

Neo-Adjuvant Chemotherapy and Radiotherapy for Locally Advanced Carcinoma of Larynx: A Method for Laryngeal Preservation

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ABSTRACT

Objective: We performed this prospective study in patients with previously untreated locally advanced (stage III and IV) laryngeal cancer to study the results of induction chemotherapy followed by definitive radiotherapy.

Patients and methods: Thirty-six patients with locally advanced cancer larynx were treated with induction chemotherapy [cisplatin (100 mg/m²) given by IV infusion over 6 hours on day 1, followed by infusion of fluorouracil (1000 mg/m² per day) on days 1-5]. Evaluation of response to chemotherapy was performed before each cycle of chemotherapy. After two cycles, only partial or complete responders received a third cycle. Patients with partial or complete response were treated thereafter by definitive irradiation 5000-7000 cGy; non-responding patients underwent conventional surgery with postoperative radiation (50-64 Gy). Salvage surgery was also performed when patients relapsed after chemotherapy and irradiation.

Results: Complete clinical regression of the primary tumor was seen in 27.8% of patients after 2 cycles of chemotherapy. A partial response was seen in 50%. Twenty-eight patients achieved complete or partial responses and received radiotherapy. Following radiotherapy, complete response rate was observed in 75% of patients (21/28). Surgical salvage was performed in 8 patients (22.2%) who did not respond to chemotherapy and in 7 patients with persistent disease (5 PR and 2 SD) after chemotherapy and radiation therapy. The median failure-free survival is 20 months, with a long-term plateau at 47.6%. There is a highly significant survival advantage for patients achieving either complete or partial response to induction chemotherapy ($p = 0.002$). Survival was not statistically correlated with patient's age or stage of the disease. At the end of the study, from the twenty-one patients who achieved CR after chemotherapy-radiotherapy, one died from other cause without evidence of disease, eight had loco-regional recurrence of disease, one had distant metastasis and one had both local and distant relapse, leaving 10 patients (10/21, 47.6%) living with laryngeal preservation. Toxicities consisted of mild to moderate myelosuppression and mucositis. The toxicity was acceptable.

Conclusion: These preliminary results suggest a new

role for chemotherapy in patients with advanced laryngeal cancer and showed that a treatment strategy involving induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a certain percentage of patients, without compromising overall survival.

Key Words: Locally advanced cancer larynx - Induction chemotherapy.

INTRODUCTION

The conventional therapy of patients with locally advanced laryngeal cancer (T3 or T4) has been total laryngectomy with neck dissection followed by postoperative radiation therapy [5,20]. Unfortunately, patients treated with laryngectomy suffer a complete loss of voice and sometimes impairment of swallowing function, leading to decreased overall quality of life in many aspects, including nutrition, social functioning and personal hygiene [2,7,18]. These problems motivated the development of laryngeal-preservation approaches. Organ-preservation approaches have included induction chemotherapy followed in responding patients by radiation or using primary radiation therapy alone with surgery reserved for treatment failures [5,9,20]. Induction chemotherapy became feasible for the treatment of head and neck cancers when cisplatin was found to be an active chemotherapeutic agent in this disease [7,15,17]. When combined with continuous infusion 5-fluorouracil (5-FU), cisplatin was found to give an overall response rate of 85%, with complete response rates ranging from 35% to 55% in previously untreated patients [15]. In initial reports of this combination regimen, patients who achieved a complete response and in particular

those patients with a complete pathological response, had a survival advantage over those who did not respond [1,5,16,17]. Unfortunately, the addition of neoadjuvant chemotherapy (cisplatin and 5-FU) to surgical therapy has not improved either locoregional control or disease-free survival in randomized controlled trials [2,5,6,10]. However, patients with at least a 50% reduction in tumor volume after cisplatin combination chemotherapy were found to respond successfully to subsequent radiation therapy, suggesting that chemosensitive tumors may also be radiosensitive [15,17]. Thus, although chemotherapy did not result in a survival benefit for patients, its usefulness in selecting patients who might benefit from subsequent organ-preserving radiation therapy was recognized [17].

