage. The inferior (recurrent) laryngeal nerve (6th pharyngeal arch) runs in the tracheoesophageal groove and enters the larynx posterior to the cricothyroid joint under the thyroid cartilage.

The symptom of ear pain (otalgia), occurs unilaterally on the same side as the lesion and is mediated by tumor involvement with the superior laryngeal nerve of the vagus nerve. The vagus nerve innervates the external ear canal via the auricular nerve (Arnold's nerve). It also innervates the hypopharynx via the internal branch of the superior laryngeal nerve. This internal branch becomes involved with tumor or regions of mucosal ulceration in some cases of advanced disease. Synapses in the jugular ganglion (pharyngeal plexus), provide the pathway for referred pain felt in the ear (Figure 4).[7]

It has been well documented in the medical literature that, for tumors of the hypopharynx, the clinical appearance of these symptoms indicate advanced stage disease (Stage III or Stage IV). Similar symptoms may occur with tumors of adjoining regions, but are associated with an earlier stage of

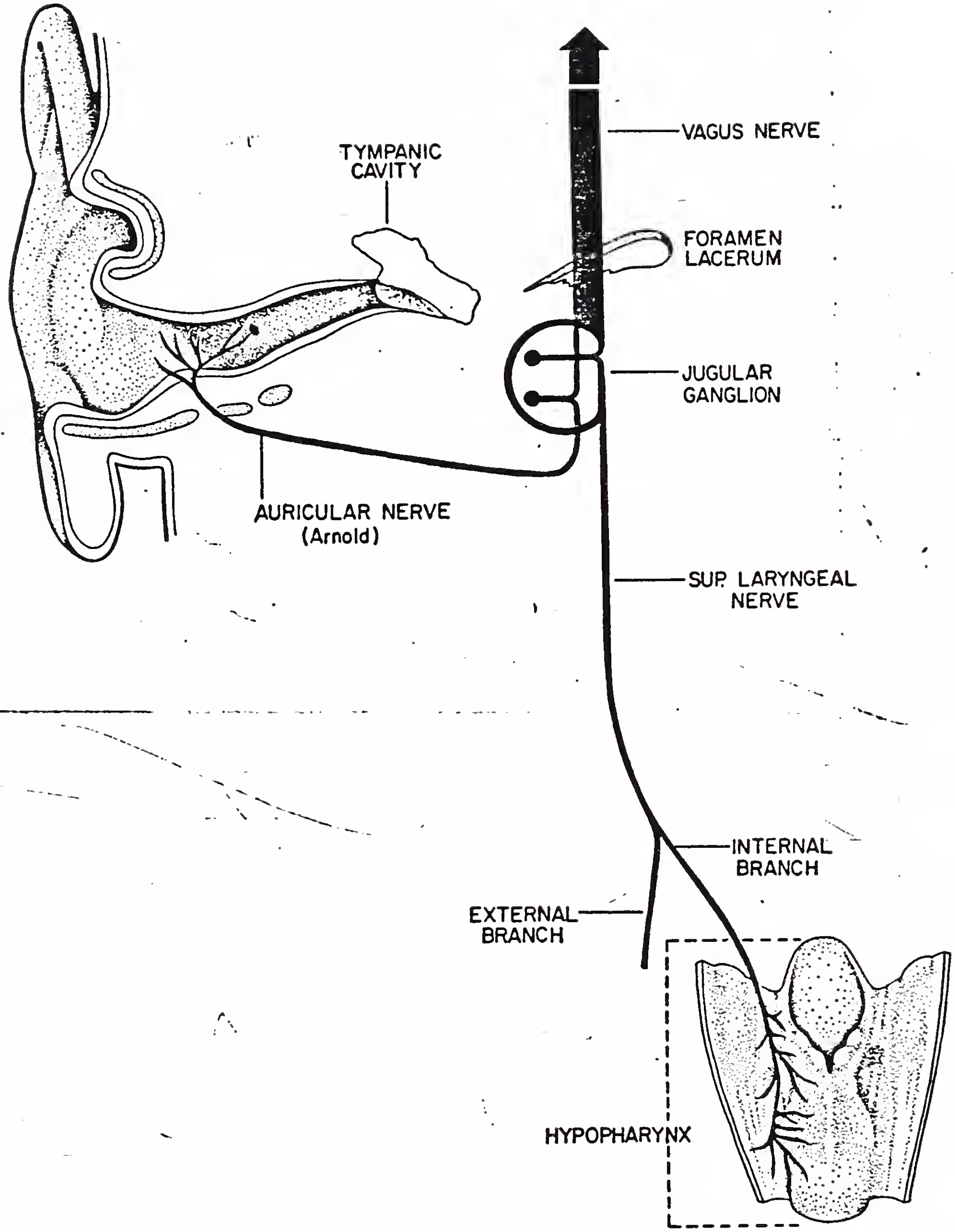


FIG. 7.4. Nerve paths by which an ulcerated lesion in the hypopharynx produces pain in the ear.

Figure 4: Donald, Paul J. Head and Neck Cancer Management of Difficult Cases, W. B. Saunders, 1984 p 223

disease. This is largely because the extensive lymphatic network of the hypopharynx (described elsewhere) leads to tumor cell seeding of lymph nodes early in the development of tumors in the pyriform sinus and hypopharynx. The tonsillar region, and floor of mouth are also richly enmeshed with lymphatic vessels and, like hypopharyngeal tumors, may first present with lymph node enlargement.

Martin (1950) established the principle that "Enlargement of Lymph Nodes Demands a Search for the Primary Growth of Cancer."[16] Martin describes the characteristics of those anatomic regions in the head and neck which lead to clinical presentation with advanced stage disease:

1 - function not affected by the presence of small or moderate sized growths

2 - a meager sensory nerve supply

3 - a relatively high proportion of primary cancer occuring at the given anatomic site

4 - the relative and absolute frequency of metastasis from growths at the given site

5 - the relative inaccessibility of the given anatomic site to physical examination.

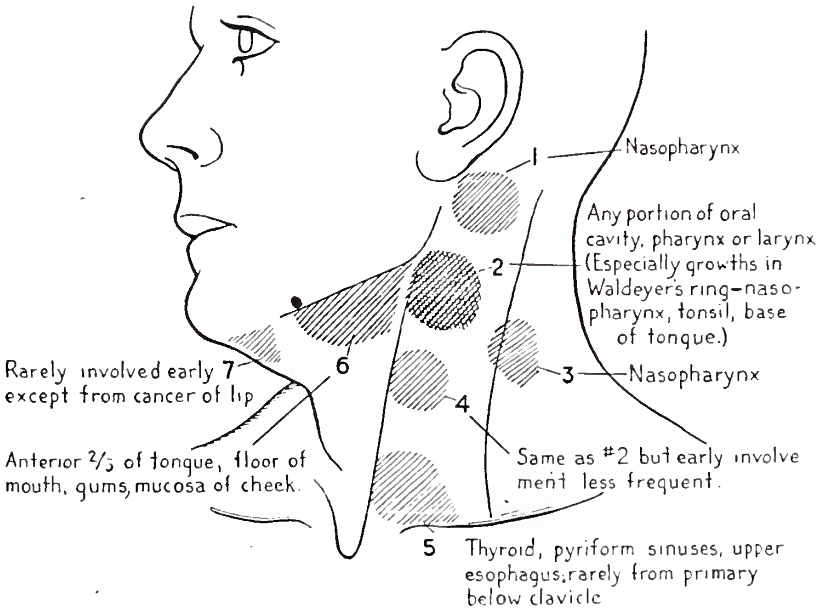
Martin further noted that the anatomy of the cervical lymphatics has uniform and constant features. He goes on to state:

> Main lymph channels are always present at the same location; e.g., the internal jugular chain, the spinal accessory chain, the submaxillary and submental node groups, etc. These lymph nodes and lymph node groups always receive the main lymph drainage from relatively specific anatomic areas although there is some overlapping and no distinct line of demarcation . . . (Martin and Morfit).[14]

The constant relationship between lymph node groups and the anatomic regions they drain allows an examiner to suspect a primary tumor in a specific site when a patient presents with a clinically palpable node in the neck (Figure 5).

Lymphatic spread of tumor occurs by embolization, but does not follow a predictable pattern along the lymphatic chain. Skip metastases are frequently seen. Primary echelon drainage from most tumor sites in the mouth and throat is to the upper deep jugular chain (subdigastric nodes, jugulocartoid nodes). Lymphatics from the pyriform sinus drain through the thyrohyoid membrane to jugulodigastric and midjugular nodes. Clinical involvement of these nodes increases the probability of lower level and contralateral neck disease. If primary echelon nodes are not involved, it is dangerous to assume that lower nodes are free of disease.[14]

Lesions of the pyriform sinus usually present with unilateral node disease, although subsequent



Various lymph node groups with the most likely sites of the primary lesions which may cause the metastases.

