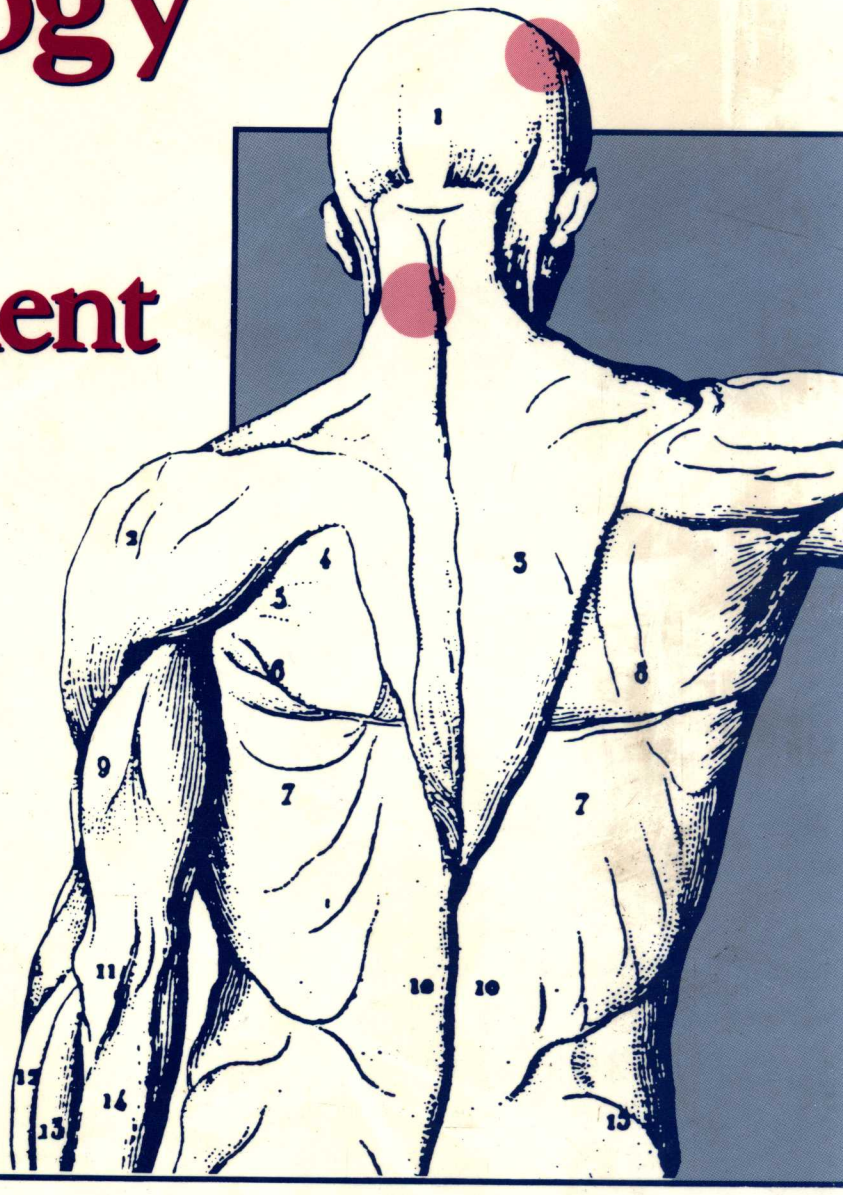
Head and Neck Oncology

Clinical Management



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Contents

Introduction

The accomplishments of modern oncology have been so magnificent that we oncologists should be able to admit mistakes gracefully. Indeed, considering the variety of effective treatment regimens, it is not surprising that some errors have been committed. Unfortunately, there is a tendency to avoid publishing errors because they may negatively reflect on the author and his institution. In addition, editors of medical journals tend to avoid articles which enumerate mistakes, since they guard the optimism so essential to the mental health of the full-time oncologist. We need to know about the previous experience of others in order to avoid repeating mistakes.

Less than half of patients with head and neck cancer are eligible for protocols in multidisciplinary management, due to severe medical problems or non-compliance. Of more importance, less than one-fifth of these eligible patients are entered on the study. It follows that 90 percent or more of patients with head and neck cancer are managed on the basis of personal preference, not randomized studies, hence the importance of the chapters in this volume. Nowhere in oncology is physician preference for a specific treatment more influential in deciding ultimate management.

We, as oncologists, have two ethical issues to examine since the majority of patients with head and neck cancer have advanced malignancy: first, our responsibility to ourselves to search out the truth; and second, through awareness of our own responsible choices, to explore what choices are *acceptable for the patient*. Survival, quality of life, and death issues take time to discuss. So we seek to combine specific parts of our knowledge into general rules related to principles, avoiding the unsatisfactory and tiresome task of individualizing discussion with patients. Is it not the truly effective clinician who goes on forever learning lists of exceptions and accumulating facts that must be isolated from the general rules? Ward, Becker, and Harrison should be congratulated for accepting the goal of providing us with their "personal" recipes for the management of the patient with advanced malignancy.

