INDUCTION CHEMOTHERAPY PLUS RADIATION COMPARED WITH SURGERY PLUS RADIATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER

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Abstract *Background.* We performed a prospective, randomized study in patients with previously untreated advanced (Stage III or IV) laryngeal squamous carcinoma to compare the results of induction chemotherapy followed by definitive radiation therapy with those of conventional laryngectomy and postoperative radiation.

Methods. Three hundred thirty-two patients were randomly assigned to receive either three cycles of chemotherapy (cisplatin and fluorouracil) and radiation therapy or surgery and radiation therapy. The clinical tumor response was assessed after two cycles of chemotherapy, and patients with a response received a third cycle followed by definitive radiation therapy (6600 to 7600 cGy). Patients in whom there was no tumor response or who had locally recurrent cancers after chemotherapy and radiation therapy underwent salvage laryngectomy.

Results. After two cycles of chemotherapy, the clinical tumor response was complete in 31 percent of the patients and partial in 54 percent. After a median follow-up of 33 months, the estimated 2-year survival was 68 percent (95 percent confidence interval, 60 to 76 percent) for both treatment groups (P = 0.9846). Patterns of recurrence differed significantly between the two groups, with more local recurrences (P = 0.0005) and fewer distant metastases (P = 0.016) in the chemotherapy group than in the surgery group. A total of 59 patients in the chemotherapy group (36 percent) required total laryngectomy. The larynx was preserved in 64 percent of the patients overall and 64 percent of the patients who were alive and free of disease.

Conclusions. These preliminary results suggest a new role for chemotherapy in patients with advanced laryngeal cancer and indicate that a treatment strategy involving induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high percentage of patients, without compromising overall survival. (N Engl J Med 1991; 324:1685-90.)

CANCER of the larynx affects more than 12,000 people each year and results in an estimated 3700 deaths.[1] The conventional treatment of patients with advanced (Stage III or IV) squamous carcinoma of the larynx consists of total laryngectomy or a combination of laryngectomy and postoperative radiation therapy; this treatment results in overall five-year survival rates ranging from 0 to 50 percent.[2-4] Because laryngectomy results in substantial functional morbidity, including the loss of the natural voice, alterations in deglutition, and the creation of a permanent tracheostoma in the neck, alternative forms of treatment have been developed.[5,6] In selected patients with moderately advanced cancers (T3N0), partial laryngeal resections that spare vocal function[7-9] or primary radiation therapy[10-13] achieve survival rates comparable to those obtained with total laryngectomy, permitting preservation of the larynx in 40 to 70 percent of these patients. For patients with more advanced disease, however, treatment by radiation alone, with salvage by surgery, if necessary, results in lower survival rates.[9-13]

The recent addition of chemotherapy before surgery or radiation in patients with advanced cancer of the head and neck[14-20] has resulted in high rates of complete tumor regression that are associated with prolonged survival[16-18,21,22] and that predict a favorable response to subsequent radiation therapy.[23-26] Randomized trials, however, have failed to demonstrate significantly enhanced survival with the use of induction chemotherapy.[14,15,19,20,27] Several pilot studies have indicated the feasibility of avoiding surgical resection in selected patients who have complete tumor regression after induction chemotherapy and who then receive definitive radiation therapy.[28-30] With such an approach, prolonged survival with preservation of the larynx has been reported for patients with cancer of the larynx or hypopharynx.[28,31]

In 1985, the Cooperative Studies Program of the Department of Veterans Affairs began a multi-institutional, randomized clinical trial to determine whether induction chemotherapy and definitive radiation, with laryngectomy reserved for salvage, represented a better initial treatment approach for patients with Stage III or IV laryngeal cancer than total laryngectomy and postoperative radiation therapy. Because of the potential importance of larynx preservation in the management of laryngeal cancer, we present an interim analysis of the survival results of this study.