Figure 5, Martin, Hayes and Morfit, Mason. "Cervical Lymph Node Metastasis as the First Symptom of Cancer" Surg Gynecol & Obstet 78:133, 1944

contralateral metastatic nodes may develop in up to 30 percent of cases.[17] Bilateral nodes at presentation usually occur with primary tumors at the midline or where lymphatic drainage is bilateral such as the posterior pharyngeal wall. This is the site of origin of 10-20 percent of hypopharyngeal tumors.[15]

The history of treatment protocols for tumor of the pyriform sinus and hypopharynx is well documented in the surgical literature and the radiation therapy literature. Tumors in this region do not present clinically until they are well advanced. Patients usually come to the clinic with Stage III or Stage IV disease and often with metastatic disease to the lymph nodes of the neck. Poor therapeutic outcomes (10-30 percent two-year survival with single modality therapy) led to efforts with combination radiation therapy and surgery.

Adjuvant chemotherapy has been attempted but the results have not been encouraging and chemotherapy has played a minor role in treatment of these tumors.

Some large patient series presented in the literature include patients with tumors in all head and neck regions. These tumors are primarily squamous cell carcinomas and are treated with the

same types of therapy as those in the hypopharynx. These reports are included because they usually represent the largest number of patients and provide significant outcome data.

Theoretically combination therapy improves patient prognosis because surgery and radiation therapy act to destroy or eliminate the malignancy in different ways. Surgery removes the primary tumor, eliminating a focus for tumor spread which occurs via direct extension into surrounding tissues or by the primary site acting as a nidus for metastatic tumor seeding presumably via lymphatic or hematologic circulation. Radiation therapy preferentially damages malignant cells preventing their growth and reproduction.

The hypopharynx of many of these patients has been chronically exposed to carcinogens and co-carcinogenic agents (especially ethanol and tobacco).[18] The regional mucosa develops metaplastic changes which increase the risk of malignancy. Whatever the mechanism of malignant transformation (e.g. breakdown of tumor immune surveillance), by convention the first clinically identified tumor site is called the primary tumor, although the entire mucosa remains at increased risk

for malignant transformation.[19] Radiation therapy attempts to sterilize the "cancerized field" and use additional rads to focus on known tumor sites.[20]

Tumor recurrence has been documented to occur rapidly in this region, 80-95 percent occur within the first two years.[15,21,22] Perhaps in some cases, these recurrent tumors represent independent cancer foci arising from this chronically insulted region.

In the 1960s, preoperative radiation therapy and surgery was attempted at numerous centers. Radiation therapy was directed at shrinking the primary tumor to improve access for surgical excision and with the hope of sterilizing subclinical disease that may have existed in the lymph nodes of the neck. Radiation therapy doses were submaximal (<5,000 rads) to minimize radiation-induced tissue changes in the surgical field. Higher doses damage tissues leading to inflammation, necrosis, and fibrosis which would interfere with surgical planes as well as increase the friability of tissues and resultant risk of puncture wounds, especially to the carotid artery. Seven thousand rads is generally regarded as the maximum therapeutic radiation dose in the region.

Some medical centers combined regionally specific

treatments, for example, radiation therapy to the primary tumor with a neck dissection, or surgery to the primary tumor with radiation therapy to the neck. Both surgery and radiation therapy were used as salvage therapy for failures of primary treatment with the other modality. Finally, surgical treatment of the primary with total laryngectomy and partial or total pharyngectomy and unilateral or bilateral neck dissection and postoperative radiation therapy received widespread trials in the 1970s as treatment became more aggressive.

The literature is replete with reports on the results of these experiences. A selection from the recent literature is reviewed here. End results data reported by various authors support different conclusions regarding optimal treatment strategies. Each conclusion is usually supported by results presented by several different authors. The few prospective studies in the literature will be discussed separately in the appropriate sections.

REVIEW OF LITERATURE

Tumor Staging at Presentation

Tumors of the hypopharynx are staged based on the classification of the 1980 American Joint Committee on Cancer Staging (AJC). These criteria have been revised periodically (1971, 1976). The essential elements of T stage, tumor size and fixation have remained consistent (e.g. T3 represents tumor extension with laryngeal fixation). Tumors are staged based on groupings of the TNM (primary Tumor, Nodal disease, distant Metastasis) classification shown below. Patient charts reviewed in this study are reported as they were staged by the authors.

Primary Tumor Staging

TIS	Carcinoma in situ
T1	Tumor confined to site of origin
T2	Extension of tumor to adjacent region without fixation of hemilarynx
T3	Extension of tumor to adjacent region or site with fixation of hemi-larynx
T4	Massive tumor invading bone or soft tissues of the neck

The AJC recommends the actual size of the nodal mass be measured. Most masses over 3 centimeters in diameter are not single nodes, but confluent nodes or tumor in soft tissues of the neck. There are three stages of clinically positive nodes: N1, N2, N3. Subgroup notations are recommended but not required. Midline nodes are considered homolateral nodes. Most authors use these staging criteria (listed below), or an abbreviated version.

Nx	Nodes cannot be assessed
No	No clinically positive node
N1	Single clinically positive homolateral node 3 cm or less in diameter
N2	Single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter or multiple 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)
Nc	Contralateral clinically positive node(s) only.

Distant metastases are staged by their presence (M1) or (MO).

Stage grouping of patients is as follows:

Stage I	T1 NO MO
Stage II	T2 NO MO
Stage III	T3 NO MO
	T1 or T2 or T3 N1 MO
Stage IV	T4 NO or N1 MO
	Any T with N2 or N3 MO
	Any T with any N and M1*

---

*The presence of any distant metastasis makes a patient Stage IV.

Treatment of Primary Tumor with Radiation

Ionizing radiation preferentially damages proliferating cells. Cancer, by definition, is the unregulated growth of cells which exceed their own natural boundaries and invade continguous regions as well as embolize via lymphatic or hematologic circulation to distant areas.

Radiation damages a cell either through ionization (ejection of an electron), or excitation (putting an electron in a different orbit in the same molecule).

> Damage may be the direct result of an ionization somewhere within a critical molecule such as DNA or it may be due to the indirect action of excited molecules which can diffuse for several seconds before reacting chemically with a critical molecule. It is the indirect portion of radiation injury which can be altered by radiosensitizing drugs including oxygen or by large changes in dose rate. Proteins and enzymes in the cell are less damaged by radiation than DNA, RNA or membranes. The result is that proliferation is the most radiosensitive function of the cell . . . A cell which has been lethally damaged by irradiation does not break up and disappear at once. It usually does so at the next cell division or even at the second or third attempt . . .
>
> In the treatment of tumors the desired result is the killing, in the sense of prevention of proliferation, of all malignant cells. In normal tissues the main effects of radiation injury are also due, directly or indirectly, to the prevention of cell replacement (Hinchcliffe and Harrison, p. 735-736).[8]

Malignant cells are preferentially affected because their reproduction is not regulated by factors which maintain normal cells within their histologic and anatomic boundaries. Cancer cells constantly reproduce at a faster rate than normal cells and are, therefore, more sensitive to radiation damage.

Cell oxygenation also affect the efficacy of radiation therapy. Tumor cells quickly outgrow their vascular supply. The maximum diffusion range of oxygen is 150 micrometers, beyond this point necrotic foci appear. Hypoxic cells are intrinsically more resistant to ionizing radiation than well oxygenated ones. This is known as the "oxygen effect." Delivery of the radiation in fractional doses allows for greater oxygenation of those regions of tumor which survived the previous dose of radiation. Drugs which mimic the radiosensitizing effects of oxygen with minimal toxic side-effects have been developed for experimental use. These are called radiosensitizers (p. 748).[9]

Radiation therapy has been used to treat primary tumor as well as metastatic disease in the neck. It seldom controls fixed nodes, or nodes greater than 3 centimeters in diameter.

Ionizing radiation has been used therapeutically

to destroy malignant cells in clinically positive nodes. It has also been used very successfully to sterilize subclinical microscopic tumor deposits and prevent the development of overt clinical disease.

The effect of radiation on lymph nodes is dependent on the rate of cellular proliferation, and the total dose of radiation (rads) delivered. Up to 3,000 rads, there is a reduction in the number of lymphocytes and some shrinkage of follicles. As the dose increases follicles are destroyed. At 4,000 rads, no recognizable lymphoid tissue is seen and small lymphocytes disappear. The final appearance following high-dose radiation therapy is an unrecognizable and hyalinized lymph node (p. 235).[23]

The use of radiation therapy is associated with numerous reactions in the mucosa which also has a high rate of cell turnover. Mucosal reactions to radiation include edema, erythema, and desquamation. Prolonged edema following completion of radiation therapy may conceal residual carcinoma. Experience shows that negative biopsies do not exclude the possibility of recurrence.[24]

Local tumor recurrence usually presents as firm nodules in the axis of the surgical scar, surrounding

skin, or mucosa. Recurrence in the area of the tracheostomy stoma is ominous and can be related to the primary tumor or involved paratracheal lymphatics. Other common sites of local/regional tumor recurrence include: pharyngeal wall, contralateral lymph nodes, ipsilateral lymph nodes, and the base of the skull.[24]

Clinical features of recurrent tumor include a mass in the neck and consequent dysphagia or odynophagia, shortness of breath due to restriction of the airway by tumor at the tracheostomy stoma or other level of the airway including the bronchi. The patient's terminal event is most often due to asphyxiation or starvation. Severe complications of radiation therapy include: necrosis, esophageal stenosis, tracheal stenosis, fibrosis, xerostomia, dehydration, dermatitis, tracheal fistula, respiratory obstruction secondary to edema, respiratory failure and hypothyroidism. It is difficult to distinguish changes such as edema and fibrosis of the epiglottis and pharyngeal walls from recurrent tumor, or more importantly to determine if nests of tumor cells are reproducing within these regions.