Logemann has analyzed the disabilities of the patient with head and neck cancer. As our understanding of how these disabilities are acquired, our patients will benefit from our empathy. However, Richardson has pointed out, many of these patients have compliance problems; which means when we instruct these patients to do what is best for them, they may refuse. We can now offer these patients considerable optimism in regard to rehabilitation, thereby improving the quality of life in the surviving patients. Beumer explores rehabilitation with regard to teeth, Schwartz with regard to the mandible, and Brånemark with regard to tissue-osseo-integrated reconstruction, which may eclipse all other methods of reconstruction. Luboinski provides a forthright analysis of voice rehabilitation.

Bone and Bataini discuss early supraglottic carcinoma from the point of view of the surgeon and radiation therapist. Note Bataini's warning to radiation therapists regarding the preepiglottic space and Bone's frank caution to surgeons concerning errors in judgment and technique. Another subject whose treatment will always be debated at tumor boards is angiofibroma; Cummings is not perplexed by all the fuss, and is he not fair with respect to an operative procedure, despite his bias toward irradiation? Adams reviews the management of "sinus" cancer, which is uncommon and often advanced.

The Institut Gustave-Roussy under Tubiana was one of the first institutions to investigate calcitonin in medullary carcinoma of the thyroid. It is the only institution known to us that has evaluated, in force, all the aspects: surgery, irradiation therapy, endocrinology, and so forth. Here by Gardet is a concise comprehensive summary of their experience.

Partial laryngectomy with decannulization can be accomplished in patients who have failed irradiation for squamous cell carcinoma of the vocal cord. In Goepfert and Campbell's series, this occurred in less than 10 percent of the total failures, and he cautions that these patients should be followed closely for recurrence.

A well-illustrated chapter by Wolfensberger shows how to operate on T_1T_2 cancers of the nasopharynx. Should we radiation oncologists rethink management of at least our failures?

If the whisper of irradiation myelitis panics every involved radiation therapist, Abbatucci repudiates this panic by clearly and logically defining the clinical factors leading to irradiation injury to the central nervous tissues.

Rice challenges the value of blind biopsy in the patient with an unknown primary, and guides us through the management of *in situ* and microinvasive carcinoma.

Chung accomplishes a great deal by giving us a replay of his

experience with the combination of surgery and irradiation by sites within the laryngopharynx, and most important, by amount of cervical lymphadenopathy.

The time and energy devoted to the administration of chemotherapy is enormous. Taylor examines whether the outcomes have been shrouded in deceitful optimisim.

Patients with head and neck cancer are so heterogeneous that attempts to pigeonhole them into treatment categories remain unsuccessful. The viewpoints of the managing oncologists often differ since the basis of judgment is a byproduct of experience.

Among oncologists who are forced to work together, each unsympathetic to the other's "bad luck," good and bad luck becomes a synonym for good and bad judgment. It is our hope that the chapters in this volume help to show that perspective changes constantly with the passing of time and, hence, the growth of wisdom.

1

Radiation and Surgery for Advanced Cancer of the Larynx and Pyriform Sinus

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Radiation therapy and surgery have long been employed individually and successfully in the treatment of small, early stage carcinomas of the head and neck. If local recurrence develops, the alternative treatment is often curative. Thus, there is little impetus to combining these two treatments for early stage head and neck cancer, and combined therapy for early stage disease will not be addressed further in this chapter. Unfortunately, the situation is very different for advanced cancers, and the use of surgery or radiation therapy alone often results in disappointment for patients with Stages III and IV squamous cell carcinoma of the head and neck.

In an effort to improve the overall salvage rate for patients with advanced head and neck cancer, many authors have advocated combined treatment programs.[5,15,21,39,43,54] Irradiation may precede or follow surgery, the goal and dose of irradiation may vary, both modes may be applied to the primary site and the neck nodes, or the primary site can be managed by one mode while the neck disease is managed by the other. In addition, a clinically negative neck (N_0) may be treated successfully with a regimen not applicable to large, metastatic adenopathy (N_2, N_3).[11,12] We define combined treatment programs to be those in which both surgery and radiation therapy are utilized in a therapeutic scheme planned at the time of evaluation and staging. The use of chemotherapy in addition to irradiation and/or surgery is a more recent development, with a voluminous literature, controversial results and conclusions, and is beyond the scope of this historical review (see Chapter 20).[19]

Before 1960, the most common treatment combinations were salvage surgery for radiation failures and palliative irradiation for surgical failures. These do not qualify as combined treatment programs according to our definition. As experience accumulated, along with a better understanding of tumor biology and a better description of the patterns of spread of malignant tumors, planned combined preoperative or postoperative irradiation programs were introduced. The dose of radiation used postoperatively was usually high enough to sterilize microscopic disease (50–60 Gy) and was limited by each group's experience and definition of an acceptable complication rate.[10,14,25] The radiation dose used preoperatively (20–60 Gy) varied widely, predominantly because of fear of inducing operative

complications, but also according to the goal of irradiation. Varying degrees of surgery were employed, ranging from local excision to radical resection.[13,16,23,27,31,43,50]

Because of small numbers of patients in each institution, analysis by primary site, stage (T versus N stage) and histological differentiation, statistically significant results often could not be obtained and prospective, controlled studies were almost impossible to conduct outside of a multi-institutional setting. The tumor control and survival results of such cooperative studies were often lower than those reported from individual institutions. Considering the wide range of radiation fractionation schemes, the differences in surgical techniques, and potential bias in patient selection, it is no wonder that most institutions continue to follow the program developed at home, which provides comparable or better tumor control and an acceptable complication rate, at least in their minds.