METHODS

Eligibility of Patients

All patients had biopsy-proved, previously untreated Stage III or IV squamous carcinoma of the larynx, according to the 1985 classi-

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fication system of the American Joint Committee on Cancer. Patients with T1N1 carcinomas, unresectable cancers, distant metastases, previous radiation therapy to the head or neck, or previous cancer were excluded. The laboratory criteria required before treatment included a score for performance status above 50 points on the Karnofsky scale,[32] a creatinine clearance ≥1 ml per second, a white-cell count ≥4000 per cubic millimeter, a platelet count ≥100,000 per cubic millimeter, and adequate auditory, nutritional, pulmonary, and cardiac status. All patients underwent pretreatment endoscopic tumor staging, tumor measurement, and standardized assessment of speech and voice. Each patient gave written informed consent. The study design and informed-consent procedures were reviewed and approved by the investigational review board for the protection of human subjects at each institution. Eligible patients were randomly assigned to one of two treatment groups and stratified according to Karnofsky score, tumor stage (III vs. IV), regional nodal involvement (N0 or N1 vs. N2 or N3), and primary tumor site (glottic vs. supraglottic).

Treatment Regimens

Chemotherapy

Induction chemotherapy consisted of cisplatin (100 mg per square meter of body-surface area) given as a rapid intravenous infusion, followed by a continuous 24-hour intravenous infusion of fluorouracil (1000 mg per square meter per day) for five days. Chemotherapy was repeated on days 22 and 43. The clinical tumor response was assessed by physical examination and indirect laryngoscopy 18 to 21 days after the start of the second cycle of chemotherapy. A complete response was defined as the complete disappearance of all clinically evident tumor. A partial response was defined as a 50 percent reduction in the sum of the product of the longest dimension and its perpendicular for each tumor, as compared with the initial tumor dimensions. The responses of the primary tumor and any apparent neck nodes were graded separately. The response of the primary tumor determined the patient's eligibility to proceed with radiation. Patients with at least a partial response at the primary tumor site and no progression of any neck adenopathy received a third cycle of chemotherapy and definitive radiation. Patients without at least a partial response in the larynx and those with any evidence of disease progression (including neck disease) underwent immediate surgical resection and postoperative radiation therapy. After the induction chemotherapy was completed, a direct laryngoscopy, a tumor assessment, and a biopsy of the primary tumor were performed to obtain histologic confirmation of the response.

Radiation Therapy

All the patients received radiation therapy, either after chemotherapy or postoperatively. Definitive radiation therapy consisted of 6600 to 7600 cGy to the primary tumor site. The doses to the nodes varied according to the initial nodal size: 5000 cGy for nodes with no involvement (N0), 6600 cGy for nodes measuring less than 2 cm in diameter, 7000 cGy for nodes 2 to 4 cm in diameter, and 7500 cGy for nodes more than 4 cm in diameter. All areas presumed to be at risk for microscopic disease received at least 5000 to 5040 cGy. The dose to the spinal cord was kept below 4500 cGy. Five daily fractions of 180 to 200 cGy per field were used for all fields. Twelve weeks after the completion of radiation therapy, the tumor response was assessed again by direct laryngoscopy. Patients with persistent disease in the larynx underwent salvage laryngectomy, whereas patients with persistent neck disease but whose primary tumor was controlled underwent neck dissection alone.

The patients randomly assigned to initial surgical resection received postoperative radiation therapy. Tissue volumes assumed to be at normal risk for microscopic disease received 5000 to 5040 cGy. Volumes at high risk for a local recurrence received the initial 5000 to 5040 cGy plus an additional 1000 cGy. Target volumes presumed to contain residual disease received 5000 to 5040 cGy plus an additional 1500 to 2380 cGy.

Surgery

The extent of surgical resection was dictated by the extent of the tumor at the initial evaluation. Classic wide-field total laryngectomy was performed for all primary tumors, except in rare instances in which a supraglottic primary tumor could be resected adequately with horizontal partial laryngectomy. Regional neck dissections were performed in all surgical patients except those with T3N0 tumors or those with midline supraglottic T4N0 tumors for whom it could not be determined which side of the neck was chiefly at risk for occult metastases. In all patients who had salvage surgery, the presence of residual primary tumor was documented by biopsy. All the patients were followed up and examined on a monthly basis for the first year after treatment, every two months for the second year, and every three months thereafter.