The strategy of laryngeal preservation for laryngeal and hypopharyngeal tumors through primary radiation therapy, using surgical salvage for persistent or recurrent disease, has been practiced at some institutions [11-14,19]. From these data it appears that primary radiation therapy of locally advanced T3 or T4, N0 glottic cancer results in successful laryngeal preservation for the majority of patients [11,14,19], however, poor results achieved in patients with advanced (> N1) nodal disease has made the use of primary radiation therapy for these patients controversial [13,19]. So, we conducted this prospective trial to study the effect of induction chemotherapy in patients with locally advanced cancer larynx and the possibility of laryngeal preservation in those patients.

PATIENTS AND METHODS

From August 1997 to July 2000, 36 patients with locally advanced cancer larynx were referred to Clinical Oncology Unit and Ear, Nose and Throat Department, Zagazig University Hospitals and evaluated for this study.

Eligibility criteria:

- 1- Previously untreated patients.
- 2- Biopsy proven squamous cell carcinoma of the larynx.
- 3- Locally advanced disease (T3 or T4 with No, N1 or N2) according to the American Joint Committee for cancer staging [10].
- 4- A performance status of ≥ 2 on ECOG scale [13].
- 5- Adequate hepato-renal, cardiac and bone marrow functions.
- 6- Adequate nutritional and auditory status.
- 7- Each patient gave written informed consent.
- 8- Age less than 70 years.

The initial evaluation included a history and physical examination, complete blood cell (CBC) count, routine serum chemistries, creatinine clearance, chest X-ray, C.T. scan or MRI of the head and neck and bone scan. Local tumor extent and regional metastases were further assessed by triple endoscopy.

Treatment plan: (Fig. 1)

- Induction chemotherapy:

Induction chemotherapy consisted of cisplatin 100 mg/m² administered IV over 6 hours in 1 L of normal saline with appropriate hydration and antiemetics. Cisplatin was followed immediately by a 5-day continuous IV infusion of 5-Fu at 1,000 mg/m². This cycle was repeated on day 22. Chemotherapy doses during cycle 2 were modified as follows:

- 1- If WBC counts of $\leq 2,500 \times 10^9/L$ or a platelet count of $\leq 75,000 \times 10^9/L$ or residual mucositis greater than grade 1 on day 22, the next cycle was delayed by 1 week.
- 2- The dose of 5-Fu was reduced by decreasing the total duration of infusion (rather than the daily dose) based on the results of a CBC count on day 22.
 - a- If WBC count $> 2,500 \times 10^9/L$ to $\leq 3,500 \times 10^9/L$ and/or platelet count $> 75,000 \times 10^9/L$ to $\leq 100,000 \times 10^9/L$ or grade 3 mucositis observed with the previous cycle or grade 3 dermatitis or in patients developed a hand-foot syndrome: 4 days 5-Fu infusion i.e. 80% of intended dose of 5-Fu.
 - b- If grade 4 mucositis, 3 days 5-Fu infusion i.e. 60% of the intended dose.
- 3- The dose of cisplatin was reduced according to the creatinine clearance (30 to 50 ml/minute, 50% of the calculated dose; < 30 ml/minute, no cisplatin administered) and according to the results of a CBC count on day 22 (WBC count $> 2,500 \times 10^9/L$ to $\leq 3,500 \times 10^9/L$ and/or platelet count $> 75,000 \times$

$10^9/L$ to $\leq 100,000 \times 10^9/L$) 75% of calculated dose administered.

Response to neoadjuvant chemotherapy was evaluated clinically by endoscopic examination before each cycle and radiologically by C.T. scan or MRI performed after the second cycle. Assessment of palpable lymph node (s) was done also by clinical examination and palpation. Responding patients (CR or PR) received a maximum of 3 courses of chemotherapy prior definitive radiation. After the third cycle, patients with CR or PR were treated with irradiation while patients with any evidence of disease progression underwent surgical resection and postoperative radiation therapy. Tumor responses were defined as complete response (CR), the disappearance of all clinically or radiologically evident tumor; partial response (PR), a $> 50\%$ reduction in the product of two perpendicular diameters of all measurable tumor but less than CR and no response (NR), anything less than the above. If there was disparity between the response at different sites, the least response was taken as a measure of tumor regression.