The standard of evaluation for recurrent tumor is

endoscopy and biopsies in the region submitted for pathologic analysis. These may give negative results when the clinical course is highly suggestive of recurrent malignancy. Benign tissue changes induced by radiation therapy may persist after completion of therapy and be difficult to distinguish from an active malignant process. Sometimes several negative biopsy results preceed a positive one. In these situations a clinical determination of tumor recurrence may supercede a histologic one. Bahduhar reviewed 52 surgical specimens of patients who received "surgical salvage" after radiation therapy.

> Fifty of the 52 cases (96 percent) showed the presence of a residual tumor in their operative specimens . . . the persistence of oedema with or without fixation of the larynx after radiation is strongly indicative of a residual/recurrent tumour, and that biopsies may be unwarranted in such cases . . . Repeated negative biopsies do not exclude the presence of a tumour and in fact only delay subsequent treatment with total laryngectomy.[24]

Radiation therapy for treatment of hypopharyngeal tumors was first attempted in the 1920s. In 1938, Colledge noted that "the results are neither so good that the method can claim to supplant simple surgical treatment, altogether, nor so bad they can be dismissed as negligible."[12] Patient series have consistently reported five-year survivals in the

range of 10-15 percent (p. 2339).[17]

Radiation therapy as the single mode of therapy for tumors of the hypopharynx and pyriform sinus has been in use for decades without appreciable improvement in survival rates. Lederman in 1962 reviewed 734 patients with tumors of the laryngopharynx from 1933-1959 treated with radiation therapy. His data shows remarkable consistency of patient presentation and treatment results. Stage III and Stage IV tumors comprised 79 percent of patients at presentation. Minimum radiation therapy doses were 5,000 rads, maximum dose was 7,000 rads. Three-year survival of patients with Stage III lesions was 20 percent, for stage IV lesions it was an abysmal 5 percent. He advocated combination therapy be employed to attempt to improve survival rates.[25]

Byhardt (1980), presented 53 patients and reviewed the literature. He tabulated the results of six authors*, found a 21 percent three-year survival rate and an 11 percent five-year survival rate with radiation therapy alone. Recurrence at the primary site occurred 42 percent of the time, at cervical

---

*Carpenter, 1976; Eisbach, 1977; Inove, 1973; Kirchner, 1977; Lord, 1973; Sagerman, 1979.

lymph nodes 76 percent of the time, and at distant metastasis 11 percent of the time.[26]

Recent authors of consecutive series comparing radiation therapy with preoperative radiation therapy followed by surgery[27-29], have found 44 percent, 61 percent, and 72 percent two-year recurrence rates (site of recurrence not consistently specified) with patients in the radiation therapy alone arm of the study.

Million in 1981 reported on 42 patients treated with radiation therapy alone. His sample consisted of patients referred for primary radiation therapy, after consultation with an otolaryngologist, unlike the consecutive patient series reported above and elsewhere in this paper. Sixty-two percent presented with T1 and T2 lesions with two-year and five-year NED survivals of 83 percent and 66 percent. Bias in his patient selection led to a skewed patient sample with a high percent of early lesions. There were sixteen T3 and T4 patients for 38 percent of the sample. The two-year absolute survival for Stage III was 62 percent and, for Stage IV, 52 percent. The five-year absolute survival was 38 percent for Stage III and 10 percent for Stage IV.[30]

Ahmad (1984) reported on an experience with 61

patients receiving high-dose radiation therapy alone with 68.8 percent (42/61) recurrence rate with a 2.5 year minimum follow-up. This included a 60.6 percent (20/33) recurrence of T3 tumors and 100 percent (14/14) recurrence of T4 lesions at two years.[27]

In summary, radiation therapy as the sole treatment modality has fairly good curative potential in early lesions Stage I and Stage II, however, three-fourths of patients will present with advanced Stage III and Stage IV disease. Two-year survival for Stage III was 20 percent and for Stage IV 10 percent or less. Two-year recurrence rates were as high as 72 percent. The maximal dose of radiation therapy has been determined to be 7,000 rads. Efforts to improve results of radiation therapy alone have consisted mainly of adjusting the radiation portals to include the neck nodes and the use of radiosensitizing drugs.[31]

Treatment of Primary Tumor with Surgery

Surgical treatment alone attempts to excise all evidence of gross tumor of the primary site and in cervical lymph nodes. Surgical techniques employed include total laryngectomy with total or partial pharyngectomy and supraglottic partial laryngectomy for early lesions not involving the apex of the sinus. Usually a unilateral or bilateral neck dissection was employed, yet as surgeons began making efforts to preserve function and improve cosmetic results the modified neck dissection was devised which preserves the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. More recently, efforts at cosmesis have led to increased efforts at tailoring the neck dissection to clinically involved lymph nodes and continguous nodal groups. Surgical treatment of metastatic disease in the neck is discussed at length in another section.

Byhardt in his compilation of data on surgical treatment alone from the published work of eleven authors* reports incidence of local and regional

---

*Byhardt compiled these figures from authors listed below, not all of whom are referenced in this study.

Barton - 1973	Harwick - 1975	McGarvan - 1963
Bryce - 1971	Inoue - 1973	Ogura - 1970
Carpenter - 1976	Jesse - 1975	Shah - 1976
Eisbach - 1977	Kirchner - 1977	

recurrence is 84 percent and 70 percent respectively within two years, with distant metastasis occurring only 12 percent of the time. Disease-free survival rates were 42 percent at three years and 31 percent at five years.[29]

The data from a number of authors indicates there may be an important role for surgery alone in treatment of these tumors. Most recently, Yates reported a 65 percent determinate survival at three years and a 56 percent determinate survival at five years.[32] These results agree with Eisbach who reported a 69 percent disease-free survival at three years and at five years in patients treated with surgery alone.[33] (Eisbach's results are included in Byhardt's summary.) Further analysis of Yates' results shows that 45 percent of his patients had Stage III or Stage IV disease. The survival data on this subgroup of patients with advanced tumors is 63 percent at five years. Yates had noted a similar trend in surgically treated patients between 1959 and 1976 in an unpublished review.

Bahadur (1985) also reports better long-term results with surgery alone than with radiation therapy alone, or radiation therapy with surgical salvage.[24]

Harrison (1970) presents a pathologic analysis of surgically managed cases which suggests that the ability of the surgeon to control recurrent disease may be determined at the primary site by the extent of submucosal invasion. His measurements showed the average submucosal extension of lesions in the pyriform sinus was 10mm and 5mm for tumors in the postcricoid region, and he emphasized the importance of a wide field of resection. He found that successful surgical control of neck disease was limited by the extent to which metastatic disease had spread beyond the jugular chain of lymph nodes.[34]

Potential complications following surgery for cancer of the hypopharynx include wound infection, wound necrosis, salivary fistula, hemorrhage, and carotid catastrophe.

Gall (1977) reviewed an eighteen-year experience at Washington University of St. Louis for rate and type of surgical complications. His most significant finding was that the only factor found to contribute to subsequent complications was the presence of margins positive for tumor in the surgical specimen. There was no variation in complication rate based on age, race, sex, site of primary, stage of tumor, or nodal fixation. An increased incidence of

complications was asssociated with an increased incidence of fatality.[35]

Among patients with tumors of the hypopharynx receiving total laryngectomy the most common complication was carotid artery exposure and/or blowout (9.3 percent). Fistula formation occurred in seven percent of these patients. Patients treated with partial laryngopharyngectomy had wound sloughing as the most frequent complication (10.3 percent), with fistula formation occurring in 7.7 percent of cases.[35]

Treatment of Cervical Lymph Nodes

The anatomy and clinical presentation of patients with metastatic disease in the cervical lymph nodes has been discussed earlier in this paper. Clinically positive cervical nodes at presentation decrease survival by approximately 50 percent in patients with tumors of the hypopharynx. This region is a frequent site of treatment failure and data from the literature on regional or nodal recurrence have been discussed in another section also. This section will present treatment results for surgery, radiation therapy, and combined therapy in the neck specifically. There are numerous articles in the literature reporting on the treatment of neck disease in large series of patients with a variety of head and neck tumors. Some of these will be reviewed here. Where specific information is available on treatment of cervical metastasis of tumors of the pyriform sinus and hypopharynx it will be indicated.

Treatment methods for nodal disease are the same as those for primary tumor surgery, radiation therapy, and combination therapy. The indications for each method and the extent to which radical measures are employed varies at different medical centers and over time.

Several authors have schematically grouped and identified the lymph nodes by anatomic region. The different locations have different clinical behavior, prognosis, and treatment (Figure 6a and 6b).