Statistical Analysis

The statistical analyses of patients' survival and disease-free interval were based on a comparison of Kaplan–Meier curves by the log-rank test. Survival and disease-free interval were measured from the date of randomization, with a disease-free interval of 0 assigned to patients who were never rendered disease-free. All randomized patients were included in the analysis. The analysis of patterns of recurrence was based on the patients who were rendered disease-free, including those who were disease-free after a salvage laryngectomy that was performed because of a lack of response to induction chemotherapy. The chi-square test and Student's t-test were used for the additional analysis of categorical and continuous variables. All P values correspond to two-sided testing for significance.

Results

Population of Patients

A total of 332 eligible patients were enrolled in the study and were assigned in equal numbers to induction chemotherapy and radiation therapy (the chemotherapy group) or surgery and radiation therapy (the surgery group). The median follow-up of all patients was 33 months (range, 11 to 62). Only seven patients (2 percent) were lost to follow-up after randomization, at times ranging from 10 to 33 months. Data on these patients were censored from the survival analysis at the time of the last follow-up.

There were no significant differences between the treatment groups with respect to age, sex, or known prognostic factors, including performance status, T class, N class, tumor stage, tumor site, tumor grade, cartilage involvement, or vocal-cord fixation (Table 1). Most patients had supraglottic cancers and Stage III tumors. Eighty percent were white. Ninety-nine percent used tobacco, and 85 percent consumed alcohol. The median age was 62 years (range, 24 to 79). A total of 321 patients were men, and 11 were women.

Toxicity

Eight patients (2 percent) died during treatment (five in the chemotherapy group and three in the surgery group). Three of these deaths were due to surgical complications, two to tumor, and two to unrelated causes. Only one death (septicemia in a patient with leukopenia) was thought to be directly related to chemotherapy. Twelve patients had toxicity that necessitated the discontinuation of chemotherapy. Overall, the frequency and types of surgical complications were similar between the treatment groups. However, the incidence of surgical complications tended to be slightly higher for salvage surgery performed after radiation than for salvage surgery after chemotherapy alone. The frequency and severity of toxic effects due to radiation therapy were similar in both treatment groups with respect to skin toxicity, dehydration, ane-

mia, and pain. The rate of grade 2 mucositis (patchy membranous mucositis and severe laryngitis) was slightly higher in the chemotherapy group (38 percent) than in the surgery group (24 percent).

Tumor Response to Chemotherapy

Complete clinical regression of the primary tumor was seen in 31 percent of the patients after two cycles of chemotherapy. A partial response was seen in 54 percent. Fourteen patients who had either a partial response or a complete response after only two cycles of chemotherapy received definitive radiation because of toxicity or because they refused further chemotherapy. A total of 117 patients went on to receive a third cycle of chemotherapy. Among these patients, a clinical complete response of the primary tumor was seen in 49 percent, and a partial response in 49 percent. There was a complete response of regional nodes in 53 percent, and a partial response in 33 percent. The combined rates of partial and complete response in the primary tumor and the involved regional nodes after two or three cycles of chemotherapy were 85 percent and 98 percent, respectively. The rate of tumor response did not differ significantly according to tumor site, tumor stage, T class, or initial tumor dimensions. A biopsy of the primary tumor site was performed after the completion of chemotherapy in 103 patients. Histologically confirmed complete tumor regression occurred in 88 percent of the patients with a clinical complete response and 45 percent of those with a clinical partial response. The overall rate of histologically confirmed complete responses was 64 percent.

Table 1. Characteristics of the Patients According to Treatment Assignment.

Characteristic	Surgery	Chemotherapy	All
No. of patients	166	166	332
Stage			
III	95	93	188
IV	71	73	144
Tumor class			
T1,2	15	16	31
T3	109	107	216
T4	42	43	85
Node class			
N0	94	86	180
N1	26	34	60
N2	21	16	37
N3	25	30	55
Site			
Glottic	63	61	124
Supraglottic	103	105	208
Cartilage invasion	13	17	30
Fixed vocal cords	98	90	188
Performance status (Karnofsky score)			
<80	40	39	79
≥80	126	127	253

Overall Survival

A total of 123 patients have died, 58 in the surgery group (35 percent) and 65 in the chemotherapy group (39 percent). The most frequent cause of death was cancer (Table 2). The distribution of disease status at the time of death (i.e., local, regional, or distant disease) was similar in the two groups. Rates of death from other causes were also similar in the treatment groups.

