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Laryngeal preservation in cases of advanced laryngeal cancer treated with platinum based induction chemotherapy before local treatment

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Abstract

In this study we analyse our preliminary results after treating 28 patients with locally advanced laryngeal cancer with platinum based induction chemotherapy followed by radiation therapy or surgery.

The median age of our patients was 60 (46–75) years and median performance status was 80 (60–100). In 18 of the 28 patients locoregional treatment was radiation therapy with an overall response of 94.4 per cent.

After a median follow-up of 26 (15–40) months 39.3 per cent of the whole group of patients are alive and disease-free and six (21.4 per cent) patients are alive and disease-free preserving their larynx.

We conclude that although more extensive studies with large groups of patients and longer follow-up is needed to reach definite conclusions, it seems that platinum based induction chemotherapy can be used successfully in locally advanced laryngeal cancer followed by radiotherapy. In those cases who respond well, the patient's larynx is preserved without compromizing the overall survival.

Introduction

Early stage laryngeal cancer can be cured either by radiotherapy or surgery alone. Advanced stage laryngeal cancer though, requires total laryngectomy or laryngopharyngectomy with or without radical neck dissection (RND), and sometimes additionally radiotherapy as well. Surgical procedures of this kind result in total loss of voice production drooping of the shoulder in some cases, and also in more or less unacceptable cosmetic results. Unfortunately even these extensive surgical procedures in many cases do not prevent local or distant recurrences, resulting in mutilated patients with low life expectancy.

Several attempts have been made during the last few years to improve the survival or at least the quality of the remaining life, avoiding operations that result in mutilation by the addition of induction chemotherapy to standard radiation therapy (Kish *et al.*, 1982; Jacobs *et al.*, 1987; Al-Sarraf, 1988). The most promising combination seems to be the one published by the Wayne State University Group with cisplatin and fluoruracil (FU) (Al-Kourainy *et al.*, 1987).

Since 1984, we have started treating patients with advanced head and neck squamous cell carcinomas (HNSCC) with platinum based induction chemotherapy before local treatment. (Fountzilas *et al.*, 1990). Among the 115 patients treated with this modality, there were 28 patients with laryngeal cancer which will be studied in this paper. One of our intentions in the first place was to examine the possibility of preserving the patient's larynx in those cases where complete response was achieved after induction chemotherapy and radiotherapy.

Material and methods

Since August 1984 the Hellenic Cooperative Oncology Group for Head and Neck Cancer designed two consecutive studies of combined modality treatment for patients with histologically confirmed locally advanced carcinomas of the head and neck region. Eligibility criteria included measurable or evaluable disease, normal hepatic and renal function, absence of distant metastases (Mo), platelets $>$ 100,000/ml and WBC $>$ 4,000/ml, age $<$ 75 years, no active ischaemic heart disease, no prior therapy and an informed consent, according to our institutional policy. Initial examination included history, clinical examination, endoscopy, laryngoscopy (with or without oesophagography), audiogram, complete blood count, and blood chemistry, ECG, chest X-ray, bone scan and CT scan. Staging was done according to the AJC/UICC criteria (1988).

Among the 115 patients with advanced HNSCC there were 28 patients with stage III and IV laryngeal carcinomas which were treated with this treatment modality.

The median age was 60 (46–75) years. All of them were male with a median Karnofsky performance status of 80 (60–100). All 28 patients were smokers and 19 (68 per cent) were alcohol abusers. Seven patients had stage III disease and 21 stage IV disease (Table I). The histology report revealed squamous cell carcinoma in all cases with various differentiation ($6G_1$, $15G_2$ and $7G_3$).

All patients before treatment were examined by the same group of otolaryngologists, medical oncologists and radiotherapists. Multiple biopsies were taken under general anaesthesia.

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TABLE I
TNM STAGING OF THE 28 PATIENTS

	N_0	N_1	N_2	N_3
T_1				
T_2			2	
T_3	7	2	5	5
T_4	4		1	2

Seven of our patients had tumours extending beyond their larynx either to the hypopharynx or the oropharynx. Seven patients had unresectable fixed neck nodes.

Induction chemotherapy for the first 12 patients consisted of: intravenous bolus injection of cisplatin 100 mg/m^2 followed by mannitol diuresis on day 1, fluorouracil (5FU) 1,000 mg/m^2 per day by continuous 120 h infusion from day 2 to day 6, bleomycin 15 U IM on days 15 and 29, mitomycin-C 4 mg/m^2 IV on day 22 and hydroxyurea 1,000 mg/m^2 p.o. on day 23–27 (Protocol A). Each cycle was repeated every 42 days.

The last 16 patients were treated with the following regimen: intravenous bolus injection of carboplatin 300 mg/m^2 on day one, followed by 120 h continuous infusion of FU 1,000 mg/m^2 per day and methotrexate (MTX) 1,200 mg/m^2 I.V. on day 15 with leucovorin rescue (Protocol B). Each cycle was repeated every 28 days.

