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Larynx preservation after initial non-cisplatin containing combination chemotherapy plus radiotherapy, as opposed to surgical intervention with or without radiotherapy in previously untreated advanced head and neck cancer: final analysis after 12 years follow-up

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Abstract

After a median follow-up of 12 years, median overall survival of 73 patients with advanced squamous cell carcinoma of the larynx was 65 months. The 61 per cent of patients responding to two courses of initial schedule A combination chemotherapy, not including cisplatin, and the 81 per cent of patients achieving a final complete remission after definitive local therapy, had median overall survival figures of 95 and 97 months respectively. Overall survival and relapse-free survival in 51 patients treated with radiotherapy only with larynx preservation, were not significantly different from the 21 patients who completed their surgery with pre- or post-operative radiotherapy: median overall figures were 71 versus 65 months. These data add weight to our proposal that use of initial combination chemotherapy followed by radiotherapy may eliminate the need for radical surgery, so preserving the larynx in patients with advanced disease, and provides evidence of some long-term benefit with 32 per cent of this entire group surviving 12 years.

Key words: Laryngeal neoplasms; Carcinoma, squamous cell; Laryngectomy; Radiotherapy; Antineoplastic agents, combined

Introduction

In 1975 we initiated a pilot study at the Royal Marsden Hospital, aimed at determining whether the initial use of two courses of a non-cisplatin combination chemotherapy protocol prior to the local treatment of advanced squamous cell carcinoma of the head and neck, altered the time to relapse. In a detailed analysis of 208 patients treated in the following seven years, we showed that response to initial chemotherapy was not automatically a favourable prognostic sign and that survival was markedly influenced by tumour site (Hill *et al.*, 1986). The best survival figures were noted in patients with either nasopharyngeal or laryngeal tumours. Detailed subset analysis of this latter subgroup of 73 patients with laryngeal carcinomas presented here, updating and extending our earlier meeting presentation (Hill *et al.*, 1988), has served to identify significant predictive factors associated with increased final complete remission rates and increased survival. Of major significance, however, is the finding that even after 12 years of follow-up, survival and relapse-free survival figures in patients receiving radiotherapy without surgery, were not significantly different from those patients who underwent total laryngectomies plus post-operative radiotherapy.

These retrospective analyses suggested that initial chemotherapy followed by definitive radiotherapy may eliminate the need for radical surgery, so preserving the larynx in patients with advanced disease. This study, and similar pilot studies from a number of groups (Pfister *et al.*, 1986; Jacobs *et al.*, 1987; Hill and Price, 1988; Karp *et al.*, 1988; Vikram *et al.*, 1988), provided the impetus for the large prospective, randomized study comparing induction chemotherapy plus radiation with surgery plus radiation in patients with advanced laryngeal cancers organized by the Department of Veterans Affairs Laryngeal Cancer Study Group. Interim analysis of the survival results of this study were presented recently (Department of Veterans Affairs Laryngeal Cancer Study Group, 1991) and appear to confirm that induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high percentage of patients without compromising overall survival.

Patients and methods

Seventy-three patients with advanced, histologically-proven, previously untreated squamous cell carcinoma of the larynx, treated between January 1975 and June 1982 at the Royal Marsden Hospital, London, were eligible for these retrospective analyses. The majority of patients