Table 2. Causes of Death, According to Treatment Assignment.

Cause	Surgery (N = 166)	Chemotherapy (N = 166)
	no. of patients (%)	
Cancer	38 (23)	42 (25)
Complication of therapy	4 (2)	4 (2)
Other	14 (8)	13 (8)
Unknown	2 (1)	6 (4)
All	58 (35)	65 (39)

The estimated two-year survival was 68 percent (95 percent confidence interval, 60 to 75 percent) for the surgery group and 68 percent (95 percent confidence interval, 60 to 76 percent) for the chemotherapy group ($P = 0.9846$) (Fig. 1). No significant differences in actuarial survival were found between treatments when the patients were grouped according to tumor stage or site. Survival rates were similar for the patients who responded to chemotherapy and those who did not ($P = 0.98$) and when these two groups were compared with the patients assigned to primary surgery ($P = 0.74$). The survival curve for the patients who had a histologically confirmed complete response after three cycles of chemotherapy did not differ significantly from the curve for the surgery group. Disease-free survival tended to be shorter in the chemotherapy group ($P = 0.1195$) (Fig. 2) than in the surgery group, but the difference was not statistically significant.

Patterns of Relapse

Overall rates of recurrence did not differ significantly between groups, but there were differences in the patterns of tumor relapse (Table 3). Six patients in

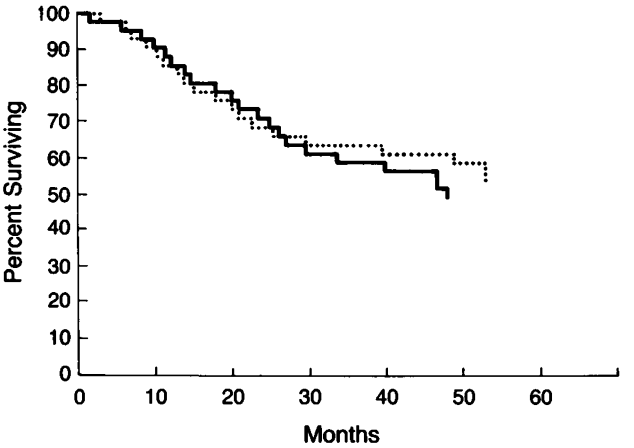

Figure 1. Overall Survival of 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

Survival rates at two years were 68 percent for both groups ($P = 0.9846$). The median follow-up was 33 months.

the surgery group and 15 patients in the chemotherapy group had persistent tumor and were not rendered disease-free (P = 0.042). Recurrences at the site of the primary tumor were less frequent in the surgery group (2 percent) than in the chemotherapy group (12 percent) (P = 0.001). Rates of recurrence in regional neck nodes were similar in the groups, but distant metastases occurred in 17 percent of the patients in the surgery group as compared with 11 percent in the chemotherapy group (P = 0.001). Rates of second primary cancers were also higher in the surgery group (6 percent) than in the chemotherapy group (2 percent) (P = 0.048).

Preservation of the Larynx

The larynx was preserved in 107 patients assigned to induction chemotherapy (64 percent). Fifty-nine patients underwent total laryngectomy, 30 before definitive radiation therapy and 29 after radiation. Eighteen of the 29 underwent laryngectomy after a planned laryngoscopy and a biopsy confirmed the presence of persistent tumor 12 weeks after the completion of radiation. One patient required only partial (supraglottic) laryngectomy. Ten patients underwent salvage neck dissection alone, with preservation of the larynx. The remaining patients were considered disease-free and were followed for any recurrence. Late salvage laryngectomy for recurrent cancer was required in 11 additional patients (7 percent) after intervals ranging from 5 to 40 months. Over 80 percent of the late salvages (9 of 11) occurred in the first year after treatment. Thus, the rate of salvage laryngectomy for persistent disease before radiation therapy or within three months afterward was 29 percent (48 of 166 patients), and the rate of salvage laryngectomy for later recurrent disease was 7 percent (11 of 166).