One of the first combined programs, consisting of preoperative irradiation (50–55 Gy) followed three to five weeks later by radical surgery for patients with advanced laryngeal and laryngopharyngeal cancer began in 1958 and Goldman et al. later reported excellent survival rates.[15,16] Powers et al. undertook a series of experimental studies in animal tumor systems to provide a rationale and achieved in vivo results demonstrating the value of preoperative irradiation.[40,41] This led to other publications by McGavran et al. (1964) and Biller et al. (1969) from the Washington University of St. Louis presenting clinical results with 30 Gy given before partial or total laryngectomy.[5,27] Jesse, Fletcher, and others from the U.T. M.D. Anderson Hospital, Houston, reported on numerous occasions about the efficacy of combining irradiation and surgery, especially postoperative radiotherapy, for advanced head and neck tumors.[9,14,21,46] Wang et al. employed a preoperative dose of 60 Gy initially but reduced this to 40–45 Gy because of a higher rate of complications, and reported improved results.[52,54]

Indeed, experience has taught us that the dose of irradiation given preoperatively is vitally dependent upon the surgery planned, total laryngectomy versus supraglottic laryngectomy. For example, we delivered 30 Gy prior to supraglottic laryngectomy and found no increase in complications compared to surgery alone. When the dose was raised to 40 Gy there were some difficulties, but no major problems after supraglottic laryngectomy. However, there was an unacceptable rate of fistulae developing after 50 Gy. The mucosal closure broke down under the trauma of secretions, food, and swallowing. Therefore, we reduced the presupraglottic laryngectomy dose to 40 Gy. In contrast, we experienced no increase in complications employing 50 Gy before total laryngectomy.[7]

Radiotherapy programs may differ in fractionation, field arrangement, and the volume treated, and the surgical procedure may be altered by irradiation or may be accomplished as if there had been no irradiation given. However, there remains controversy as to whether combined therapy should be employed for all patients with Stages III and IV cancer or reserved for particular primary sites or nodal situations. It is also controversial whether combined therapy improves long-term survival and whether the irradiation should be given before or after surgery. Resolution of these questions has now become even more complex as chemotherapeutic agents have been added to treatment programs for patients with advanced cancers of the head and neck. The chemotherapeutic agents were given in varying doses and combinations, for different lengths of time, and before, after, or sandwiching surgery. Despite the many individual institutional reports of the benefit or lack of benefit of combined irradiation/surgery treatment programs for advanced head and neck cancer, it fell to the Radiation Therapy Oncology Group (RTOG) to undertake a multi-institutional prospective study in 1973 in order to answer these questions. The RTOG results favored postoperative radiation therapy for patients with laryngopharyngeal, oral, and oropharyngeal cancers.[47] Criticisms leveled at this study included: (1) there was no mechanism to monitor the extent of resection, although the protocol stated that "surgery should be done as if there were no radiation therapy given for patients receiving preoperative irradiation"; (2) within Stages III and IV there are patients with a better prognosis (eg., T_4N_0) and with a worse prognosis (eg., T_2N_3), as suggested by Hahn et al. and Mendenhall et al.[17,34,35,36]

Changing fashions in management, including an overwhelming interest in adjuvant chemotherapy led us to review 20 years of experience with 360 patients treated for Stages III and IV laryngopharyngeal cancer by a closely integrated group of head and neck surgeons and radiation oncologists between 1968 and 1984, at the SUNY Health Science Center at Syracuse, New York to establish a data base against which the results of new protocols might be evaluated. This allowed us to compare preoperative with postoperative irradiation, as the treatment programs have changed during the years, and to look at each site and stage independently. (As is true in so many institutions, we were not able to obtain agreement to mount a randomized, prospective, intrainstitutional study.) This was due to strongly held beliefs and the relative paucity of patients in any one category/stage, eg., supraglottic larynx, T_2N_2 versus T_1N_3 versus T_3N_0. Nevertheless, all patients were seen and treated according to the then current protocol, and there were very few losses to follow up. Thus, we can report an experience based upon the geographical population available (750,000 persons) with little deliberate selection for one or another scheme outside of changing fashion.

Our preoperative radiation therapy program, initiated in 1968, delivered 50 Gy tumor dose in 25 fractions (2 Gy/fraction) over a five-week period through large, bilateral, parallel opposed fields including the primary site and cervical lymphatics; since 1973, a lower, anterior, cervical-supraclavicular field has been added. The addition of the lower neck field resulted in improved local control, 90 percent versus 68 percent, especially by decreasing stomal recurrences.[43] A total laryngectomy, usually with radical neck dissection, followed four to six weeks later. Fifty Gy was employed as there was a profound effect on the tumor seen clinically and in surgical specimens, of which 20 to 30 percent showed no residual tumor. This dose was also considered to be effective in controlling 90 percent of subclinical, microscopic disease, as reported by Fletcher et al.[12,34,42]

A trend away from preoperative irradiation began in 1976 and by 1978 postoperative irradiation became dominant; the tumor dose now ranged from 54 Gy to 70 Gy, determined by the completeness of surgical removal of the tumor and other clinical and histological criteria. Postoperative irradiation was usually started three to six weeks after surgery and was given through parallel opposed lateral fields with an additional lower

anterior neck field to include the tumor bed, cervical lymphatic channels, stoma, and supraclavicular fossae. During both eras, all fields were treated daily but the postoperative dose varied from 2.0 to 1.8 Gy/fraction.