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TABLE I

PATIENT CHARACTERISTICS AND RESPONSE RATES TO INITIAL CHEMOTHERAPY AND FOLLOWING DEFINITIVE LOCAL THERAPY

Variable	Patient nos.	Response to initial chemotherapy R (%)	NR	NA	Final response rate after local therapy CR (%)	RD	NA
No. of patients	73	41 (61%)	26	6	58 (81%)	14	1
Age (years)							
<60	37	18 (56%)	14	5	29 (78%)	8	0
≥60	36	24 (69%)	11	1	28 (80%)	7	1
Sex							
Male	61	38 (66%)	20	3	49 (80%)	12	0
Female	12	3 (33%)	6	3	9 (82%)	2	1
Site							
Supraglottic	36	17 (55%)	14	5	25 (71%)	10	1
Glottic	30	19 (66%)	10	1	27 (90%)	3	0
Transglottic	5	3 (60%)	2	0	4 (80%)	1	0
Subglottic	2	2	0	0	2	0	0
Stage							
II	22	15 (64%)	6	1	19 (90%)	2	1
III	34	17 (57%)	12	5	28 (85%)	5	1
IV	17	9 (53%)	8	0	9 (53%)	8	0
T status							
T_1	3	2	0	1	2	0	1
T_2	27	15 (60%)	10	2	23 (85%)	4	0
T_3	34	19 (61%)	12	3	27 (79%)	7	0
T_4	9	5 (56%)	4	0	6 (67%)	3	0
N status							
N_0	48	27 (63%)	16	5	42 (88%)	6	0
N_1	15	8 (57%)	6	1	11 (79%)	3	1
N_2	2	2	0	0	0	2	0
N_3	8	4 (50%)	4	0	4 (50%)	4	0
Histologic grade							
Well-differentiated SCC	16	10 (77%)	3	3	13 (81%)	3	0
Mod-differentiated SCC	10	6 (67%)	3	1	6 (67%)	3	1
Poorly-differentiated SCC	34	18 (54%)	15	1	28 (82%)	6	0
Undifferentiated	4	8	2	1	3	1	0
SCC–no other details	9	6 (67%)	3	0	7 (78%)	2	0

R = responder; NR = non-responder; NA = not assessed; diff = differentiated; CR = complete response; RD = residual disease; SCC = squamous cell carcinoma.

were male (84 per cent) with an age range of 37–76 (median 59 years). Patient characteristics are listed in Table I. The 30 per cent of patients with late stage II tumours (T_2N_0) were considered 'bad risk', for example because of tumour extension to an adjacent site, or the involvement of two sites.

Details of the non-cisplatin containing combination chemotherapy protocol termed Schedule A have been provided earlier (Price and Hill, 1977; Hill *et al.*, 1986). In brief, patients received a combination of vincristine, bleomycin, methotrexate and 5-fluorouracil, together with hydrocortisone over a period of 24 hours followed by a standard folinic acid rescue. The patients were given two courses of Schedule A chemotherapy as initial treatment on days 1 and 14. On day 28, patients were assessed for chemotherapy response and 'curative' local treatment was initiated. Radiotherapy only was administered to 51 patients who received approximately 65 Gy given over 6–7 weeks as 2 Gy fractions daily for five days per week, as detailed earlier (Price *et al.*, 1983). Fourteen patients had similar radiotherapy, but to a total dose of only 40 Gy, and then went onto surgery, while seven patients electively had total laryngectomies followed by post-operative radiotherapy.

Standard definitions of response were used (see Hill *et al.*, 1986). Response to initial chemotherapy was assessed in 67 patients. Six exceptions were due to inadequate tumour measurements in three patients, surgery was commenced after only one course of chemotherapy in two patients, and one patient died following a chemotherapy protocol violation (see below). Final complete response rate after local therapy was assessed in 72 patients. Response rates were compared using the chi-squared test. Survival was calculated by a product-limit and compared using the Mantel test. The Cox regression model was used in multivariate analysis.

Results

Response to initial chemotherapy

Of the 67 patients assessed for response to two courses of initial Schedule A chemotherapy, 41 (61 per cent) achieved at least a partial response and 26 were classed as non-responders, although six of these had a minimal 20–30 per cent response. Full details of the response rates to initial chemotherapy are provided in Table I. This overall data set was used to attempt to identify prognostic factors for chemotherapy response by logistic regression. Site, stage, T and N classification, age, sex and histologic grade were tested and none was predictive of chemotherapy response.

Toxicities

Provided the standard medical precautions detailed earlier (Price and Hill, 1982) were always observed, the administration of schedule A chemotherapy was associated with minimal toxicity and full patient compliance.