The indications for surgery in the neck determine the treatment objective in performing the procedure. It is "therapeutic" when palpable nodal disease is present, "elective" when nodes are removed which contain microscopic tumor but are not clinically detectable, and "deferred" when previously unpalpable nodes develop into clinically positive metastasis. Treatment with radiation therapy is characterized as "therapeutic" when the goal is to control clinically positive nodes and "prophylactic" when the objective is to sterilize microscopic nests of tumor cells, (p. 234).[23]

Surgical treatment of cervical lymph nodes is based on the standard radical neck dissection, first described by Crile in 1906. This procedure removes en bloc, lymph node bearing structures from the mandible to the clavicle and from the midline of the neck to the trapezius muscle, in their associated fascial envelopes. Modifications in this technique

are described below. Hayes Martin in his comprehensive articles of the 1940s and 1950s[14,16]

popularized the radical neck dissection and articulated the principles for clinical evaluation and surgical intervention in metastatic disease to the cervical lymph nodes.

The extent of the radical neck dissection sometimes included the parapharyngeal lymph nodes and retropharyngeal nodes of Rouviere. Structures important to daily functioning and cosmesis were removed including the spinal accessory, nerve (cranial nerve XI) leading to atrophy of the trapezius and shoulder droop which is painful in some patients. The sternoclediomastoid muscle is removed leading to a functional deficit and cosmetic deformity. The internal jugular vein is sacrificed without much impact in most patients due to collateral circulation. Morbidity associated with the radical neck dissection includes shoulder drop, skeletal pain, limitation of neck and limb motion, and cutaneous anesthesia of the region.

In the 1960s, Bocca began tailoring neck dissections to remove the lymph nodes at highest risk for metastatic disease, preserving nerves, vessels, and muscles not grossly involved with tumor in an attempt to improve the functional and cosmetic results without sacrificing already modest control

and survival outcomes. This led to the development of the modified radical neck dissection or modified neck dissection. In the modified radical neck dissection, these three structures: spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein, are preserved if they are not involved grossly with tumor. The retropharyngeal lymph nodes are rarely dissected. "Modified neck dissections are conservative with respect to function, but radical with respect to cancer control."[15]

In the 1970s, other surgeons focused on this tailored approach and variations of the modified neck dissection were popularized. Variations of the modified neck dissection are described in Appendix A.

"Preservation of the spinal accessory nerve (cranial nerve XI), a common feature of modified neck dissections should not be attempted when fixed nodal disease (N3) is present in the upper anterior cervical triangle, when metastatic posterior cervical nodes are present, or when the nerve is directly involved with cancer."[15]

Failure in the neck region is frequently associated with recurrence of tumor at the primary site. "Elective neck dissection for occult metastasis will control the neck for about one-half

of all patients. Deferred neck dissections only control about one-third of cases."[23]

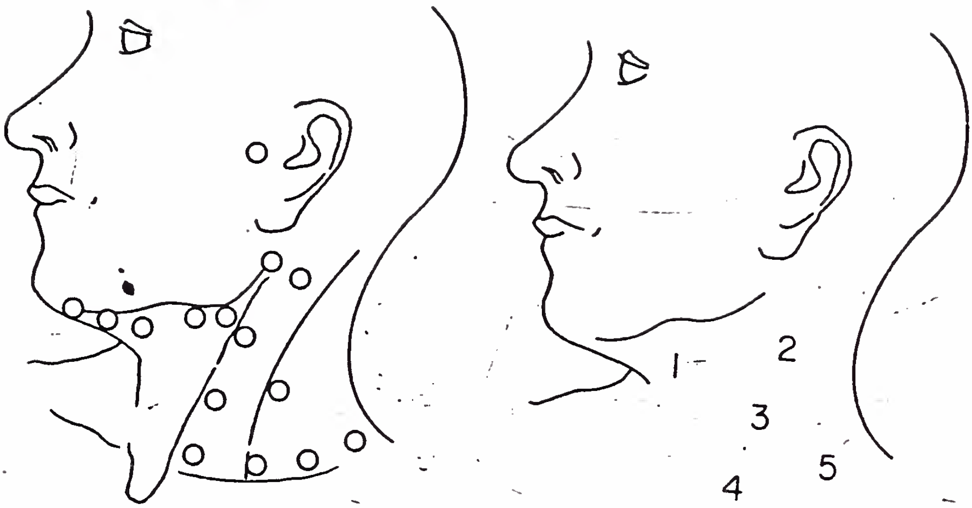
Patients with extracapsular nodal disease have been shown to have a higher recurrence rate than patients whose nodal disease had been contained within the capsule. Physicians began to treat patients with extracapsular disease with preoperative radiation therapy.[36] The rationale for preoperative radiation therapy in nodal disease is to kill tumor cells and diminish their ability to implant in the surgical field or metastasize below the clavicle.

Treatment of nodal metastasis with radiation therapy has been a common practice for over 50 years.

> The radiation field extends from the mandible to the clavicle and from the midline anteriorly to the line of the transverse cervical processes posteriorly. The tissues of the neck should be adequately irradiated to a depth of 3 cm, but treatment is individualized according to need . . . The primary tumor must be adequately encompassed, and if it crosses the midline then the cervical lymph nodes on both sides of the neck should be irradiated. In general, higher doses of radiation are required to destroy gross tumor whereas smaller doses will eliminate the better oxygenated occult micrometastases, Kagan, p. 235.

Tumors of the floor of the mouth, tonsillar fossa, and anterior two-thirds of the tongue are

Figure 15.1



The main chains of lymph nodes in the neck. Group 1 includes the submental and submaxillary nodes; groups 2, 3, and 4 the upper, middle, and lower deep cervical nodes; group 5 includes nodes in the posterior triangle of the neck.

Figure 6a, Kagan and Miles, Eds. Head and Neck Oncology, Controversies in Cancer Treatment, G.K. Hall Medical Publishers, 1981

easily visible and subject to detection of early T stage (T1-2). These tumors have not had the time to develop significant metastasis, so the patients often present without clinically positive neck nodes (NO). In these patients, the primary tumor can be treated equally effectively with either radiation therapy or surgery. Treatment of the microscopic tumor cells invariable present in the lymph nodes is with radiation therapy in the range of 3,000-5,000 rads principally in the subdigastric and submaxillary regions (region 1 and 2, Figure 6a and 6b) which are the first level to be involved.[31]

Primary lesions of the hypopharynx present at a much more advanced tumor stage (T3-T4) and with more advanced nodal disease. The rich lymphatic drainage of the region permits the early development of metastatic seeding to cervical nodes. Patients frequently present with clinically positive necks and require more aggressive treatment, usually in the form of combination therapy. Primary tumors are frequently surgically excised. The presence of clinically positive lymph nodes in regions 3 and 4 (see Figure 6a and 6b) implies that microscopic malignant cells are present in region 1 and 2. It increases the likelihood of tumor cells in the

retropharyngeal area (region 5).

Barkley et al. (1972) at M.D. Anderson Hospital reviewed 596 patients of whom 181 had hypopharyngeal tumors. Patients with nodal disease received a total laryngectomy with total or partial pharyngectomy and ipsilateral radical neck dissection. Patients received postoperative radiation therapy for the following indications:

1) surgical resection incomplete
2) cancer cells or in situ mucosal changes close to the surgical margin
3) clear surgical margins, but primary disease extended outside the hypopharynx
4) nodes were positive at multiple levels
5) cancer had broken through the nodal capsule
6) primary lesion was in the midline with a high probability of bilateral lymph node metastases.[21]

He concluded that for patients with hypopharyngeal tumors and clinically negative necks, elective irradiation of only the subdigastric and mid-jugular nodes is necessary if the primary tumor is treated with irradiation. In patients with clinically positive nodes, combined treatment is superior to either modality alone.[28]

Schneider et al. (1975) studied 183 patients with positive lymph nodes from squamous cell carcinoma of

the oral cavity, oropharynx, supraglottic larynx, and hypopharyx. Radiation doses were grouped at three levels 5,500 rads, 6,500 rads, and greater than 6,500 rads. Doses in the range of 6,500 rads to a single lymph node, 3 cm or less in diameter produced 90 percent control. When a non fixed lymph node of at least 3 cm is present, or there are multiple clinically positive nodes, radiation therapy should not be relied upon for control.[19] Increased recurrence rates occur with positive nodes at multiple levels, with nodes in inferior jugular and posterior triangle areas, and with soft tissue invasion.

Ninety to ninety-five percent of recurrent neck disease is manifested within two years of initial treatment.[21,22] Recurrent neck disease may develop from microscopic tumor cells located in lymphatic channels, from nodes incompletely removed during neck dissection, or by seeding from uncontrolled primary tumor. In hypopharyngeal tumors, the size of the primary tumor does not correlate with the presence of nodal metastasis as it does in patients with primary tumors of the oral cavity and oropharynx.