Details of these two protocols have been reported previously (Fountzilas *et al.*, 1991).

After the completion of the second course of induction chemotherapy patients with laryngeal cancer were re-evaluated for response. Those who responded with reduction of the tumour size of more than 50 per cent received the third course of induction chemotherapy. The rest of the patients underwent local treatment consisting of surgery and/or radiotherapy. After the third course of induction chemotherapy those patients who achieved a complete response (CR) underwent endoscopic evaluation and multiple biopsies were taken from their larynx. Histologically confirmed CRs were treated with radiotherapy only.

Radiotherapy was given with Cobalt^{60} equipment or linear accelerator. Patients received 70 Gy to their larynx and 4.5 Gy to the rest of the neck. Five fractions per week of 2 Gy each, were delivered.

Patients with partial response in the lymph modes and their larynx, but with considerable remaining tumour in the primary site were treated surgically and afterwards with post-operative radiotherapy. Those who achieved PR with small remaining tumour in the larynx were treated with a full course of radiotherapy and if they did not achieve a CR post-radiotherapy underwent surgery. Patients with stable or progressive disease were treated surgically, if their tumour was resectable.

The response was evaluated by clinical examination and CT scan prior to each treatment modality. CR was defined as a complete disappearance of all clinically evident disease for at least four weeks. Partial remission (PR) was defined as a decrease of more than >50 per cent in the sum of the products of the largest perpendicular diameters of the measurable lesions. Stable disease (SD) was defined as objective response without satisfying the criteria of PR or an increase <25 per cent in the absence of new lesions. Progressive disease (PD) was a >25 per cent increase of the above measurements or the appearance of a new lesion.

Survival was estimated from the initiation of induction chemotherapy to the date of last follow-up or until the patient's death. The time to progression was defined as the time between initiation of chemotherapy and progression documented clinically and/or radiologically. Patients who died from causes other than disease progression were included if they were disease-free at the time. Product limit survival and time to progression were calculated using the Kaplan-Meier method (1958). Median age and performance status of the patients in the two studies (Protocols A and B) were compared with the student t-test, while the sex and stage distribution in these groups of patients were compared with the Fisher's exact test. Finally response rates were compared using the χ^2 test by Armitage method (1971) and survival curves using the log rank test (Mantel, 1966); $p = 0.05$ was chosen as the level of significance.

Results

Response to chemotherapy: All patients received at least one course of induction chemotherapy and are evaluable for toxicity. One patient died from a brain infarct a few hours after the completion of the first FU infusion. One patient refused to continue the induction chemotherapy after the first course and underwent total laryngectomy. Another patient refused any kind of treatment after the second course of chemotherapy, achieved a PR and died five months later, and one more patient with progressive disease after the second course underwent surgical treatment and post-operative radiotherapy. So 28 patients received the first course, 26 patients the first and the second course and 24 patients three courses of induction chemotherapy. Twenty-six patients were eligible for assessment of their response to chemotherapy.

Since we did not find any statistically significant differences between the two groups of patients (Protocol A and B) in terms of age, performance status, stage distribution, response of induction chemotherapy and survival, we decided to consider all patients as one group. Thus response to induction chemotherapy was as follows:

Three (11.5 per cent) patients achieved a complete response both at the primary site and the lymph nodes, 20 (76.9 per cent) a partial response, two patients had stable disease and one progressive. Overall response rate was 88.5 per cent.

Locoregional treatment: Of the 28 patients, 18 were treated with a full course of radiotherapy after the completion of induction chemotherapy. Response to radiotherapy was: 7 CRs (38.9 per cent), 10 PRs (55.5 per cent) and 1 PD. Overall response was 94.4 per cent.

Seven of the 10 patients who achieved PR after radiotherapy were operated (one of them only RND, the rest total laryngectomy) and the remaining three refused surgical treatment.

Seven out of the 28 patients were treated surgically after induction chemotherapy (one of them received only the first course). Two of them also received post-operative radiotherapy. Among the 13 patients who underwent a laryngectomy, four also had a radical neck dissection.

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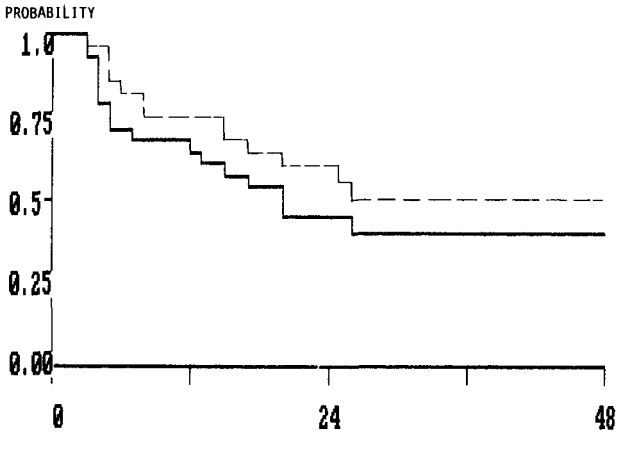

FIG. 1

Survival (– – –) and time to progression (———) of all patients.