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TABLE II
INCIDENCE OF SIDE EFFECTS FROM 149 TREATMENT CYCLES OF SCHEDULE A CHEMOTHERAPY GIVEN TO 73 ELIGIBLE PATIENTS

Side effects	No. of patients
Myelosuppression:	
wbc nadir 2500–2000/mm^3	1
<2000/mm^3	1*
Mucositis (no intubation)	5 (7%)
Nephrotoxicity	0
Peripheral neuropathy (mild)	3 (4%)
Pulmonary (chest pains)	1
Cardiovascular (atrial fibrillation)	1
Skin rash (mild—7: severe—1)	8 (14%)
Alopecia (mild)	2 (3%)
Nausea and vomiting	6 (8%)
Malaise or lethargy	5 (7%)
Constipation	2 (3%)
Deaths (protocol violation)	1*

*Refers to the same patient.

Forty-six patients experienced no side-effects at all and details of those reported in the remaining 27 patients are provided in Table II. There was one treatment-related death resulting from a protocol violation, as reported earlier (Hill *et al.*, 1988). This patient with known impaired renal function (creatinine clearance of 70 ml/min) did not receive a prolonged folinic acid rescue.

Response to local therapy

Following completion of local therapy, patients were classified as being either in complete clinical remission or with residual disease present. Details of the final response rates achieved after local therapy are provided in Table I. The overall final clinical complete remission rate was 81 per cent in the 72 patients evaluated. Logistic regression analysis of the overall data set revealed that only stage (p = 0.005) and nodal status (p = 0.001) were predictive factors. Neither response to initial chemotherapy nor the type of local therapy administered significantly influenced the final clinical complete remission rate.

Survival data

The overall median survival of all patients treated between January 1975 and June 1982 with a median follow-up of 12 years, was 65 months (95 per cent confidence intervals 32 and 97) and 33 per cent of these patients were alive at 12 years. Patients achieving a final clinical complete remission had a median survival of 95 months (95 per cent confidence intervals 53 and 120) and 38 per cent were alive at 12 years. Prognostic factors for overall survival as judged by univariate analysis are listed in Table III. These data indicate survival benefit for younger patients (aged <60 years) and those with Stage II or III disease, with glottic or transglottic lesions and least nodal involvement. Multivariate analysis revealed superior survival for final complete responders (p<0.0001), for female patients (p = 0.008) and for those aged <60 years (p = 0.001). Omitting complete remission from the analysis, both younger age and node negative disease proved highly significant factors (p = 0.0001), with median survival in these patients not being reached by 12 years.

At this final analysis 40 patients have died, 10 of non-cancer related causes, while the remaining 30 patients had predominantly local or regional recurrences with metastases reported in only eight patients (see Table IV). Sixteen patients from Libya, Iran, Iraq or Turkey have been lost to follow-up: four with disease at 3, 4, 35 and 60 months, and 12 disease-free at periods ranging from 4–42 months.

Relapse-free survival was analysed in terms of the endpoint of (i) relapse or death from any cause or (ii) relapse

TABLE III
PROGNOSTIC FACTORS FOR OVERALL SURVIVAL AND RELAPSE-FREE SURVIVAL AS JUDGED BY UNIVARIATE ANALYSIS

Variable	Patient nos.	Deaths	p Value	Relapse or death from any cause	p Value	Relapse or death from from cancer	p Value
Age (years)			0.004		0.01		0.08
<60	37	13		19		14	
≥60	36	27		28		20	
Sex			0.70		0.20		0.90
Male	61	30		36		28	
Female	12	10		11		6	
Site			0.02		0.06		0.08
Supraglottic	36	22		25		20	
Glottic + transglottic	35	17		21		14	
Stage			0.06		0.04		0.001
II	22	13		15		8	
III	34	16		18		12	
IV	17	11		14		14	
T status			0.20		0.60		0.20
T_1	3	3		2		2	
T_2	27	16		19		10	
T_3	34	16		18		15	
T_4	9	5		8		7	
N status			0.0002		0.02		<0.001
N_0	48	25		31		19	
N_1	14	7		6		5	
N_2	3	2		3		3	
N_3	8	6		7		7	
Local therapy			0.70		0.80		0.90
DXT only	51	26		33		23	
Surgery plus DXT	21	14		13		10	