There is evidence that the filtering and trapping efficiency of lymph nodes is decreased by several

factors associated with the presence and treatment of malignancy including tumor growth, inflammation, and fibrosis secondary to radiation.[15]

In 1975, Lindberg and Jesse reported on five-year follow-up of treatment of positive cervical lymph nodes in patients treated between 1954 and 1965. Eighty-six percent of patients had pyriform sinus primary tumors and were treated with total laryngectomy and ipsilateral radical neck dissection. In patients with pyriform sinus tumors, superior regional control was achieved with combination therapy (14 percent recurrence at five years), compared to surgery alone (30 percent). Combination therapy improved regional control, but did not improve five-year survival outcome due to the increased incidence of distant metastatic disease.[36]

Byers (1985) reported on a retrospective study of the largest single institution experience with the modified neck dissection reported in the world literature. Nine hundred sixty-seven patients received 1,372 modified neck dissections (each side of the neck is counted separately) between January 1970 and December 1979. The study included patients with primary tumors of the oral cavity, oropharynx, larynx, and hypoharynx.[36]

Among all patients treated the recurrence rate was 7 percent with surgery alone, 9.5 percent with preoperative radiation therapy and 6.6 percent with postoperative radiation therapy. Seventy-two percent of patients with single or multiple nodes 3 cm or greater demonstrated pathologically positive or extracapsular disease.

Distant metastasis occurred in 15.8 percent (143/967) of all patients. Among these patients 9.3 percent received surgery alone, 27.5 percent received preoperative radiotherapy and 21.7 percent received postoperative radiotherapy. Patients with one clinically positive node over 3 cm had a 29.3 percent incidence of distant metastasis.[36]

Distant metastasis correlated more strongly with staging of nodal disease (N), than of primary tumor (T), a finding also reported by Grandi et al. in Italy.[38] There was an inverse relationship of distant metastasis with above the clavicle recurrence. He surmises that patients selected for radiation therapy had worse locoregional disease. Achievement of improved locoregional control places the patients at greater risk for systemic disease. He also speculates on the role of perioperative radiation on the evolution of distant metastasis

either directly or through effect on a patient's immune system.[36]

Marks et al. (1985) did a pathologic study to determine the presence of occult tumor in patients with clinically negative necks. He found the greatest incidence of occult disease in patients with pyriform sinus tumors (47 percent). The risk of nodal recurrence for patients with clinically negative necks and without occult disease was determined to be 8 percent compared to 88 percent for patients with occult or clinically positive nodes. They recommend that the low risk of recurrence without occult disease indicates pathologic analysis of the neck dissection specimen for occult disease should be performed in order to determine suitability for radiation therapy. The finding of occult disease greatly increases the risk of nodal recurrence and indicates the necessity for radiation therapy.[30]

In summary, the extent of cervical node involvement has been consistently demonstrated to have prognostic significance for recurrent local, regional, and distant metastatic disease. The clinically negative neck can be judiciously treated with radiation therapy. Single positive nodes greater than 3 cm in diameter can be most effectively

controlled with modified neck dissection and postoperative radiation therapy. Positive nodes at multiple levels can also often be controlled with surgery and postoperative radiation, but there is a greater risk of distant metastatic disease. The increased rate of systemic disease (more apparent with increased locoregional control provided by combination therapy) accounts for failure to improve five-year survival rates.

One author summarized location of distant metastatic disease including results found at autopsy as follows (Figure 7):

Lung	60 percent (48)
Mediastinum	38 percent (30)
Liver	28 percent (22)
Bone (Rib/Skeleton)	(25)

Other sites of distant metastases included brain, heart, pleura/chest wall, adrenal gland, kidney, skeleton, and other abdominal sites.[39]

Combination Therapy

The hypopharynx is situated in the throat, inaccessible to direct radiation exposure. The deep anatomic location of the pyriform sinus and the late stage of the tumor at presentation (T3 and T4) (23a, 25a, 1a) led to the use of surgical ablation as a principle form of therapy for tumors in this region. Dissatisfaction with high failure rates measured by duration of disease-free survival and absolute survival led to attempts to improve success rates. Teams of radiation therapists and otolaryngologists provided combination therapy irradiating the primary tumor and metastasis to cervical lymph nodes prior to surgery.[33, 40-44]

The theoretical rationale for preoperative radiation therapy is to devitalize tumor cells and diminish their ability to implant in the surgical field during handling at surgery, or metastasize below the clavicle. The goals of preoperative radiation therapy were to reduce the bulk of primary tumor to provide better surgical access and wider surgical margins, and to sterilize any subclinical disease in cervical lymph nodes and vesels. Planned preoperative radiation therapy in this region utilizes submaximal doses, usually 4,500 to 5,500

rads.[33,41,44]

In some cases, the surgical treatment was only utilized after tumor recurrence, usually in the primary site or regional nodes. This "surgical salvage" followed radiation therapy in doses up to 7,000 rads utilized for attempted cure.[27,44] The reported time interval between radiation therapy and surgery varied from six weeks to six months.[44]

Experience showed there were many problems with operating on radiated tissues. Tissue friability, decreased vascularity and increased morbidity and surgical complications led physicians to experiment with postoperative radiation therapy.

Survival

Byhardt's review of the literature covering treatment experiences at several medical centers in the 1960s and 1970s showed no significant advantage in three-year NED survival between preoperative radiation therapy and surgery 42 percent (120/288) and surgery alone 42 percent (77/185). Both were superior to radiation therapy alone 21 percent (29/141). Surgery with postoperative radiation therapy had less accumulated experience at that time, but indicated a tendency toward an improved

three-year survival rate of 69 percent (15/22). At five years, survival rates for preoperative radiation therapy and surgery, and postoperative radiation therapy, were grouped together at 31 percent, and 33 percent. Radiation therapy alone had a dismal survival rate of 11 percent.[29]

Wang (1972) reported on 152 patients treated with high-dose radiation therapy (7,000 rads) with planned surgical treatment if tumor did not show satisfactory regression by the time 4,500 rads had been delivered. "Satisfactory regression" was not defined. Laryngectomy was performed between six weeks and six months. His report did not specify whether patients early in the series who received the highest radiation doses were also treated with laryngectomy. His results were encouraging with three-year NED survival of 63 percent (39/62) for T3 lesions and 33 percent 15/45 for T4 lesions with an overall survival of 58 percent.[44]

Despite the optimism of early reports on preoperative radiation therapy and surgery, a consistent trend of improvement has failed to emerge.

Reasons presented for the apparent failure of preoperative radiation therapy and surgery to improve

survival outcome have included: 1) obscuring of surgical margins by tissue changes induced by radiation therapy[33] and 2) decreased cellular immunity secondary to radiation. The effects of ionizing radiation on lymph nodes could compromise the body's ability to deal with tumor emboli leading to increased rates of tumor recurrence both locally[32] and distantly.[43]

Recurrence

Recurrence in the primary site or neck is associated with increased morbidity and decreased quality of life due to difficulty with swallowing or breathing with the presence of a mass lesion. Patients are sometimes subjected to repeated surgical procedures in an effort to relieve tracheal stenosis or esophageal stricture. Combination therapy has been directed at achieving improved local and regional disease-free survival, even if absolute survival results remain discouraging. Literature on recurrence rates with nodal disease is discussed elsewhere.

It is well established in the literature that 80-95 percent of recurrence in the primary or cervical nodes occurs within two years.[27] In

Byhardt's* review, there was an 83 percent rate of recurrence at the primary site and 68 percent recurrence in the neck among patients receiving preoperative radiation therapy and surgery. Distant metastasis occurred 21 percent of the time.

In the Kirchner study with fifty-five pyriform sinus tumors, 76 percent had local recurrence within three years.[40]

Yates, who found that "positive surgical margins were not lethal in surgery alone patients as in those having combined therapy," concluded that "patients in the combined [therapy] groups are somehow rendered less capable of dealing with residual disease." He also focuses on the issue of compromised cellular immunity secondary to radiation. With regard to preoperative irradiation, he writes:

> Compromised immune responses at the time of tumor surgery could interfere with the body's ability to deal with tumor cell embolization and implantation whether it be lymphatic, intravascular, or in the surgical field. This could explain increased local recurrence with preoperative irradiation.[32]

---

*Cachin	- 1975	Marks	- 1978
Eisbach	- 1977	Ogura	- 1970
Inoue	- 1973	Sugerman	- 1979
Kirchner	- 1977	Wang	- 1972
Lord	- 1978		

Strong (1978) in a prospective randomized study of 100 patients compared surgery alone with preoperative radiation therapy (2,000 rads) and surgery. Of fifteen patients who failed due to recurrent cancer in the combination therapy group, 27 percent had primary recurrence compared to 39 percent among surgery only patients. The recurrence rate for nodal disease was virtually the same in the two groups at 72 percent for surgery alone and 73 percent for combined therapy. He found that preoperative therapy appeared to increase the incidence of distant metastasis when compared to surgery alone, although he found no significant difference between the two treatment groups when comparing nodal recurrence, or three-year survival.[43] It may be that low-dose radiation levels serve to stimulate the growth and spread of microscopic tumor foci.