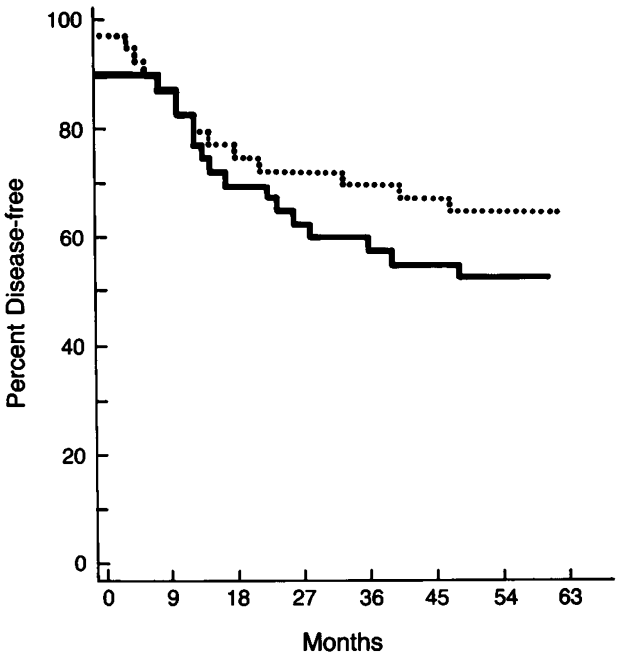

Figure 2. Disease-free Interval for 332 Patients Randomly Assigned to Induction Chemotherapy and Radiation Therapy (Solid Line) or Conventional Laryngectomy and Postoperative Radiation (Dotted Line).

The disease-free interval survival was shorter in the chemotherapy group, but the difference was not statistically significant (P = 0.1195).

Table 3. Patterns of Tumor Recurrence According to Treatment Group.

Site of Recurrence	Surgery (N = 166)	Chemotherapy (N = 166)
	no. of patients (%)	
Primary*	4 (2)	20 (12)
Regional	9 (5)	14 (8)
Distant	29 (17)	18 (11)
All	42 (25)	52 (31)

*Includes recurrences with either positive or negative nodes.

When the patients were grouped according to initial tumor characteristics, salvage laryngectomy was required more often in those with glottic cancers (43 percent) than in those with supraglottic cancers (31 percent), in those with fixed vocal cords (41 percent) than in those with mobile vocal cords (29 percent), and in those with gross invasion of cartilage (41 percent) than in those with no involvement of cartilage (35 percent), but these differences were not statistically significant (P = 0.146, 0.103, and 0.608, respectively). Salvage laryngectomy was required, however, in 44 percent of the patients with Stage IV cancers as compared with 29 percent of the patients with Stage III cancers (P = 0.048), and in 56 percent of the patients with T4 cancers as compared with 29 percent of the patients with smaller primary tumors (P = 0.001).

For all 166 patients assigned to the chemotherapy group, the estimated rate of larynx preservation after two years was 66 percent. Of these patients, 101 remain alive at this writing with no evidence of disease, 65 of whom have a functioning larynx (39 percent) and 36 of whom have had total laryngectomy (22 percent). Thus, of the surviving patients treated successfully, 64 percent (65 of 101) retained a functioning larynx. Of the 65 patients assigned to induction chemotherapy who died, 42 (65 percent) retained their larynx.

Discussion

A major finding of the current study was that the larynx could be successfully preserved in 64 percent of the patients randomly assigned to induction chemotherapy combined with definitive radiation therapy. This result was achieved without reducing the estimated two-year survival rate, as compared with the rate for the conventional treatment of laryngectomy and postoperative radiation therapy.