These results could also be compared with those for patients with advanced carcinoma of the laryngopharynx who received radiation therapy as the sole treatment, having refused surgery or having been deemed to be medically inoperable; some of these patients with recurrent or persistent tumor did later undergo salvage surgery despite the initial judgment.

Survival was calculated as recommended by the American Joint Committee on Cancer.[2] There were many patients who died of intercurrent disease in this patient group as anticipated from their history of smoking, alcohol abuse, and general condition. Thus, analyzing crude survival rates would not reflect accurately the results of treatment.[51] Therefore, we have shown also the percentage of patients dying of their cancer.

With our data, along with data from literature, we are trying to answer the following questions:

1. Should combined therapy be employed for all patients with Stages III and IV cancers of the larynx and hypopharynx?
2. Should irradiation be given before (preoperative) or after (postoperative) surgery?
3. Does combined therapy improve long-term survival?
4. Does combined therapy improve locoregional tumor control?
5. Does combined therapy alter the rate of distant metastasis?
6. Are there alternative therapies to this combined surgery and radiation?

PRETREATMENT EVALUATION

A carefully obtained history is very important; a history of smoking may lead to a diagnosis of unsuspected lung cancer. A laryngeal cancer might present with hoarseness while still in an early stage whereas hypopharyngeal cancers may not cause symptoms until the disease becomes quite large, giving rise to presenting signs such as dysphagia or enlargement of the neck nodes. Otalgia may be present as a referred pain suggestive of deeper invasion.

In order to select optimal therapy, meticulous physical examination must be carried out and remains the foundation for management, to be supplemented by computed tomography (CT) scan and/or magnetic resonance imaging (MRI) when necessary. Look carefully for synchronous second primary cancers in this population and determine if precancerous changes have occurred in normal appearing mucosa. Evaluate carefully the primary tumor in terms of size, sites of involvement and character, mobility of the vocal cords, adequacy of the airway, size and location of the regional lymph nodes, and presence or absence of distant metastasis. Direct inspection and indirect laryngoscopy are the simplest and easiest ways to determine the extent and character of the tumor. Careful palpation of the neck is essential to detect and classify cervical adenopathy. Palpation of cartilage should be accomplished, including listening for the laryngeal click. Radiographic examination can aid in tumor localization and detect nonpalpable extension, determine the presence of bony or cartilage invasion and destruction, and detect nodal involvement. Cartilage destruction may be seen on plain films of the larynx, and anteroposterior tomography may show the extent of subglottic disease. Computed tomography is quite helpful in determining or confirming all of these factors and is excellent for visualization of extension outside the larynx, such as invasion of the preepiglottic space, and may uncover nonpalpable soft tissue or nodal involvement, including extracapsular extension.[3,28,39,43] Although soft tissue radiography of the neck may be helpful in visualizing the extent of disease outside the hypopharynx, computed tomography has replaced it. The chest x-ray is essential to rule out distant metastasis or second primary tumor. (Although CT scan of the chest may detect more or smaller lesions, it is not now recommended as a routine study.) At the present time, MRI is not routinely recommended but may be helpful in certain clinical situations such as invasion of deep tongue muscles. Following this noninvasive investigation, direct panendoscopy and biopsy should be performed prior to final staging and recommending any therapy.

LARYNX

Anatomically, the larynx can be divided into three separate areas: (1) glottic, (2) subglottic, and (3) supraglottic. The embryological derivation of the glottic and subglottic portions is from tracheobronchial anlage while the supraglottis is derived from buccogingival anlage; this difference in derivation is expressed by differences in the behavior and the pattern of spread of tumors originating in these areas. As a primary tumor becomes more extensive it becomes more difficult to pinpoint its origin; when massive tumor is seen it is most often considered supraglottic. Glottic tumors originate from the vocal cord and the anterior and posterior commissures. The supraglottic area includes the epiglottis, aryepiglottic folds, arytenoids, false cords, and laryngeal ventricles. Subglottic lesions arise from the area approximately 1 cm inferior to the true vocal cord down to the lower border of the cricoid cartilage or the first tracheal ring. Subglottic tumors are rare, do not have a high incidence of nodal metastasis and are usually managed surgically, without need for irradiation; they will not, therefore, be discussed further. By far the most common, histological type of cancer of the larynx is squamous cell carcinoma of varying degrees of differentiation.