Strong reported an increased incidence of positive surgical margins with preoperative irradiation. Strong theorizes that the low dose preoperative radiation treatments (2,000 rads):

> . . . may in fact increase the potential for distant metastases, perhaps by producing a depression of the patient's immunologic defenses, thereby allowing microscopic foci of tumor cells to flourish in distant regions of the body.[43]

He speculates that a higher incidence of distant metastases would have been detected if all patients had been autopsied.

Reports by Eisbach, Strong, and most recently Yates have reported a failure to show improved cure rates with preoperative radiation therapy and surgery when compared to surgery alone. Yates (1983) has found that surgery alone demonstrated better three-year and five-year survival results (65 percent and 56 percent) compared to preoperative radiation therapy and surgery (50 percent and 36 percent).[32] It should be noted that retrospective studies showing better results with surgery alone, Eisbach and Yates, involve small numbers of patients, 19 and 21 respectively.

In summary, despite some indication in Strong's prospective study that preoperative radiation therapy may afford greater local control, the preponderance of retrospective data indicates no consistent advantage to preoperative radiation over surgery alone. In fact, there are indications that preoperative radiation may increase the rate of nodal and distant metastasis.

Surgery and Postoperative Radiation Therapy

Early surgical reconstructive techniques required staged procedures over several months and were fraught with high morbidity associated with multiple surgical procedures including infection and wound dehiscence. These reconstructions were also subject to unravel as a result of radiation therapy delivered postoperatively in excess of modest doses (>5,500 rads). Improved reconstructive techniques have made it possible to deliver high-dose postoperative radiation (5,500 to 7,000 rads), beginning as soon as three weeks postoperative. The difficulties of operating on heavily irradiated tissues increased tissue friability, decreased vascularity, and increased incidence of wound infections.

Survival

Byhardt reported a 69 percent (15/22) survival at three years which fell to 36 percent (39/107) at five years. These were patients from an older series who received radiation therapy to the level of 4,500 rads.[29] Yates reported a 50 percent (5/10) determinate two-year survival with no evidence of disease (NED), and a 25 percent five-year NED survival. Patients in his series received a minimum

of 4,500 rads.[32]

Sasaki and Badawi both reported on patients who had received high-dose postoperative radiation (5,000 to 7,000 rads). Badawi reported 50 percent (63) three-year NED survival and 40 percent (50) five-year NED survival.[28] Sasaki reported a figure for overall survival rate in patients followed-up from two to 15 years of 26 percent (13/50). Two-year NED survivals for Stage III patients were 45 percent and for Stage IV patients 15 percent.[2]

Sasaki also characterized his survival rates by the number of nodes found to be histologically involved with tumor, 50 percent for zero to one node, 31 percent for two to three nodes, and 16 percent for four or more nodes. He concluded that the number of involved nodes is the most important determinant of NED survival.[2]

Badawi concluded that statistical differences in control above the clavicles and in five-year survival was in favor of planned combined treatment, and that failures of postoperative radiation increase with increasing time interval between the surgical procedure and the beginning of radiation therapy. He also characterized the causes of death between two and five years as due to intercurrent disease,

distant metastatic disease, and second primary tumors.[28]

These two-year survival rates for postoperative radiation are considerably better than the 42 percent reported by Byhardt in his compilation of preoperative radiation series, but comparable to the two-year survival rates reported by Yates (50 percent) for surgery alone and three-year survival reported by Wang (63 percent) for preoperative radiation. The five-year survival rates for postoperative radiation reported by Byhardt (36 percent) is comparable to the 40 percent achieved by Badawi with high-dose postoperative radiation. Yates reports only 25 percent five-year survival while Sasaki's 26 percent follow-up figure includes patients followed up to 15 years for "overall cure."

Byhardt's five-year survival for preoperative radiation falls right between these figures at 31 percent. Yates found a similar five-year survival rate of 36 percent for preoperative radiation and none of these five-year results match the 56 percent survival he found in the surgery alone arm of his study.

Recurrence

Byhardt reported a discouraging 83 percent local and 68 percent regional recurrence rate in his compilation from nine authors. The reports of subsequent authors are more encouraging Yates (10 percent), Badawi (11 percent), and Sasaki (32 percent) for regional recurrence, for Yates and Sasaki respectively.

In summary, the results of the articles reviewed here indicate that postoperative radiation improves locoregional control. Although there appears to be a tendency toward improved two-year and five-year survival rates, this is not a consistent finding. The best two-year survival has been reported with postoperative radiation (Byhardt 69 percent), although Wang reported 63 percent with preoperative radiation. The best five-year survival has been reported with surgery alone (Yates 56 percent). The best five-year survival reported for combination therapy was with postoperative radiation (Badawi 40 percent). Five-year survival rates for preoperative radiation therapy were all grouped around thirty percent. Among articles reviewed here, five-year survivals for postoperative radiation and surgery were in two groups one between 35-40 percent and the

other around 25 percent.

Current retrospective reports focus on different details of specific aspects of clinical presentation to determine prognosis, e.g. the presence of clinically positive lymph nodes at multiple levels in the neck, rather than just the total number of nodes as reported by earlier authors. More specific aspects of treatment and outcome are also being scrutinized and reported on, e.g. the presence or absence of positive margins at the time of surgical resection, the time interval between surgery and radiation therapy, the presence or absence of histologically positive lymph nodes in the specimen, and the specific sites of recurrences. In this way, surgeons hope to provide an improved quality of survival for patients with a disease in which survival outcome has not been affected by all treatment efforts to date. There are few retrospective reports which include all this data because it is often inconsistently reported in patients' charts.

Retrospective studies which utilize consecutive series of patients have been criticized as obscuring patient selection bias which develops over time. Accumulated surgical experience evolves more specific

criteria for utilization of particular treatment methods. There is a natural tendency to improve surgical therapy and technique over time.[25,28]

Other authors defend these studies as reasonable because the nature of ablative surgery has not fundamentally changed over time, although more emphasis has been placed on reconstructive aspects with an increased tendency toward conservation surgery in more recent years.

Prospective randomized studies would have to be very lengthy to accumulate adequate numbers of patients with this uncommon tumor. Alternatively, multi-center prospective randomized studies include larger numbers of patients in a shorter time, but are costly, and difficult to organize. Retrospective studies provide a convenient method for summarizing and analyzing the accumulated experience of a specific medical center, although the results should be reviewed and evaluated cautiously.[24]

Prospective Studies

In 1977, Vandebrouck reported on a prospective randomized trial of preoperative radiation therapy and surgery versus surgery and postoperative radiation. He found a 56 percent five-year survival

with postoperative radiation compared to a 20 percent five-year survival with preoperative radiation (some patients received high doses to 7,000 rads). His study was discontinued after 49 patients due to the high rate of perioperative mortality caused by hemorrhage (38 percent from the carotid artery) in the preoperative radiation therapy group.[46]

In 1981, Snow published his second preliminary report on a prospective, randomized, multicenter trial comparing preoperative radiation therapy and surgery with postoperative radiation therapy. This study included patients with lesions of the oral cavity, oropharynx, and hypopharynx, although results are reported separately by region. Two-year survival rates for all sites are 54 percent for preoperative radiation. The estimated two-year survival rates for hypopharyngeal tumors is 42 percent for postoperative radiation and 38 percent for preoperative radiation. The locoregional recurrence rate was 26 percent for preoperative radiation and 16 percent for postoperative radiation.[47] Although survival rates were not significantly different, there was a trend in favor of postoperative radiation therapy. Postoperative radiation showed a clear advantage over preoperative radiation in locoregional control. He

found disease stage at presentation is a significant prognostic factor for survival in patients with lesions of the hypopharynx as well as oropharynx and supraglottic larynx. Disease stage was not a significant factor affecting locoregional control, although apparently sequence of therapy is. His results for two-year survival show little advantage of either sequence of combination therapy, although both are considerably lower than the best results reported in retrospective series discussed earlier.

MATERIALS AND METHODS

Patient Population

This study covered the years from January 1963 through the end of December 1984. All patients were treated with radiation therapy and surgery for tumors of the pyriform sinus and hypopharynx by the Yale Section of Otolaryngology and the Yale Department of Radiation Therapy. Patients were identified through the Tumor Registry of Yale-New Haven Hospital.

Eighty-six patients were reviewed who were planned to receive combination therapy. Fifty-nine were excluded who received salvage therapy or where there was recurence prior to initiation of second mode of treatment. Six patients were excluded who had early stage lesions (Stage I or Stage II). The remaining patients (17) were excluded whose follow-up records were incomplete regarding date of diagnosis, dates of treatment, or without a minimum of two years

follow-up.

The population includes patients treated at the West Haven Veteran's Administration Hospital and the private and community services of the Yale-New Haven Hospital. Patient records were reviewed for prior smoking history, prior drinking history, presenting symptoms, physical exam of primary tumor and cervical nodes, date of biopsy diagnosis, pretreatment staging, treatment plan, surgical complications, surgical pathology and follow-up to recurrence, metastasis, and/or death. Record review was done by the author at the Medical Records Departments of the Yale-New Haven Hospital, the West Haven Veteran's Administration Hospital, and the clinic records of the Yale Section of Otolaryngology. Follow-up was also conducted at the Yale Tumor Registry. Where possible patient's families were directly contacted.