Because of the substantial impact that loss of the larynx has on the quality of life, interest in its preservation in advanced laryngeal cancer is not new.[6] In an attempt to preserve the larynx, definitive radiation has

been used in selected patients, with laryngectomy reserved for patients with cancers that recur after radiation, but overall rates of cure have generally been reduced.[6,11-13,33] The largest studies found three-year rates of disease-free survival of 20 to 40 percent for patients with advanced Stage III or IV cancers, with larynx preservation in less than half the cured patients.[11-13,33] The best results with this approach have been reported from Canada and Europe. In 89 patients with T3N0 glottic carcinoma, Harwood et al. reported a 49 percent five-year survival rate and a 65 percent rate of larynx preservation in the cured patients.[34] In 265 patients with supraglottic T3N0 or T4N0 cancers, Harwood et al. also reported a five-year survival of 51 percent, with larynx preservation in 64 percent of the survivors.[35] Croll et al. reported similar results in 55 selected patients with T3 or T4 cancer without invasion of the cartilage or regional metastases; there was a 52 percent cure rate, with larynx preservation in 65 percent of all the patients and 73 percent of the survivors.[36]

Similar results were achieved in the current study, although generally in patients with more advanced disease. Nearly two thirds of these patients had supraglottic primary tumors, and nearly half had advanced primary cancers or advanced nodal disease. Such patients are not typically considered good candidates for primary radiation with surgical salvage, because of the poor cure rates attained with that therapeutic approach.[37] The high rate of larynx preservation achieved in these patients with advanced cancers suggests that initial chemotherapy enhanced the effectiveness of definitive radiation therapy — a result that argues for the adoption of this new treatment strategy. Until, however, radiation therapy alone is compared directly with induction chemotherapy and radiation in similarly staged patients, the precise contribution of chemotherapy remains uncertain, particularly in patients with more limited laryngeal cancers. Furthermore, because the rates of tumor control and survival with radiation therapy are higher for laryngeal cancers than for cancers of the oral cavity, oropharynx, or hypopharynx, our results cannot be extrapolated to patients with nonlaryngeal cancers.

No significant differences in duration of survival were detected between the two treatment groups when the patients were grouped and analyzed according to tumor site (glottic vs. supraglottic), tumor stage (Stage III vs. Stage IV), or response to chemotherapy. The last of these results is of interest because it suggests that in the case of laryngeal cancer, a lack of substantial tumor response to induction chemotherapy was not associated with reduced survival, as has been suggested in smaller retrospective studies of patients with head and neck cancer arising from other sites. This difference may be due to the surgeon's ability to obtain wide, oncologically safe surgical margins with standard wide-field laryngectomy. For other tumor sites, determining adequate margins on the basis of the extent of the original tumor can be difficult after the tumor has been reduced by preoperative chemotherapy.

Local recurrences were significantly more common and distant metastases less frequent in the chemotherapy group. The local-relapse rate was similar to historical rates of local recurrence after radiation alone in patients with more limited (T3) glottic primary tumors (40 to 70 percent)[10,33,36,37] and for T3 supraglottic cancers (30 to 40 percent).[34,38,39] Over 70 percent of the local and regional recurrences in advanced laryngeal cancer are detected in the first year after therapy,[10,13,40] and nearly all after two years.[36] With a median follow-up of 33 months, substantial changes in the rates of local recurrence are not expected.

The high rate of local recurrence indicates that more effective local therapy is needed to improve rates of larynx preservation. Chemotherapy regimens that achieve higher rates of complete response, newer schemes of radiation fractionation, or other combinations of radiation and chemotherapy may prove beneficial in this regard. Whether the reduction seen in distant disease was due to an effect of chemotherapy on microscopic disseminated disease or to a delay in the appearance of distant metastases is unknown. A longer period of follow-up is required to determine the ultimate effect of induction chemotherapy on distant metastases and second primary cancers.

The successful application of this new approach to treatment requires a high level of skill and cooperation among the various disciplines involved. Adequate compliance from patients, careful documentation of the extent and response of the tumor, and appropriate timing and frequency of surveillance laryngoscopy are essential to the successful treatment of these patients. Further improvement in overall rates of cure in advanced laryngeal cancer will also require developing adjuvant regimens specifically to address the problems of distant metastases and second primary cancers.