Glottic Tumors

Ninety-seven patients with Stages III and IV squamous cell carcinoma of the glottis were treated. There were 84 males and 13 females; their ages ranged from 39 to 81 with a median of 62 years. Seventy-seven patients underwent combined treatment and 72 patients were available for evaluation, 37 receiving preoperative radiation therapy (preoperative group) and 35 treated with postoperative radiation therapy (postoperative group). An additional 19 patients underwent radiation therapy, some having salvage surgery after radiation failure (RT group). The sex and age distribution were comparable in each group; staging is shown in Table 1-1. The percentage of patients clinically staged N_0 was 54 percent (20/37) for the preoperative group and 70 percent (25/35) for the postoperative group. In addition to total laryngectomy ± partial pharyngectomy, radical neck dissection was performed in 29 patients (78 percent), including 13 of 20 patients classified as N_0 in the preoperative group in contrast to 18 patients (51 percent), 8 of 25 patients

Table 1-1. Distribution by Stage for Glottic Carcinoma

	T2			T3			T4			Total		
	Preop	Postop	RT ± S	Preop	Postop	RT ± S	Preop	Postop	RT ± S	Preop	Postop	RT ± S
N0				12	16	14	8	9	3	20	25	17
N1				3	2		4	3		7	5	
N2	1	1		3	3	1	3			7	4	1
N3	1						2	1	1	3	1	1
	2	1		18	21	15	17	13	4	37	35	19

with N_0 in the postoperative group. Seventeen of 19 patients (90 percent) treated by radiation therapy only were classified as N_0.

The overall five-year adjusted actuarial recurrence-free survival rate was 69 percent for the preoperative group and 50 percent for the postoperative group; these differences are not statistically significant ($Z = 1.65 < 1.96$). For the radiation therapy only group, the disease-free actuarial five-year survival rate was 64 percent; no recurrences were noted in eight patients, including one T4 patient; one patient died during treatment. There were recurrences in ten patients; four of the six undergoing surgery were salvaged. Only seven patients died of their cancer.

Table 1-2 shows the percentage of patients dying with disease in each group. Although the preoperative group did best, with a 30 percent failure rate, the differences between groups did not reach statistical significance. For the combined treatment group, patients with N_+ neck did significantly worse than those without palpable cervical nodes, 56 percent (12/27) versus 29 percent (13/45), respectively.

Since there were only two patients with positive nodes among the radiation only group, each group with N_0 category was compared and no advantage was noted with combined therapy over radiation alone, 13 of 45 versus 5 of 17. Furthermore, 8 of the 17 patients (47 percent) in the radiation therapy alone group were cured with their voice preserved. Wang reported 57 percent disease-free survival with the larynx preserved in 32 percent of patients who had T_3N_0 vocal cord cancer.[52] Harwood et al. reported a five-year corrected actuarial survival rate of 69 percent for T_3N_0 and 63 percent for T_4N_0 with the larynx preserved in 45 percent and 56 percent, respectively.[18] Our results for T_3N_0 are in accordance with these and others.[8,22,32,38] Accordingly, we conclude that there is no advantage for the combined treatment program for patients with T_3N_0 glottic cancer.

Table 1-2. Proportion of Patients Dying with Glottic Cancer According to N Stage and Treatment

Number of Patients Dying/Total Number of Patients

	Combined Therapy		Combined Therapy Total	RT + Salvage
	Preop	Postop		
N0	3/20	10/25	13/45	5/17*
N1	3/7	4/5	7/12	
N2	4/7	2/4	6/11	1/1
N3	1/3	1/1	2/4	1/1
	11/37	17/35	28/72	7/19
%	30%	49%	39%	39%

*6 had salvage surgery; 4 of 6 were NED at 2–10 years.
*8 patients had voices preserved.

After reviewing publications from several institutions, Terz and Lawrence, Jr. concluded that there was no survival advantage with preoperative irradiation versus surgery alone. We believe this kind of survival analysis, from different institutions with different treatment programs, can be misleading and that each institution must evaluate carefully its own results. For example, many authors demonstrate an advantage in local tumor control and survival for advanced head and neck cancer.[4,14,21,24,49] We have had a similar experience but do not have enough patients or a prospective study to prove this statistically. We would recommend radiation therapy ± salvage surgery for those patients with T_3N_0 lesions who are reliable and agree to attend for frequent follow-up examination.

T_4 glottic tumors are large, involve multiple structures, and are often difficult to classify as to structure of origin and to distinguish from supraglottic primaries except for those patients with invasion of cartilage or thyroid gland. They used to be classified as "transglottic." Although Harwood et al. have published excellent results, there is not enough data available in our material or from others to confirm his recommendation.[18] Our present policy is to manage with combined surgery and irradiation.

There were only two patients with an N_+ neck in the radiation therapy alone group and both died of their disease; in contrast, 44 percent (12/27) of N_+ patients were long-term, disease-free survivors when treated with combined surgery and irradiation. As we have demonstrated with larger numbers of patients, we believe that combined irradiation and surgery is the treatment of choice for N_+ disease.