Demographics of the patient series reviewed is consistent with that reported by authors in the literature. The mean age was 61.6 years. Ninety-five percent of the patients were caucasian (there were three Afro-Americans). Eighty-five percent of the patients were male. The longest patient follow-up was 20 years, 8 months in the preoperative radiation group. Both groups had

several patients surviving nine years.

Clinical staging by the TNM classification was determined by the clinician at the time of treatment. All patients included in the study had advanced disease (Stage III and IV), which includes patients with any clinical nodal disease at primary tumor stage T1 or T2 as well as any primary T3 or greater. See Table 1.

The two-year and five-year survival data was evaluated using the chi-square method for analysis of significance. The mean survival difference was evaluated using the student's t test on the geometric mean.

Table 1 Clinical Staging of Tumors

Preoperative Radiation

	T1	T2	T3	T4
No			3	4
N1	1	2	2	2
N2		2	4	
N3		2	3	3

Postoperative Radiation

	T1	T2	T3	T4
No			3	4
N1	3	3	4	3
N2		2	4	
N3		2	3	3

All diagnoses were histologically confirmed by biopsy or surgical pathology specimen. All patients

were diagnosed with squamous cell carcinoma. The distribution of histologic classification is shown in Table 2.

Table 2 Histologic Classification of Tumors

Preoperative Radiation Group

Poorly Differentiated	Moderately Differentiated	Well Differentiated	Total
9	5	14	28

Postoperative Radiation Group

Poorly Differentiated	Moderately Differentiated	Well Differentiated	Total
9	11	10	30

Treatment

In the preoperative radiation therapy group, radiation was delivered in the low (-4,000 rads), moderate (4,000-5,500 rads), and high (5,500-7,000) dose ranges (see Table 3). Among the 29 patients in the preoperative radiation therapy group, 59 percent (17) received moderate dose (4,000-5,500 rads), for most of these the dose was 4,500 rads or less. Surgical treatment consisted of total laryngectomy in all cases except one. Radical neck dissections were performed in all cases except three. There were two functional neck dissections and one supraonohyoid dissection.

In the postoperative radiation therapy group, radiation was delivered in the moderate and high dose ranges (see Table 3). Among the 30 patients in the postoperative radiation therapy group, 53 percent (16) received high-dose radiation (5,500-7,000 rads). Surgical treatment consisted of total laryngectomy in all cases. Nodal disease was treated with radical neck dissection in 70 percent of patients (21/30). Eight patients received functional neck dissections and there was one modified neck dissection.

Table 3 Radiation Therapy Doses

Preoperative Radiation Therapy Group

Thousands of Rads	3	3.5	4	4.5	5	5.5	6	6.5	7	Total
# of Pts	3		11	3	3		1	4		29

Postoperative Radiation Therapy Group

Thousands of Rads	3	3.5	4	4.5	5	5.5	6	6.5	7	Total
# of Pts			3	3	8	4	9	2	1	30

The mean time interval between therapeutic modes in the preoperative radiation therapy group was 67.5 weeks. In the postoperative radiation therapy group, the time interval between therapeutic modes was planned to be as close to three weeks as possible. The mean interval in the postoperative radiation group was five to six weeks. Correcting for one patient whose planned four-week interval was extended to 16 weeks due to surgical complications, the mean interval was four to seven weeks. Table 4 shows the time intervals in both groups.

Table 4 Time Interval Between Therapeutic Modes

Preoperative Radiation Group

Number of Weeks	2	4	6	8	10	12	Total
Number of Patients	1	8	9	6	3	2	29

Postoperative Radiation Group

Number of Weeks	2	3	4	5	6	7	8	9	10	12	14	16	Total
Number of Patients	2	9	6	3	5		3			1		1	29

Disease-free survival was determined as time from completion of initial mode of therapy (whether radiation or surgery) to documented date of tumor recurrence, death of the patient, or date last seen. Recurrent tumor was evaluated based on clinical behavior of growths in primary site and in the neck, and in most cases was confirmed by biopsy. Second primary tumors reported in the chart by the clinician present are accepted as such and not considered recurrences.

RESULTS

Both patient groups were comparable regarding staging of primary tumor and nodal disease (see Table 1). The most common presenting symptoms were hoarseness (77 percent), difficult or painful swallowing (47 percent), mass in the neck (40 percent). Other frequently reported symptoms included excess weight loss (30 percent), sore throat (28 percent), and ear pain (25 percent). Symptoms that were rarely reported included shortness of breath, persistent cough, hemoptysis, and stridor.

Seventy-one percent of patients were documented as heavy smokers, 64 percent were documented as heavy drinkers. There were a number of patients whose smoking and drinking habits could not be documented because patient records had been consolidated for storage purposes.

Two patients in the preoperative radiation therapy group died in the perioperative period from

exsanguination due to carotid rupture. Fifty-two percent of patients (15/29) died in less than one year. The mean survival time was 42.4 months. The two-year NED survival was 45 percent (13/29), the five-year survival was 24 percent (7/29).

Among patients receiving postoperative radiation therapy and surgery, the mean survival time was 26.7 months. Forty-seven percent (14/30) of postoperative therapy patients died in less than one year. The two-year NED survival was 37 percent (11/30). The five-year NED survival was 17 percent (5/30). These results are shown in Table 5.

Table 6 shows the duration of disease-free survival by tumor stage. The difference in survival under different treatment groups did not achieve significance using the chi-square method.

Table 5 NED Survival (Percent)

	Two-Year	Five-Year
Pre-Op	45 (13/29)	24(7/29)
Post-Op	37 (11/30)	17 (5/30)

Table 6 Survival by Tumor Stage (Percent)

	Two-Year	Five-Year
Pre-Op		
Stage III	5	3
Stage IV	8	4
Post-Op		
Stage III	3	1
Stage IV	8	4

Patients in a number of cases died of intercurrent disease related to the ravages of their lifestyle and not due to the initial malignancy. Some of these causes were cirrhotic liver disease, diabetic renal disease, and suicide. Some patients died of causes secondary to treatment induced changes--these included airway obstruction and respiratory arrest, secondary primary tumor, and aspiration pneumonia.

Among patients in the preoperative radiation therapy group recurrence and/or distant metastasis were documented in 45 percent of patients (13/29). Two patients had both recurrent and metastatic disease. Nine recurrences occurred in local or regional sites (31 percent). There were six patients with documented distant metastasis (20 percent). Sites of distant metastasis included lung (4), liver (1), and renal (1).

In the postoperative radiation therapy group, recurrence and/or distant metastasis was documented in 13 patients (43 percent). One patient had both recurrent and metastatic disease. Six patients had local or regional recurrences (20 percent). There were eight patients with documented distant metastasis (26 percent). Sites of distant metastasis

included lung (4), liver (2), and bone (2).

The surgical complication rate in the preoperative radiation therapy group was 30 percent (9/30). This includes two perioperative mortalities. There were three fistulas, three lung infiltrates and one wound abscess. The surgical complication rate in the postoperative radiation therapy group was 28 percent (8/29). There were three fistulas, two aspiration pneumonias, two wound infections, and one pulmonary infiltrate.

DISCUSSION

Several factors make it difficult to draw significant conclusions from this study. It is a retrospective study using historical controls. The limitations of retrospective studies are discussed earlier. The large number of patients lost to follow-up, 17 (19 percent of patients reviewed), further weakens our ability to draw significant conclusions from this data.

The patient groups included similar numbers and were comparable based on tumor staging, surgical treatment and dose of radiation therapy received. Preoperative radiation therapy and surgery was demonstrated to provide a slightly higher rate of two-year and five-year survival, although these results are not statistically significant. These results disproved my hypothesis.

One reason the postoperative radiation therapy group did not have a better outcome may be that many

patients in this group (47 percent) received submaximal radiation doses of 5,500 rads or less. The maximum therapeutic dose in the head and neck region is 7,000 rads.

My literature review showed no clear consensus has emerged regarding the most effective form of treatment for these desperate patients. Although encouraging five-year survival results have been reported by individual authors for surgery alone, preoperative radiation therapy, and postoperative radiation therapy, other authors have not reproduced these results. The most definitive study in the literature, the randomized multicenter study reported by Snow, found that preoperative radiation therapy and surgery was equivalent to surgery and postoprative radiation therapy. The recurrence and survival results in the two treatment groups reported here are also equivalent.

It is clear that patients diagnosed with advanced stage squamous cell carcinoma of the pyriform sinus and hypopharynx have a disease with an extremely grave prognosis which is essentially using any current form of treatment. Perhaps some inroads can be made with immunotherapy using activated lymphocytes or using triple therapy combining

surgery, radiation, and chemotherapy. Greater control of the disease may also be achieved through screening and early detection of high risk patients.

The two perioperative mortalities due to carotid rupture in the preoperative radiation therapy group are cause for concern. Postoperative radiation therapy seems to carry less risk of perioperative mortality and should be utilized for its practiced advantage if other risk factors are equal.