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References

1. Silverberg E, Lubera JA. Cancer statistics, 1988. CA 1988; 38:5-22.
2. Shah JP, Tollefsen HR. Epidermoid carcinoma of the supraglottic larynx: role of neck dissection in initial surgical treatment. Am J Surg 1974; 128:494-8.
3. Hawkins NV. The treatment of glottic carcinoma: an analysis of 800 cases. Laryngoscope 1975; 85:1485-93.
4. Jesse RH. The evaluation of treatment of patients with extensive squamous cancer of the vocal cords. Laryngoscope 1975; 85:1424-9.
5. Harwood AR, Rawlinson E. The quality of life of patients following treatment for advanced laryngeal cancer. Int J Radiat Oncol Biol Phys 1983; 9:335-8.
6. McNeil BJ, Weichselbaum R, Pauker SG. Speech and survival: tradeoffs between quality and quantity of life in laryngeal cancer. N Engl J Med 1981; 305:982-7.
7. Ogura JH, Session DG, Spector GJ. Conservation surgery for epidermoid carcinoma of the supraglottic larynx. Laryngoscope 1975; 85: 1801-15.
8. Som ML. Cordal cancer with extension to vocal process. Laryngoscope 1975; 85:1298-307.
9. Harris HS Jr, Watson FR, Spratt JS Jr. Carcinoma of the larynx: a retrospective study of 144 cases. Am J Surg 1969; 118:674-84.
10. Harwood AR, Bryce DP, Rider WD. Management of T_3 glottic cancer. Arch Otolaryngol 1980; 106:697-9.
11. DeSanto LW. T_3 glottic cancer: options and consequences of the options. Laryngoscope 1984; 94:1311-5.
12. Kazem I, van den Broek P. Planned preoperative radiation therapy vs. definitive radiotherapy for advanced laryngeal carcinoma. Laryngoscope 1984; 94:1355-8.
13. Harwood AR, ENT Group. The management of advanced supraglottic carcinoma by delayed combined therapy. Int J Radiat Oncol Biol Phys 1982; 8:Suppl 1:101-2. abstract.
14. Adjuvant chemotherapy for advanced head and neck squamous carcinoma: final report of the Head and Neck Contracts Program. Cancer 1987; 60:301-11.
15. Schuller DE, Metch B, Stein DW, Mattox D, McCracken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. Laryngoscope 1988; 98:1205-11.
16. Thyss A, Schneider M, Santini J, et al. Induction chemotherapy with cisplatinum and 5-fluorouracil for squamous cell carcinoma of the head and neck. Br J Cancer 1986; 54:755-60.
17. Ervin TJ, Clark JR, Weichselbaum RR, et al. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. J Clin Oncol 1987; 5:10-20.
18. Price LA, Hill BT, Macrae K. Increased survival in stage III and IV squamous cell carcinomas of the head and neck using an initial 24-hour combination chemotherapy protocol without cisplatin: 6 year follow-up. In: Wagener DJT, Blijham GH, Smeets JBE, Wils JA, eds. Primary chemotherapy in cancer medicine. Vol. 201 of Progress in clinical and biological research. New York: Alan R. Liss, 1985:159-67.
19. Holoye PY, Grossman TW, Toohill RJ, et al. Randomized study of adjuvant chemotherapy for head and neck cancer. Otolaryngol Head Neck Surg 1985; 93:712-7.
20. Taylor SG IV, Applebaum E, Showel JL, et al. A randomized trial of adjuvant chemotherapy in head and neck cancer. J Clin Oncol 1985; 3:672-9.
21. Norris CM Jr, Clark JR, Frei E, et al. Pathology of surgery after induction chemotherapy: an analysis of resectability and locoregional control. Laryngoscope 1986; 96:292-302.
22. Kies MS, Gordon LI, Hauck WW, et al. Analysis of complete responders after initial treatment with chemotherapy in head and neck cancer. Otolaryngol Head Neck Surg 1985; 93:199-205.