- Radiation therapy:

All patients received radiotherapy, either immediately after chemotherapy in patients with CR or PR or postoperatively after closure of the wound in patients not responding to chemotherapy (median time to wound healing 14 days, range 11-34). In both cases, the irradiated volumes included the primary site and both sides of the neck. Patients were irradiated in supine position with megavoltage radiation using a conventional fractionation (1 fraction of 2 Gy/day), 5-days/week. In case of definitive irradiation after chemotherapy, a dose of 5000 cGy was given, followed by a booster dose of 2000 cGy to the tumor site and palpable node(s), if present. When delivered postoperatively, a dose of 5000 cGy was delivered and a booster dose of 14 Gy was given to sites of positive margins and/or of extracapsular spread and/or of three or more positive lymph nodes, if any. In all instances, the spinal cord dose was kept below 4500 cGy. Twelve weeks after the completion of radiation therapy, the tumor response was assessed again. 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.

- Surgery:

The interval between surgery and the last cycle of chemotherapy was 3 to 4 weeks. 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, Regional neck dissections were performed in all surgical patients except those with T3N0 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:

Data were entered, checked and analyzed using EPI-INFO (version 6.1) software package [4].

RESULTS

The study included 36 patients, thirty male and six female. The median age was 59 years (range 46-68 years). The patient's characteristics are presented in Table (1), the T and N stage in Table (2).

Table (3) shows the response to induction chemotherapy and after 12 weeks of radiotherapy. Complete clinical regression of the primary tumor was seen in 27.8% of patients after 2 cycles of chemotherapy. A partial response was seen in 50%. Twenty-eight patients received radiotherapy after 3 cycles of chemotherapy. Complete response was observed in 75% of patients (21/28). Surgical salvage was performed in 8 patients (22.2%) who did not respond to chemotherapy and in 7 patients with persistent disease (5 PR and 2 SD) after chemotherapy and radiation therapy (Table 4). All patients with partial response after chemotherapy and radiotherapy had CR at the primary site without a CR for the nodes in the neck; four patients underwent regional neck dissection and one patient modified radical neck dissection.

With a follow-up of 6+ to 36+ months, disease-free survival and overall survival are shown in Figs. (2&3) respectively. The median

failure-free survival is 20 months, with a long-term plateau at 47.6%. Fig. (4) shows the survival according to the response to chemotherapy. There is a highly significant survival advantage for patients achieving either complete or partial response ($p = 0.002$). Survival was not statistically correlated with age, performance status or stage.

The toxicities observed with neoadjuvant chemotherapy are summarized in Table (5). Nausea and vomiting were generally well controlled by antiemetics. Myelosuppression was generally mild to moderate. Renal toxicity was also mild to moderate and reversible in all cases. Mucositis was the dose-limiting toxicity and was seen in 30 of 36 patients treated with intended dose of 5-FU during cycle 1. Six percent of patients developed grade III mucositis and the 5-FU infusion needed to be stopped before completion of 5 days of therapy because of early onset of mucositis in two patients. During cycle 2, only twenty-seven of 36 patients (75%) were able to receive 100% of the intended 5-FU dose while 8 patients received $\geq 80\%$ of the intended 5-FU dose according to the 5-FU dose modification schedule. At that dose, the majority of patients developed only mild to moderate mucositis. Only 28 patients with response to induction chemotherapy received the third cycle of chemotherapy. During the 3rd cycle of chemotherapy, 22 patients received 100% of the intended 5-FU dose, 5 patients received $\geq 80\%$ of the dose and one patients received $< 80\%$ of intended 5-FU dose. Additional toxicities were seen in some patients and included the hand-foot syndrome, diffuse vasculitis and generalized dermatitis.

The patterns of failure (loco-regional, or distant) at 36 months in 15 patients with no response to chemotherapy and underwent surgical resection and postoperative radiotherapy were: 5 patients had locoregional recurrence, 2 patients had distant metastases and 1 patient had both locoregional and distant relapse. On the other hand, in twenty-one patients who achieved CR (21/28, 75%) after chemotherapy-radiotherapy, one died without evidence of disease due to other causes, eight had locoregional recurrence of disease, one had distant metastasis and one had both local and distant relapses, leaving 10 patients living with laryngeal preservation.

Table (1): Patients characteristics.