APPENDIX A

TYPES OF MODIFIED NECK DISSECTION

APPENDIX A

VARIATIONS OF THE MODIFIED NECK DISSECTION*

NAME	DISSECTED NODAL GROUPS
SUPRAHYOID	Submental and submaxillary
SUPRAOMOHYOID	Submental, submaxillary, subdigastric, upper posterior cervical, mid-jugular
ANTERIOR	Subdigastric, midjugular, lower jugular
POSTERIOR	Upper, middle, lower posterior cervical
LOWER	Lower posterior cervical, supraclavicular, lower jugular
FUNCTIONAL	Submental, submaxillary, subdigastric, midjugular, lower jugular, and upper, middle, lower posterior cervical

*From Byers, 1985.

References

1. American Joint Committee on Cancer, _Staging of Cancer of Head and Neck Sites and of Melanoma_, 1980, p. 15.

2. Sasaki, T.M. et al. "Aggressive Surgical Management of Pyriform Sinus Cancer: A Fifteen Year Experience," _Am J Surg_ 141:590, 1986.

3. Olfsson, J. et al. "Laryngeal Cancer: Correlations of Roentogenography and Histopathology," _Am J Roentol, Rad T & Nuc Med_ 117:526, 1973.

4. Larson S. et al. "Differentiation of Pyriform Sinus Cancer from Supraglottic Larynx Cancer by Computed Tomography," _Radiology_ 141:427, 1981.

5. Lutkin, et al. "Larynx and Hypopharynx: Magnetic Resonance Imaging with Surface Coils," _Radiology_ 158:747, 1986.

6. Silverman, P.M. et al. "Carcinoma of the Larynx and Hypopharynx: Computed Tomographic Histopathologic Correlations," _Radiology_ 151:697, 1984.

7. Mattox, Douglass. "Cancer of the Hypopharyx," in Gates, George (ed.) _Current Therapy in Otolaryngology, Head and Neck Surgery_, 1984.

8. Looser, K.G. et al. "The Significance of 'Postive' Margins in Surgically Resected Epidermoid Carcinomas," _Head and Neck Surgery_ 1:107, 1978.

9. Hinchcliffe, Ronald and Harrison, Donald (eds.) _Scientific Foundations of Otolaryngology_, William Heinemann Medical Books, 1976.

10. Ward, Grant and Hendrick James. _Diagnosis and Treatment of Tumors of the Head and Neck_, Williams and Wilkins, 1950.

11. Donald, Paul J. _Head and Neck Cancer Management of Difficult Cases_, W.B. Saunders, 1984.

12. MacComb, Williams and Fletcher, Gilbert H. Cancer of the Head and Neck, Williams and Wilkins, 1967, p. 219.

13. Kirchner, John. "Pyriform Sinus Cancer: A Clinical and Laboratory Study," Ann Otolaryngology 84:793, 1975.

14. Martin, Hayes and Morfit, Mason. "Cervical Lymph Node Metastasis as the First Symptom of Cancer," Surg Gynecol & Obstet 78:133, 1944.

15 Ballenger, John Jacob. Diseases of the Nose, Throat, Ear, Head and Neck, 1985, p. 664.

16. Martin, Hayes and Romieu, Claude. "The Diagnostic Significance of a 'Lump in the Neck'" Postgraduate Medicine 11(6):491, 1952.

17. Paparella, Michael and Shumrick, Donald. Otolaryngology, W.B. Saunders, 1980, p 2339.

18. Rothman, K. et al. "The Effect of Joint Exposure to Alcohol and Tobacco on Risk of Cancer of the Mouth and Pharynx," Journal of Chronic Disease 25:711, 1972.

19. Schneider, J.J. et al. "Control by Irradiation Alone of Nonfixed Clinically Positive Lymph Nodes From Squamous Cell Carcinoma of the Oral Cavity, Oropharynx, Supraglottic Larynx, and Hypopharynx," Am J Roentol, Rad T & Nuc Med 123(1):42, 1975.

20. Gluckman, J.L. et al. "Multicentric Squamous Cell Carcinoma of the Upper Aerodigestive Tract," Head and Neck Surgery 3:90, 1960.

21. Barkley, H.T. et al. "Management of Cervical Lymph Node Metastases in Squamous Cell Carcinoma of the Tonsilar Fossa, Base of Tongue, Supraglottic Larynx, and Hypopharynx," Am J Surg, 124:452, 1972.

22. Lindberg, R. et al. "Treatment of Cervical Lymph Node Metastasis from Primary Lesions of the Oropharynx Supraglottic Larynx, and Hypopharynx," Am J Roentol 102:133, 1968.

23. Kagan, Robert and Miles, John. Head and Neck Oncology Controversies in Cancer Treatment, G.K. Hall Medical Publishers, 1981.

24. Bahadur, S. et al. "The Enigma of Post-Radiation Edema and Residual or Recurrent Cancer of the Larynx and Pyriform Fossa," J Laryngol and Otol 99:763, 1985.

25. Lederman, M. et al. "Carcinoma of the Laryngopharynx: Results of Radiotherapy," J Laryngol and Otol 76:317, 1962.

26. Byhardt, R. et al. "Patterns of Failure and Results of Preoperative Irradiation Versus Radiation Therapy Alone in Cancer of the Pyriform Sinus," Int J Rad Onc Biol Phys 6:1135, 1980.

27. Ahmad, K. et al. "High Dose Radiation Therapy in Cancer of the Pyriform Sinus," Cancer 53:2901, 1984.,

28. Badawi, S.A. et al. "Squamous Cell Cancer of the Pyriform Sinus," Laryngoscope 92:357, 1982.

29. Harwick, R.D. et al. "Cancer of the Pyriform Sinus," Am J Surg 130:493, 1975.

30. Million, R.R. et al. "Radical Irradiaton for Cancer of the Pyriform Sinus," Laryngoscope 91:439, 1981.

31. Fletcher, G.H. et al. "Elective Irradiation of Sub Clinical Disease in Cancer of the Head and Neck," Cancer 29:1450, 1972.

32. Yates, A. et al. "Surgical Treatment of Pyriform Sinus Cancer: A Retrospective Study," Laryngoscope 94:1586, 1984.

33. Eisbach, K.J. et al. "Cancer of the Pyriform Sinus: A Comparison of Treatment Modalities," Laryngoscope 87:1904, 1977.

34. Harrison, D.F.N. et al. "Pathology of Hypopharyngeal Cancer in Relation to Surgical Mangement," J Laryngol and Otol, April 1970, 349.

35. Gall, A.M. et al. "Compliations Following Surgery for Cancer of the Larynx and Hypopharynx," Cancer 39:624, 1977.

36. Byers, R.M. et al. "Modified Neck Dissection: A Study of 967 'Cases from 1970-1980'" Am J Surg 150:414, 1985.

37. Jesse, R.H. et al. "The Efficacy of Combining Radiation Therapy with a Surgical Procedure in Patients with Cervical Metastasis from Squamous Cancer of the Oropharynx and Hypopoharynx," Cancer 35:1163, 1975.

38. Grandi, C. et al. "Prognostic Significance of Lymphatic Spread in Head and Neck Carcinomas: Therapeutic Implications," Head and Neck Surgery 8:67, 1985.

39. Stefani, S. et al. "Cancer of the Hypopharynx, A Study of Distant Metstasis, Treatment Failures, and Multiple Primary Cancer in 215 Male Patients," Laryngoscope 81:1491, 1971

40. Kirchner, J.A. et al. "Five Hundred Cancers of the Larynx and Pyriform Sinus," Laryngoscope 87:1288, 1977.

41. Lord, I.J. et al. "A Comparison of Preoperative and Primary Radiotherapy in the Treatment of Carcinoma of the Hypopharynx," British J Radiol 46:175, 1973.

42. Rush, B.F. et al. "Integrated Irradiation and Operation in Treatment of Cancer of the Larynx and Hypopharynx," Am J Roentol, Rad T & Nuc Med 102(1):129, 1968.

43. Strong, M.S. et al. "A Randomized Trial of Preoperative Radiotherapy in Cancer of the Oropharynx and Hypopharnx," Am J Surg 136:494, 1978.

44. Wang, C.C. et al. "Combined Radiation Therapy and Surgery for Carcinoma of the Supraglottic and Pyriform Sinus," Laryngoscope 82(10):1883, 1972.

45. Marks, J.E. et al. "The Need for Elective Irradiation of Occult Lymphatic Metastases from Cancers of the Larynx and Pyriform Sinus," Head and Neck Surgery 8:3, 1985.

46. Vandenbrouck, C. et al. "Results of a Randomized Clinical Trial of Preoperative Irradiation vs Postoperative Irradiation in Treatment of Tumors of the Hypopharynx," Cancer 39:1445, 1977.

47. Snow, J.B. et al. "Comparison of Preoperative and Postoperative Radiation Therapy for Patients with Carcinoma of the Head and Neck," Acta Otolaryngol 91:611, 1981.

YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

NAME AND ADDRESS	DATE
Dale Johnson 333 Cedar St	7/12/88
Mark Binoli 159 [illegible] st.	8/24/89
John A Kirchner 333 Cedar St Dept of Surgery	6/5/91