Supraglottic Tumors

One hundred and fifty-nine patients with Stages III and IV squamous cell carcinoma of the supraglottis were treated. There were 123 males and 36 females. One hundred and three of the 114 patients receiving combined therapy were suitable for evaluation, 79 in the preoperative group and 24 in the postoperative group. Forty-five patients received definitive irradiation with surgery reserved for radiation failure. The distribution of stages in each group is shown in Table 1-3. The neck was clinically N_0 in 29 of the 79 patients (37 percent) in the preoperative group, 12 of 24 (50 percent) in the postoperative group and

Table 1-3. Distribution by Stage for Supraglottic Carcinoma

	T2			T3			T4			Total		
	Preop	Postop	RT + S	Preop	Postop	RT + S	Preop	Postop	RT + S	Preop	Postop	RT + S
N0		2*		8	5	14	21	5	6	29	12	20
N1		1*		7	1	4	11	3	4	18	5	8
N2	4		2	2	3	1	8		5	14	3	8
N3	2			4		2	12	4	7	18	4	9
	6	3	2	21	9	21	52	12	22	79	24	45

*Surgical specimen showed much more extensive disease.

20 of 45 patients (44 percent) of the irradiation alone group. Radical neck dissections were done in 65 patients (82 percent), including 20 of 29 patients with N_0, in the preoperative group and in 17 (71 percent), including 5 of 12 patients with N_0, in the postoperative group.

The overall five-year actuarial recurrence-free survival rates are similar, being 61 percent for the preoperative group and 62 percent for the postoperative group, in contrast to 41 percent for the radiotherapy with salvage surgery group ($P > 0.05$). Table 1-4 shows the percentage of patients dying with cancer in each group according to nodal status. For the irradiation only group, 16 patients showed no evidence of recurrence, 11 (24 percent) with their larynx preserved. Thirteen of 34 patients with recurrent or persistent disease underwent radical surgery and 5 of the 13 were salvaged.

However, for patients with N_0 neck, the trend is similar to the glottic patients, with the failure rate worse for the postoperative group than for the preoperative group (50 percent versus 29 percent respectively ($P > 0.05$)). The failure rate for patients with N_0 neck was statistically similar between combined therapy and radiation therapy with salvage surgery, 34 percent versus 45 percent respectively; although not statistically significant, there is a general trend for results to be better among those treated by combined surgery and radiation. For patients with N_+ neck, combined therapy failed to control disease in 40 percent (25/62) but 80 percent (20/25) could not be salvaged in the radiation therapy alone group.

Combined Glottic and Supraglottic Tumors

It is clear that classifying patients as glottic versus supraglottic, by T stage and by N stage, yields small numbers in each subcategory and results that are not significantly different or of only borderline significance. Clinical experience suggested that combining categories of patients, glottic and supraglottic and T stage, but distinguishing them by N stage might be worthwhile. This proved to be the case for our patients. There was a clear distinction between N_0 and $N_{2,3}$ (Table 1-5). Patients with N_1 disease fared far better than those with $N_{2,3}$ disease. The difference between N_0 and N_1 was small enough to lead us to combine these two categories and to compare them with the N_2 and N_3 category. The difference in failure between N_0-N_1 versus N_2-N_3 is highly significant in each treatment group (Table 1-5). For N_0 N_1, preoperative irradiation was better than postoperative irradiation with only 19 of 74 patients dying of disease versus 20 of 47 ($0.025 < P < 0.05$). However, no difference was noted when the radiation therapy alone group was compared to the preoperative group, the postoperative group, or to the two groups together. The small advantage for the preoperative versus the postoperative group was a persistent trend in all of our material and stands in contrast to the conclusion of the RTOG study.[47] The only bias between these two groups was that, for N_0, more patients (33/49) in the preoperative group underwent elective radical neck dissection than in the postoperative group (13/37). In any event, postoperative radiation therapy is clearly not superior and may be less effective than preoperative radiotherapy.

Table 1-4. Proportion of Patients Dying with Supraglottic Cancer According to N Stage and Treatment

Number of Patients Dying/Total Number of Patients

	Combined Therapy			
	Preop	Postop	Combined Total	RT + Salvage
N0	8/29	6/12	14/41	9/20
N1	5/18	0/5	5/23	4/8
N2	7/14	1/3	8/17	8/8
N3	10/18	2/4	12/22	8/9
	30/79	9/24	39/103	29/45*
%	(39%)	(38%)	(38%)	(59%)

*12 patients had salvage surgery; 5 of the 13 were NED at 2–10 years.
*11 patients had their larynxes preserved.

Table 1-5. Treatment for Laryngeal* Carcinoma Versus N Stage

	Number of Patients Dead with Disease/ Total Number of Patients			
	Preop	Postop	Combined	RT Alone
N_0	11/49	16/37	27/86	14/37
N_1	8/25	4/10	12/35	4/8
$N_0 + N_1$	19/74	20/47	39/121	18/45
N_2	11/21	3/7	14/28	9/9
N_3	11/21	3/5	14/26	9/10
$N_2 + N_3$	22/42	6/12	28/54	18/19

*Glottic and supraglottic.