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TABLE IV
CAUSES OF DEATH IN 40 OF THE 73 ELIGIBLE PATIENTS

Cause of death	No. of patients
Cancer—primary tumour	14
—primary tumour + metastatic disease	5
—metastatic disease only	1
Bronchopneumonia—tumour present	4
—tumour absent	2
Cardiac death—tumour present	2
—tumour absent	5
Respiratory arrest during obstruction—tumour present	1
Bone marrow failure—chemotherapy induced due to protocol violation	1
Second primary—lung (primary tumour absent)	2
Total body burns—tumour absent	1
Alcoholism—tumour absent	2

or death from cancer. The results of univariate analysis are listed in Table III. These show that the significant factors using both end-points were age, site, stage and nodal status. Multivariate analysis using the first model involving 47 events (32 deaths or relapses and 15 never disease-free) showed that age and nodal status proved significant with p values of 0.008 and <0.001 respectively. For the second model, involving 34 events (19 deaths or relapses and 15 never disease-free), again age <60 years (p = 0.05) and N_0 disease (p = <0.001) were significant.

Overall survival and relapse-free survival data in patients receiving radiotherapy without surgery, were shown not to be significantly different from those patients who had total laryngectomies with or without additional radiotherapy (see Fig. 1). Median overall survival and relapse-free survival figures were 71 months and 107 months for the radiotherapy group in which the larynx was preserved, versus 65 months and 67 months for the group which had undergone laryngectomy. These data therefore, provide some evidence of long-term benefit from initial chemotherapy and radiotherapy, with 32 per cent of the patients retaining their larynx surviving 12 years.

Discussion

The high response rates achievable using initial or neo-adjuvant chemotherapy programmes in the treatment of squamous cell carcinoma of the head and neck has not translated into improved survival in randomized trials, as reviewed recently (Hill and Price, 1990; Jacobs and Makuch, 1990; Bosl *et al.*, 1991; Forastiere, 1991). This apparent failure, however, needs to be viewed in its proper perspective. After taking into account the many limitations of these randomized studies, it is justifiable to conclude that the addition of initial chemotherapy may be beneficial but the concept has not been tested adequately. For example, optimal regimens have not been used either in terms of the intensity of the combination chemotherapy administered or the number of chemotherapy cycles given and many randomized trials enrolled an inadequate number of patients to be able to detect a small increment in survival benefit with adequate statistical power (Bosl *et al.*, 1991). Another factor may be the heterogeneity of this disease, with survival differences dependent on both site and stage. Indeed, we reported earlier on the impact of primary site in assessing both chemotherapy response and survival in our large series of 208 patients (Hill *et al.*, 1986) and, as reviewed recently, the site of primary has been extensively reported as a potentially significant prognostic factor (Clavel and Maged Mansour, 1991). There may, therefore, be particular subgroups who would benefit from initial chemotherapy, but when combined with other subgroups in which initial chemotherapy is not particularly beneficial, that advantage may not be apparent. Jacobs and Makuch (1990) have also stressed recently that trials with more prolonged follow-up may be necessary to detect modest differences that are important from a broader public health perspective. It is particularly noticeable in reviewing the literature, that studies reporting two-