Conclusively after induction chemotherapy: five patients were treated surgically only, 11 patients received only radiotherapy treatment and nine patients received both radiotherapy and surgical treatment. One patient with PR and one with SD after induction chemotherapy refused any further local treatment and one died during the first course of chemotherapy.

After the completion of locoregional treatment 25 patients were eligible for evaluation of response and there were: 17 CRs (68 per cent), 5 PRs (20 per cent), 1 SD and 2 PDs. Overall response rate was 88 per cent.

Recurrences: Among the seven patients who achieved a CR after induction chemotherapy and radiotherapy plus one who underwent RND only, two presented with a recurrence (one was CR after induction chemotherapy) 17 and 12 months later. So the remaining six patients are disease-free survivors preserving their larynx for a median period of 25 months.

From the group of the 17 complete responders after the whole treatment, six (35.3 per cent) recurred and three died. Five recurrences were locoregional and one distant (lung).

Survival: Up to December 1990, 15 patients are alive and 13 have died. Eleven (39.3 per cent) are alive and disease-free, while six (21.4 per cent) of them have also preserved their larynx. Median follow-up was 26 (15–40) months. The cause of death was disease progression in 12 patients and a brain infarct in one.

Median survival is 26 months and median time to progression is 20 months (Fig. 1).

Toxicity: Toxicity depended upon the regimen used. Vomiting was seen more frequently with regimen A than with regimen B (50 per cent *vs* 36 per cent). Alopecia was seen exclusively with regimen A (85 per cent *vs* 0 per cent). Stomatitis was more frequent with regimen B (35 per cent *vs* 67 per cent). Grade 4 toxicity was not observed. More details about the toxicity of the two protocols have been already published (Fountzilas *et al.*, 1990).

Discussion

The five-year survival of stage III and IV laryngeal cancer and especially in cases with extended cervical lymph nodes is usually below 23 per cent (Smith *et al.*, 1961; Ackerman and del Regato, 1977).

We examined the possibility of omitting surgical extirpation of larynx in those cases who responded well (CR and PR) after the second course of platinum based induction chemotherapy and demonstrated a CR after radiotherapy, without decreasing the overall survival.

The percentage of the CRs achieved after induction chemotherapy was 11.5 per cent which is very low compared to the one reported by the Wayne State University Group (Kish *et al.*, 1982). We believe that this is mainly due to the fact that they report their results in a population of patients with HNSCC of various sites and their CRs were not histologically confirmed in all cases. Jacobs *et al.* (1987) reported 33 per cent of CRs in a population of 30 patients with different HNSCCs which included only three patients with N_3 nodal disease, where as in our population there were seven N_3 and eight N_2. All their patients were operable while about one-third of our patients were not, due to fixed nodes.

Finally, seven of our patients achieved a CR both in their larynx and their neck after radiotherapy and one more after RND which followed radiotherapy. Among these eight patients (28.6 per cent) out of 28 who preserved their larynx two recurred, so six (21.4 per cent) are disease-free having avoided laryngectomy.

Comparison of the survival of the non-surgical group with the one which includes the CRs after laryngectomy (nine patients) reveals that one of the eight died from the first group and two out of nine laryngectomized patients. Since the number of patients is small, no statistically significant conclusions can be drawn.

After a mean follow-up exceeding two years (26 months), 53.6 per cent of the patients are alive, 39.3 per cent disease-free and 21.4 per cent preserved their larynx. Jacobs *et al.* (1987) reported that the two year survival of patients with stage III and IV head and neck carcinomas treated with standard surgery and postoperative irradiation was 59 per cent and the disease-free survival was 55 per cent.

Our preliminary results suggest that the longevity was not compromised by our protocols, since the median survival was 26 months for the whole group of patients. The same conclusion was reached by Jacobs *et al.* (1987) after treating 30 patients with a protocol similar to ours. Forty per cent of their patients avoided laryngectomy and 26 per cent were disease-free preserving their larynx. Baker (1988) and Pfister *et al.* (1989) have published their preliminary results after treating patients with the concept of preserving their larynx, which seems to be promising.

A randomized multi-institutional study conducted by the VA laryngeal cancer study group (Hong, 1989) is expected with great interest to reach definite conclusions regarding the issue of preserving the larynx of patients with advanced stage cancers treating them with induction chemotherapy and radiotherapy. Further controlled studies are needed in order to make sure that this treatment policy is better than the conventional one.

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