For patients with N_2-N_3 disease, 18 of 19 patients treated by irradiation alone died in contrast to 28 of 54 patients (52 percent) in the combined treatment group ($P < 0.001$). The survival curves are shown in Fig. 1-1. These results lead to our strong belief that all patients with N_2 and N_3 cervical adenopathy should be treated with combined therapy whenever possible, as suggested by others for advanced neck disease.[6,9,48,55]

When tumor margins are not likely to be critical, such as is the case for laryngeal cancer because the entire larynx and part of the pharynx will be removed, we believe that preoperative irradiation should be given. In special circumstances, such as when complete surgical resection may be questionable, it should be strongly preferred. For those patients with only a fixed vocal cord and no other visible large tumor, preoperative irradiation should be given; if the cord becomes mobile, one may be justified in completing a radical course of radiation therapy and reserving surgery for salvage after recurrence.

In contrast, those patients with extensive carcinoma of the glottis or supraglottis with laryngeal stridor, requiring emergency tracheostomy, are better treated by laryngectomy, to be followed by postoperative irradiation. As can be seen in Tables 1-1 and 1-3 we have but nine patients with T_4N_0 laryngeal cancer. This precludes reaching conclusions but our preference is to deliver combined treatment, either preoperative or postoperative radiation therapy.

HYPOPHARYNX—PYRIFORM SINUS

The hypopharynx extends from the plane of the hyoid bone and the epiglottic pharyngeal fold superiorly to the plane of the lower border of the cricoid cartilage inferiorly. It surrounds the larynx and can be divided into three regions: the posterior pharyngeal wall, the pyriform sinus, and the postcricoid area. Extensive posterior pharyngeal wall tumors are considered inoperable and are rarely treated by combined surgery and radiation.[32,37,54] Postcricoid tumors are, in fact, tumors of the upper cervical esophagus and are the least common. These two areas will be excluded from this review of hypopharyngeal cancer because they are most often treated palliatively and in varying fashions.

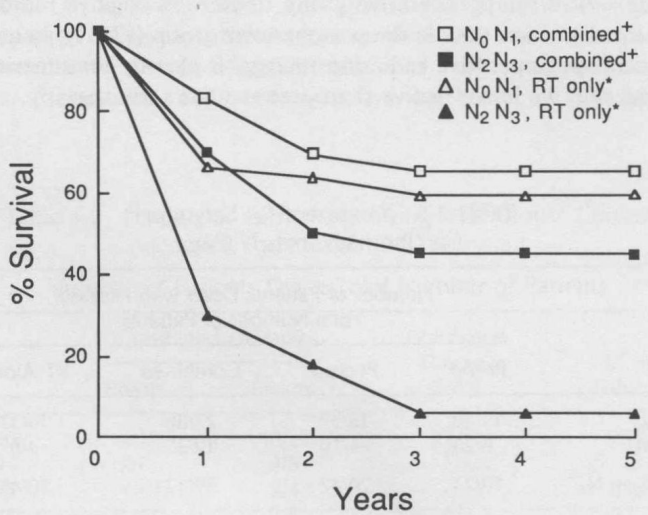

Figure 1-1. Survival versus N Stage for laryngeal carcinoma.

The pyriform sinus is the most common site of hypopharyngeal cancer and has three walls: anterior, lateral, and medial. The anterior and lateral walls are bounded by the thyrohyoid membrane and thyroid ala and the medial wall is bounded by the aryepiglottic fold and arytenoid. The apex of the pyriform sinus is bordered by the ala of the thyroid cartilage and usually extends below the true vocal cord to the level of the cricoid cartilage. More than 90 percent are squamous cell carcinoma but, in contrast to supraglottic cancers, these are almost all poorly differentiated and have a tendency to infiltrate the adjacent structures with involvement of underlying cartilage or musculature. Accordingly, most tumors are discovered in their late stage and the majority have already metastasized to the lymph nodes.

One hundred and four patients with Stages III and IV squamous cell carcinoma of the pyriform sinus were treated. There were 88 males and 16 females. Seventy-nine patients underwent combined treatment and 64 were available for evaluation, 46 in the preoperative group and 18 in the postoperative group. The remaining 25 patients were treated by radiation therapy alone and were almost all judged as "inoperable." The distribution by N stage is shown in Table 1-6. More than 70 percent of patients had positive neck nodes in all groups and an almost equal proportion of patients underwent radical neck dissection in the preoperative (38 patients) and the postoperative (16 patients) group.

The overall five-year adjusted actuarial recurrence-free survival rate was 37 percent for preoperative and 40 percent for postoperative irradiation but only 8 percent (two patients) for the irradiation alone group (Table 1-7); only two patients (T_3N_0, T_4N_0) were suitable for salvage surgery, but without success. Even for patients with an N_0 neck at diagnosis, the radiation therapy alone group did not compare well with the combined treatment groups. For N_0 patients, the preoperative radiotherapy group seems to do better than the postoperative group, 43 percent dying with disease versus 75 percent respectively. This is similar to glottic and supraglottic tumors, but the difference is not statistically significant. We recommend combined treatment with surgery and irradiation be given either pre- or postoperatively.