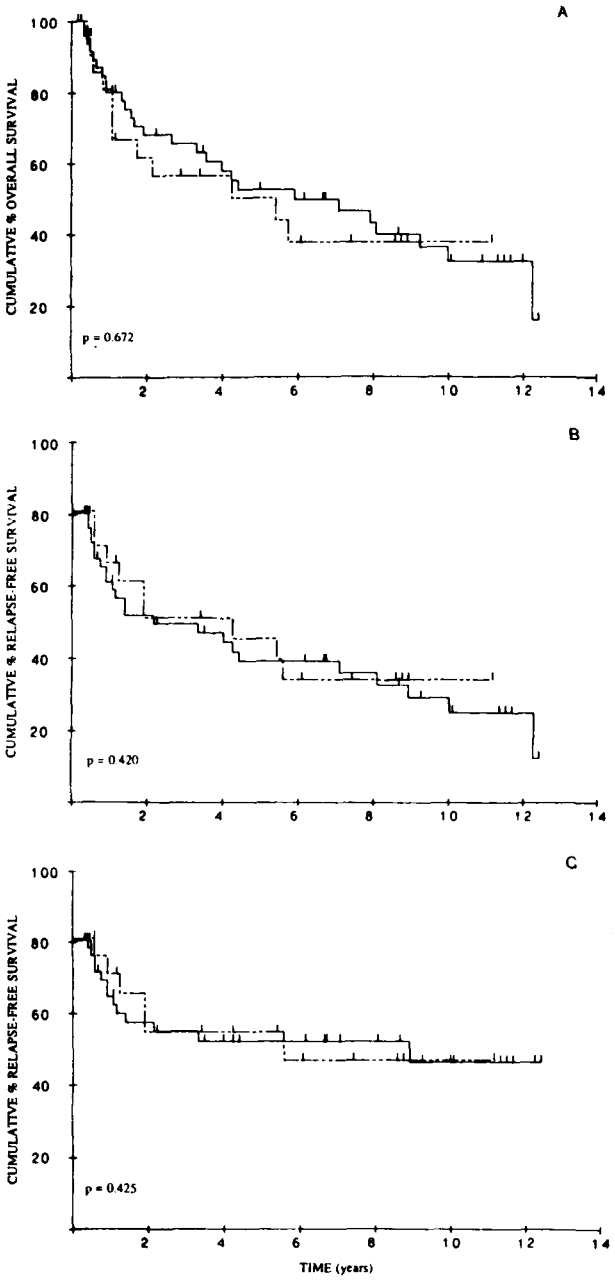

FIG. 1

Actuarial survival analysis of all patients depending on the local therapy received.
A—Cumulative overall survival data.
B—Relapse-free survival data—from any cause.
C—Relapse-free survival data—cancer related.
Solid line—patients receiving radiotherapy only; Dotted line—patients undergoing laryngectomies with or without additional radiotherapy.

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TABLE V
SURVIVAL DATA FOR 73 PATIENTS WITH ADVANCED LARYNGEAL TUMOURS AFTER 12 YEARS FOLLOW-UP

Patient group	Overall survival figures Median	5-year	10-year
All patients	65 months	51%	33%
Chemotherapy responders	95 months	53%	33%
Chemotherapy non-responders	65 months	50%	30%
Final complete responders	97 months	64%	39%

year survival figures considerably outnumber those providing five-year figures, and reports of ten-year follow-up data are exceedingly rare.

With this background we have carried out this subset analysis of 73 patients with advanced laryngeal squamous cell carcinomas, since this group was identified from our earlier overall analysis of 208 patients with head and neck tumours as having the longest median survival duration. In contrast to our finding however, a recent subset analysis from the Head and Neck Contract study (Jacobs and Makuch, 1990) identified no marked overall survival benefit in 148 cases of laryngeal carcinoma. In our study a favourable response to two courses of initial Schedule A chemotherapy was recorded in 61 per cent of patients, this is comparable with the 65 per cent figure reported in 40 patients by Pfister *et al.* (1991) but lower than the 85 per cent rate obtained in 332 patients receiving three cycles of a combination of cisplatin and 5-fluorouracil, published by the Department of Veterans Affairs Laryngeal Cancer Study Group (1991). In our series, multivariate analysis failed to identify any significant predictive factors for chemotherapy response, consistent with our earlier overall analysis of our whole data set on 208 patients (Hill *et al.*, 1986) which revealed that only tumour site was predictive of chemotherapy response. After definitive local therapy, 81 per cent of this group of patients achieved a clinical complete remission, comparable with figures of 78–92 per cent reported by other groups for laryngeal tumours (Bosl *et al.*, 1991; Department of Veterans Affairs Laryngeal Cancer Study Group, 1991; Karp *et al.*, 1991; Pfister *et al.*, 1991). Stage and nodal status proved predictive factors for achieving a clinical complete remission but in this subgroup, both chemotherapy responders and non-responders had comparable complete remission rates, unlike the advantage noted for chemotherapy responders in our overall series (Hill *et al.*, 1986) and reported by others (Bosl *et al.*, 1991; Pfister *et al.*, 1991). Similarly, the use of radiotherapy only without surgery did not compromise the final complete remission rate in our study.