Characteristic	Number of patients
<i>Sex:</i>	
Male	30
Female	6
<i>Age:</i>	
Median	59 y.
Range	46 to 68 y.
<i>Performance status:</i>	
0	8
1	22
2	6

Table (2): T and N stage.

	T2	T3	T4	Total
N0	-	5	3	8
N1	-	14	4	18
N2	5	3	2	10
Total	5	22	9	36

Table (3): Response of patients to induction chemotherapy and 12 weeks after radiotherapy.

	Response after Cth.	Response after Rth.
Number of patients	36	28
Complete response (%)	10 (27.8)	21 (75)
Partial response (%)	18 (50)	5 (17.9)
Stable disease (%)	8 (22.2)	2 (7.1)

Table (4): Types of surgical salvage in the present study.

Surgical salvage after neoadjuvant chemotherapy (n=8)			
		Unilateral regional neck dissection	Bilateral regional neck dissection
Total laryngectomy with partial pharyngectomy	1	-	1
Total laryngectomy	4	3	1
Hemi laryngectomy	3	3	-
Surgical salvage after chemotherapy and radiation therapy (n=7)			
Total laryngectomy	-	-	-
Hemi laryngectomy	2	1	1
Neck dissection only	5	4	1

Table (5): Toxicities of induction chemotherapy.

	No. of patients
WBC (x103/μl), mean nadir, 3.0:	
1.0-1.9	8
0.5 < 1.0	1
Platelet (x103/μl), mean nadir, 163:	
25-75	1
< 25	1
Serum creatinine (μg/mL) mean peak, 1.6:	
> 2.0-4.0	6
> 4.0	1
Serum magnesium (μg/mL) mean peak, 1.5:	
1.0-4.0	10
< 1.0	2
Mucositis (grade):	Cycle 1 Cycle 2 Cycle 3
0	6 7 3
1	23 20 15
2	5 7 6
3	2 2 4
Percent of intended 5-FU dose:	
100%	34 27 22
≥ 80%	2 8 5
< 80	0 1 1

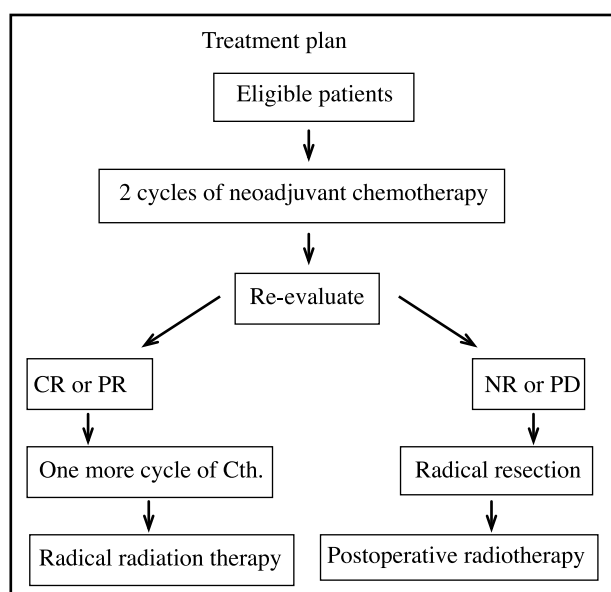


Fig. (1): Treatment plan.

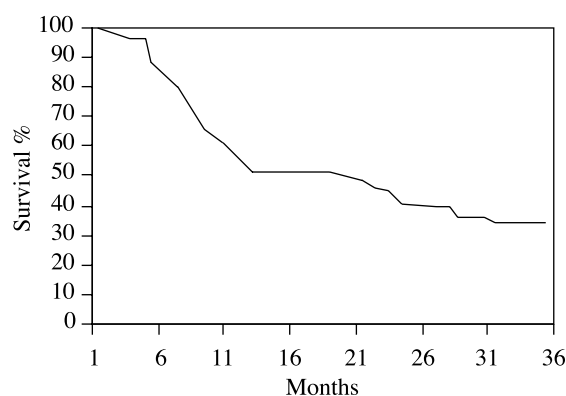


Fig. (2): Overall survival of 36 patients.