23. Ensley JF, Jacobs JR, Weaver A, et al. Correlation between response to cisplatinum-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. Cancer 1984; 54:811-4.
24. Hong WK, O'Donoghue GM, Sheetz S, et al. Sequential response patterns to chemotherapy and radiotherapy in head and neck cancer: potential impact of treatment in advanced laryngeal cancer. In: Wagener DJT, Blijham GH, Smeets JBE, Wils JA, eds. Primary chemotherapy in cancer medicine. Vol. 201 of Progress in clinical and biological research. New York: Alan R. Liss, 1985:191-7.
25. Schuller DE, Wilson HE, Smith RE, Batley F, James AD. Preoperative reductive chemotherapy for locally advanced carcinoma of the oral cavity, oropharynx and hypopharynx. Cancer 1983; 51:15-9.
26. Price LA, MacRae I, Hill BT. Integration of safe initial combination chemotherapy (without cisplatin) with a high response rate and local therapy for untreated stage III and IV epidermoid cancer of the head and neck: 5-year survival data. Cancer Treat Rep 1983; 67:535-9.
27. Stell PM, Dalby JE, Strickland P, Fraser JG, Bradley PJ, Flood LM. Sequential chemotherapy and radiotherapy in advanced head and neck cancer. Clin Radiol 1983; 34:463-7.
28. Karp D, Carter R, Vaughan C, et al. Voice preservation using induction chemotherapy plus radiation therapy as an alternative to laryngectomy in advanced head and neck cancer: long term follow-up. Proc Am Soc Clin Oncol 1988; 7:152. abstract.
29. Jacobs C, Goffinet DR, Goffinet L, Kohler M, Fee WE. Chemotherapy as a substitute for surgery in the treatment of advanced resectable head and neck cancer: a report from the Northern California Oncology Group. Cancer 1987; 60:1178-83.
30. Urba S, Forastiere AA, Wolf GT, et al. Intensive continuous infusion high dose cisplatin, 5-fluorouracil, and mitoguazone induction chemotherapy for advanced head and neck cancer. Proc Am Soc Clin Oncol 1989; 8:172. abstract.
31. Demard F, Chauvel P, Santini J, Vallicioni J, Thyss A, Schneider M. Response to chemotherapy as justification for modification of the therapeutic strategy for pharyngolaryngeal carcinomas. Head Neck 1990; 12:225-31.
32. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutics in cancer. In: MacLeod CM, ed. Evaluation of chemotherapeutic agents. New York: Columbia Press, 1949:191-205.
33. Razack MS, Maipang T, Sako K, Bakamjian V, Shedd DP. Management of advanced glottic carcinomas. Am J Surg 1989; 158:318-20.
34. Harwood AR, Hawkins NV, Beale FA, Rider WD, Bryce DP. Management of advanced glottic cancer: a 10 year review of the Toronto experience. Int J Radiat Oncol Biol Phys 1979; 5:899-904.
35. Harwood AR, Beale FA, Cummings BJ, et al. Supraglottic laryngeal carcinoma: an analysis of dose-time-volume factors in 410 patients. Int J Radiat Oncol Biol Phys 1983; 9:311-9.
36. Croll GA, Gerritsen GJ, Tiwari RM, Snow GB. Primary radiotherapy with surgery in reserve for advanced laryngeal carcinoma: results and complications. Eur J Surg Oncol 1989; 15:350-6.
37. Meredith APDE, Randall CJ, Shaw HJ. Advanced laryngeal cancer: a management perspective. J Laryngol Otol 1987; 101:1046-54.
38. Fletcher GH, Lindberg RD, Hamberger A, Horiot JC. Reasons for irradiation failure in squamous cell carcinoma of the larynx. Laryngoscope 1975; 85:987-1003.
39. Goepfert H, Jesse RH, Fletcher GH, Hamberger A. Optimal treatment for technically resectable squamous cell carcinoma of the supraglottic larynx. Laryngoscope 1975; 85:14-32.
40. Eiband JD, Elias EG, Suter CM, Gray WC, Didolkar MS. Prognostic factors in squamous cell carcinoma of the larynx. Am J Surg 1989; 158:314-7.