Analysis of survival data showed an overall median survival of 65 months in this group of 73 patients, with those responding to initial chemotherapy and those achieving a final complete remission having longer medians of 95 and 97 months respectively. However, an examination of five and 10-year survival figures (see Table V), whilst confirming benefit for patients achieving a final complete remission, indicate no significant survival benefit for chemotherapy responders. This latter observation is in line with the findings from the large Department of Veterans Affairs Laryngeal Cancer Study Group (1991) that response to chemotherapy did not influence survival, although this was reported as a significant factor in smaller retrospective studies (Bosl *et al.*, 1991). Although our five-year survival figures of 50–60 per cent appear higher than those of 33 and 35 per cent reported by other groups (Karp *et al*, 1991; Pfister *et al.*, 1991), when it is remembered that our study included some 'bad risk' T_2N_0 (late Stage II) patients, our figures fall within the same range and are consistent with the estimated two-year survival figures of 68 per cent reported by the Department of Veterans Affairs Laryngeal Cancer Study Group (1991). It is, however, noticeable that all these results are comparable with the five-year published survival rates for patients with primary laryngeal cancer which range from <30 per cent for patients receiving radiotherapy only, to 65 per cent for patients undergoing both surgery and radiation therapy (Bosl *et al.*, 1991). In our series though, neither overall survival nor relapse-free survival was influenced by the type of local therapy used. Therefore, these results confirm several other reports of non-randomized studies (Jacobs *et al.*, 1987; Karp *et al.*, 1988; Urba *et al.*, 1989) indicating that laryngeal preservation is both feasible and effective, a finding confirmed by the preliminary results of the randomized study of the Department of Veterans Affairs Laryngeal Cancer Study Group (1991) showing 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. Furthermore, a recent report suggests that larynx preservation is feasible in patients with hypopharyngeal tumours as well (Shirinian *et al.*, 1992). Therefore, we suggest that even if the use of initial chemotherapy plus radiation therapy only yields survival rates no better than the more 'standard' therapy employing surgery with or without post-operative radiotherapy, this modified approach preserving the larynx is likely to be associated with a significantly better quality of life.

Finally, it has been suggested that subgroup analyses may help to design more focused trials in which large treatment differences in particular categories of patients may be more likely to occur (Jacobs and Makuch, 1990). In this present subgroup analysis, improved survival and disease-free survival was noted in younger patients with less extensive nodal disease. This may not be unexpected, but might be considered in subsequent studies evaluating laryngeal preservation by targeting patients with less extensive disease where a definite impact on survival might be identified.

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References

Bosl, G. J., Strong, E., Harrison, L., Pfister, D. G. (1991) Chemotherapy and the management of locally advanced squamous cell carcinoma of the head and neck: role in larynx preservation. In *Important Advances in Oncology 1991*. (DeVita, V. T., Hellman, S., Rosenberg, S. A., eds.), J. B. Lippincott Company, Philadelphia, p 191–203.

Clavel, M., Maged Mansour, A. R. (1991) Head and neck cancer: Prognostic factors for response to chemotherapy. *European Journal of Cancer* **27:** 349–356.

Department of Veterans Affairs Laryngeal Cancer Study Group (1991) Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *New England Journal of Medicine* **324:** 1685–1690.

Forastiere, A. A. (1991) Randomized trials in induction chemotherapy: a critical review. In *Hematology and Oncology Clinics of North America*. (Vokes, E. E., ed.), W. B. Saunders Co., Philadelphia, vol. 5, p 725–736.

Hill, B. T., Price, L. A. (1990) The role of adjuvant chemotherapy in the treatment of advanced head and neck cancer. *Acta Oncologia* **29:** 695–703.