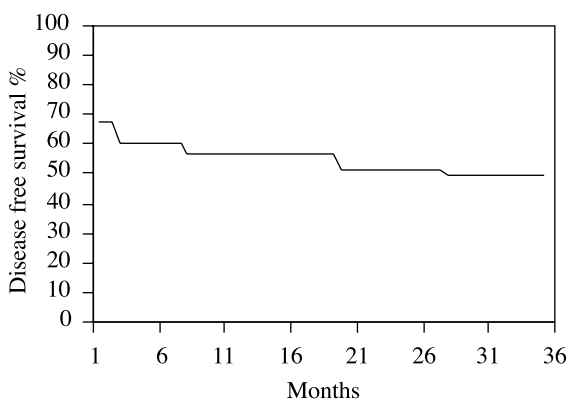


Fig. (3): Disease free survival of 36 patients.

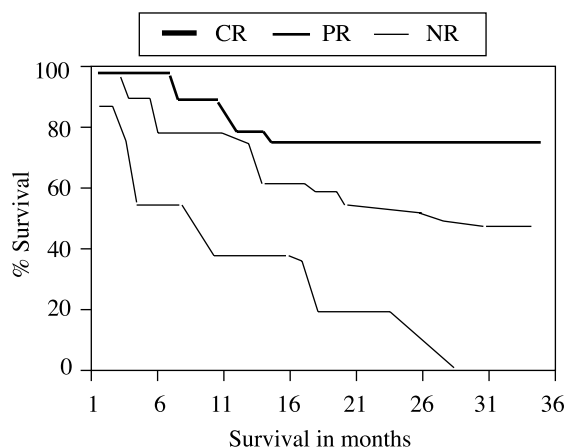


Fig. (4): Failure-free survival and chemotherapy response.

DISCUSSION

In the treatment of head and neck cancer, two issues are of utmost importance. The first is survival and the second is preservation of organ function (quality of life) [1,3,6,8]. Although, survival differs by cancer site within the head and neck, it is generally poor in stages III and IV. Since the end of the 1970s, numerous studies have been published on induction or neoadjuvant chemotherapy in patients with head and neck cancer. Most investigators have concluded that induction chemotherapy was quite disappointing, since no improvement in survival or in disease control had been demonstrated. However, several studies [15-18,20,21] suggest, that neoadjuvant chemotherapy may play an important role in preserving laryngeal function (phonatory speech). Recent data from a large number of published studies [2,5,9,10] indicate that induction PF chemotherapy followed by radiotherapy can achieve laryngeal preservation in 30% to 50% of patients, even with long-term follow-up. Furthermore, no compromise in survival was associated with the delay in surgery and radiotherapy in whom chemotherapy failed. Our results of a 28% laryngeal-preservation rate in laryngeal cancer is consistent with other studies and supports the further investigation of laryngeal-preservation strategies in patients with locally advanced laryngeal cancer [5,6,9,15,16]. 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 [8,11-14,19]. The largest studies found three-year rates of disease-free survival of 20% to 40% for patients with advanced stage III or IV cancers, with larynx preservation in less than half the cured patients [11,14]. In 89 patients with T3N0 glottic carcinoma, Mendenhall, reported a 49% five-year survival rate and a 65% rate of larynx preservation in the cured patients [11]. In 265 patients with supraglottic T3N0 or T4N0 cancers, Mendenhall, also reported a five-year survival of 51%, with larynx preservation in 64% of the survivors [13]. Patients in our study had more advanced disease than those reported by Mendenhall. 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. The encourag-

ing results achieved in these patients with advanced cancers suggest that initial chemotherapy enhanced the effectiveness of definitive radiation therapy [2]. No significant difference in duration of survival was detected in our study when the patients were grouped and analyzed according to tumor stage (III vs. IV), age or performance status but there was a highly significant survival advantage when were analyzed according to the response to induction chemotherapy ($p = 002$). These results agree with those obtained by a number of studies [1,9,18]. Local recurrences were more common and distant metastases less frequent in the present study. The local-relapse rate was similar to historical rates of local recurrence after radiation therapy alone in patients with more limited (T3) glottic primary tumors (40 to 70 percent) [11,13,14,18] and for T3 supraglottic cancers (30 to 40 percent) [5,8,10,12]. 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 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.

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 induction chemotherapy can be used successfully in locally advanced laryngeal cancer followed by radiotherapy and can be effective in preserving the larynx in a certain percentage of patients, without compromising the overall survival.

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