COMPLICATIONS

The incidence, variety, and severity of complications were similar for the glottic, supraglottic, and pyriform sinus cancer groups. Accordingly, we have combined the groups and categorized the complications as major or minor. Major complications were defined as wound healing problems that caused delay in alimentation, required unplanned second surgery, or increased the length of hospitalization beyond expected. All pharyngocutaneous fistulae were considered major complications regardless of the time of onset and the mode of closure, except for those secondary to recurrent cancer. Minor complications included wound hematoma, stitch abscess, minor wound separation, and cervical flap cellulitis. Also included

Table 1-6. Distribution by Stage for Pyriform Sinus Cancer

	T2			T3			T4			Total		
	Preop	Postop	RT ± S	Preop	Postop	RT ± S	Preop	Postop	RT ± S	Preop	Postop	RT ± S
N0				6	2	3	8	2	4	14	4	7
N1	2			3	2	2	4		2	9	2	4
N2	3	1	2	3	3	1	8	5		14	9	3
N3	3	1	2	3		3	3	2	6	9	3	11
	8	2	4	15	7	9	23	9	12	46	18	25

with minor complications were medical problems associated with surgery requiring consultation and special supportive treatment which could not be ascribed to irradiation or surgery. If two or more complications occurred, only the worst complication was counted so that each listed complication reflects one patient. Table 1-8 shows the incidence of complications according to each category; there is not much difference between preoperative and postoperative irradiation. This result is in accordance with the RTOG study.[29] The major complication rate was 14 to 21 percent for glottic and supraglottic cancer whether given pre- or postoperative irradiation; for the pyriform sinus group it was also 19 percent for preoperative irradiation but rose to 33 percent for postoperative irradiation. This is a direct consequence of the surgical procedure, pharyngectomy, as contrasted with only laryngectomy. Fistula was the most common major complication in each category. Minor complications were a little higher among the preoperative groups versus the postoperative groups, but this difference was not significant. It was our experience that once a fistula developed in the preoperative group, it took longer to heal than was true for patients not irradiated.

The incidence of complications, the difficulties attending surgery in preoperatively irradiated patients, and the results obtainable remain areas of high controversy. We believe this reflects variations in surgical and preoperative techniques as well as patient selection and irradiation variables (dose, fractionation, field size), and we are not aware of valid studies which might resolve the questions. We think this has led some groups to avoid preoperative irradiation without having given it a fair trial themselves. Although some authors suggest a higher incidence of healing problems when irradiation is given before surgery, our results do not confirm this prejudice.

Table 1-7. Proportion of Patients Dead with Pyriform Sinus Cancer According to N Stage and Treatments

	Number of Patients Dead with Disease/Total Number of Patients			
	Combined Therapy			
	Preop	Postop	Combined Total	RT + Salvage
N0	6/14	3/4	9/18	6/7*
N1	6/9	1/2	7/11	4/4
N2	9/14	5/9	14/23	2/3
N3	8/9	2/3	10/12	11/11
	29/46	11/18	40/64	23/25

*2 patients underwent salvage surgery.

CONCLUSION

Although we could not mount a prospective, randomized study, the two programs (preoperative versus postoperative irradiation) were due to a change in treatment philosophy with time. Throughout, some patients received radiation therapy as the sole treatment because they were considered medically inoperable or refused surgery; some of these patients later underwent salvage surgery after recurrence or persistence of disease. Judging "operability" and comparing patients from different institutions is almost impossible; each physician has his or her own imprecise and variable criteria. We believe that our conclusions, which are based on comparable patient groups, are reasonable rather than reflecting bias between the preoperative and postoperative programs. All patients were seen and operated by a harmoniously integrated interdisciplinary group during these 20 years.

We believe that patients should be classified as glottic, supraglottic, or hypopharyngeal, by T stage and by N stage, and according to the surgical procedure to be utilized. Having accomplished classification, we judge "operability" including all pertinent medical and psychosocial considerations. We think that N stage, N_0-N_1 versus N_2-N_3 is the great divider for all laryngeal cancer, rather than T stage. For the N_0 patient, even when T_4, both the preoperative and the postoperative treatment programs were quite effective, favoring slightly the preoperative program. Radiation treatment alone, with consideration for surgical salvage for radiation failure, is a reasonable alternative, and this may be the treatment of choice for certain patients with T_3N_0 laryngeal cancer as 30 to 50 percent of

Table 1-8. Complications

	Glottis	Supraglottis	Pyriform Sinus
Preop			
Major	8/37 (21%)	13/79 (17%)	8/46 (19%)
Minor	6/37 (16%)	13/79 (17%)	6/46 (14%)
Postop			
Major	5/35 (14%)	4/24 (17%)	7/21 (33%)
Minor	3/35 (9%)	3/24 (13%)	5/21 (5%)

these patients preserve their voice. Resolution of these alternatives will require a randomized, prospective study to avoid the bias inherent against patients judged inoperable initially and when considering salvage surgery. Despite these factors, there was no statistical difference in survival or control of tumor among these groups of our patients. Among patients with N_0-N_1 disease, only 32 percent (39/121) died of disease either locoregional and/or metastatic. However, for patients with N_2-N_3 disease, the overall control rate runs approximately 50 percent as shown in the tables for combined treatment; radiation therapy alone yields worse results and combined treatment is clearly to be preferred. With more than one half of patients with N_2-N_3 laryngeal cancer and the majority of all pyriform sinus patients failing current combined treatment programs, we must investigate better treatment methods, such as new chemotherapy regimens, altered fractionation irradiation, radiation sensitizers, and hyperthermia, if we hope to improve results.

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