Hill, B. T., Price, L. A., Love, S. (1988) Induction combination chemotherapy without cisplatin followed by radiotherapy without radical surgery as definitive treatment for advanced laryngeal cancer. In *Neo-Adjuvant Chemotherapy*. (Jacquillat, C. M., Weil, M., Khayat, D., eds.), Colloque INSERM/John Libbey Eurotext Ltd., London, Vol. 169, p. 303–308.

Hill, B. T., Price, L. A., MacRae, K. (1986) Importance of primary site in assessing chemotherapy response and seven-year survival data in advanced squamous-cell carcinomas of the head and neck treated with initial combination chemotherapy without cisplatin. *Journal of Clinical Oncology* **7:** 335–340.

Karp, D., Carter, R., Vaughan, C., Willett, B., Heeren, T., Calarese, P., Zeitels, S., Hong, W. (1988) Voice preservation using induction chemotherapy plus radiation therapy as an alternative to laryngectomy in advanced head and neck cancer: Long term follow up. *Proceedings of the American Society of Clinical Oncology* **7:** 152.

Karp, D. D., Vaughan, C. W., Carter, R., Willett, B., Heeren, T., Calarese, P., Zeitels, S., Strong, S., Hong, W. K. (1991) Larynx preservation using induction chemotherapy plus radiation therapy as an alternative to laryngectomy in advanced head and neck cancer: A long-term follow-up report. *American Journal of Clinical Oncology* **14:** 273–279.

Jacobs, C., Goffinet, D. R., Kohler, M., Fee, W. E. (1987) 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* **60:** 1178–1183.

Jacobs, C., Makuch, R. (1990) Efficacy of adjuvant chemotherapy for patients with resectable head and neck cancer: A subset analysis of the head and neck contracts program. *Journal of Clinical Oncology* **8:** 838–847.

Pfister, D., Bosl, G. J., Vikram, B., Gerold, G., Shah, J., Sessions, R., Strong, E. (1986) Larynx preservation in patients with advanced head and neck cancer: Neoadjuvant chemotherapy and primary radiation therapy. *Proceedings of the American Society of Clinical Oncology* **5:** 140.

Pfister, D. G., Strong, E., Harrison, L., Haines, I. E., Pfister, D. A., Sessions, R., Spiro, R., Shah, J., Gerold, F., McVure, T., Vikram, F., Fass, D., Armstrong, J., Bosl, G. J. (1991) Larynx preservation with combined chemotherapy and radiation therapy in advanced but resectable head and neck cancer. *Journal of Clinical Oncology* **9:** 850–859.

Price, L. A., Hill, B. T. (1977) A kinetically-based logical approach to the chemotherapy of head and neck cancer. *Clinical Otolaryngology* **2:** 339–345.

Price, L. A., Hill, B. T. (1982) Safe and effective induction chemotherapy without cisplatin for squamous cell carcinoma of the head and neck: Impact on complete response rate and survival at five years, following local therapy. *Medical and Pediatric Oncology* **10:** 535–548.

Price, L. A., MacRae, K., Hill, B. T. (1983) 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: Five-year data. *Cancer Treatment Reports* **67:** 535–539.

Shirinian, M., Weber, R., Dimery, I., Choski, A. J., Kramer, A., Heyne, K., Goepfert, H., Byers, R., Hong, W. K. (1992) Laryngeal preservation using induction chemotherapy followed by definitive radiation therapy for patients with advanced stage head and neck squamous cell carcinoma requiring a total laryngectomy. *Proceedings of the American Society of Clinical Oncology* **11:** 242.

Urba, S., Forastiere, A. A., Wolf, G. T., Baker, S. R., Sullivan, M., Thornton, A., Husted, S. (1989) Intensive continuous infusion high dose cisplatin, 5-fluorouracil and mitoguazone induction chemotherapy for advanced head and neck cancer. *Proceedings of the American Society of Clinical Oncology* **8:** 172.

Vikram, B., Bosl, G. J., Pfister, D., Assad, W., Strong, E. W., Spiro, R. H., Sessions, R. B., Gerold, F.P., Shah, J. P. (1988) New strategies for avoiding total laryngectomies in patients with head and neck cancer. *National Cancer Institute Monographs* **6:** 361–364.

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