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Final Results Following Platin-based Exclusive Chemotherapy for Selected Patients with Squamous Cell Carcinoma of the Larynx and Pharynx

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Abstract

Purpose—To determine the long-term outcomes for patients with squamous cell carcinoma of the larynx and pharynx treated with platin-based exclusive chemotherapy (EC) after complete clinical response (CCR) to induction chemotherapy.

Materials and Methods—142 patients who achieved a CCR after platin-based induction chemotherapy were treated exclusively with additional chemotherapy. 98.6% were followed for a minimum of 3 years or until death; 35 patients had >10yrs of follow-up.

Results—Survival at 1- and 5-year was 95.8% and 61.2%, respectively. The main causes of death were metachronous second primaries (27) and intercurrent disease (21). Death related to EC was not encountered and only two patients (1.4%) had grade 4 toxicity. In multivariate analysis, primary tumor arising outside the glottic larynx ($p=.0001$), and Charlson comorbidity index >1 ($p=.0001$) were associated with a statistically significant reduction in survival. The 1-and 5-year Kaplan-Meier local control estimates were 76.1% and 50.7%, respectively. Salvage treatment resulted in an observed final 93.0% local control rate and varied from 97.2% in patients with glottic cancer to 88.7% in patients with tumor originating from other sites ($p = .097$). PF chemotherapy allowed for successful modulation of local therapy in 54.9% of patients.

Conclusions—For selected patients, EC may provide long-term durable disease control. For patients with relapse after EC, this approach does not diminish survival and maintains function in a majority of patients. Future work should be directed to select markers of response to PF chemotherapy and thereby to identify which patients are optimally suited for this approach.

Keywords

larynx; pharynx; carcinoma; induction chemotherapy; complete response

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Introduction

Since its introduction by El Sarraf¹ and Jacobs², the use of platin-based induction chemotherapy has evolved from experimental therapy to an integral part of the comprehensive care³⁻⁶ of patients with invasive squamous cell carcinoma (SCC) of the head and neck. Beginning in 1981, we began to use induction chemotherapy prior to conservation laryngeal surgery.^{7, 8} Our experience as well as that of others^{3-5, 9-14} has since shown that the use of platin-based induction chemotherapy prior to conventional treatment results in a 20-40% rate of complete clinical response (CCR). Based on these encouraging results, a novel approach based on the use of platin-based chemotherapy alone termed “exclusive chemotherapy” (EC) was pioneered at our institution. There were no specific criteria that were used initially to select patients for this approach. At first, certain patients with no residual cancer after a CCR refused surgery or radiation but would consent to further chemotherapy. Nonetheless, using this empiric approach, we first studied in a series of 21 patients with glottic cancer.⁷ The initial results achieved were confirmed in a larger cohort of 67 patients with selected SCC of the larynx and hypopharynx with CCR.⁸

In this final report, we review all patients treated with EC at our department from 1981-2004 resulting in a much larger cohort of 142 patients with a longer duration of follow-up. We critically appraise this experience in order to identify the limits and benefits of this experimental approach and in particular to determine the feasibility of extending this approach more broadly to head and neck cancer patients. We hypothesize that certain patients with head and neck cancer (HNC) would achieve long-term durable remission with chemotherapy alone. For those patients with residual disease after EC, we studied whether or not the systematic use of additional chemotherapy after CCR would allow us to down-modulate the intensity of local therapy. Here we present the results of this novel experience in terms of overall survival, local-recurrence free survival, causes of death, as well as chemotherapy-related toxicity.

Patients and Methods

From 1981 to 2004, 2271 patients with a previously untreated, moderately to well differentiated invasive squamous cell carcinoma (SCC) of the larynx or pharynx (excluding nasopharynx and velum) were managed with an induction therapy regimen at our institution. Of these patients, 23.9% (545/2271) achieved a complete clinical response. Complete clinical response after induction chemotherapy was defined as the absence of tumor on control endoscopy as well as by corroborating radiographic studies following induction chemotherapy. Of these 545 complete clinical responders, 26.1% (142/545) were managed with exclusive chemotherapy (EC) and are analyzed in the current retrospective series.

In this inception cohort of 142 patients, the tumor originated from the glottic larynx in 71 patients, non-glottic endolarynx in 9 patients, the epilarynx^{15, 16} or hypopharynx in 43 patients, and from the oropharynx in 19 patients respectively. The epilarynx is defined as mucosa along the “margins” of the larynx as it transitions into the surrounding pharynx. The epilarynx is divided in anterior epilarynx (the suprahoid epiglottis), lateral epilarynx (aryepiglottic folds), and posterior epilarynx (arytenoids).^{15, 16} Table 2 documents the TNM staging according to the 2002 International Union Against Cancer staging classification system.¹⁷ Metachronous second primary tumors were defined by the criteria first proposed by Warren and Gates^{18,19}; thus, each newly diagnosed tumor was at least 2-cm from the treated field margin from the previous tumor.

Internal review board protocols were not routinely used in France when this approach was first begun; therefore, the decision to use EC was made after a multidisciplinary discussion

where the roles and benefits of standard therapy (surgery, radiation, chemoradiation) as well as the dangers of chemotherapy were presented to the patient. Table 1 documents the demographic and comorbidity status according to the Charlson²⁰ index-weighted score (excluding the index cancer).

Prior to the start of the induction chemotherapy regimen, 93 patients (65.5%) were considered to be amenable to radiation therapy or to a partial resection sparing the physiologic functions of phonation, respiration and deglutition. These patients were defined as Group A. Among the remaining 49 patients, 43 (30.3%) were amenable only to a surgical resection that did not spare the physiologic functions of the tumor-laden organ (mandibular resection for 4 patients with oropharyngeal cancer or permanent stoma and loss of voice for 42 patients with laryngeal or hypopharyngeal cancer). These patients were categorized as Group B. The last six patients with CCR (4.2%) were considered unresectable prior to the induction chemotherapy regimen and were defined as Group C.

The number of induction chemotherapy cycles varied from 2 to 3 (depending on the toxicity and the response). The number of cycles and agents given was not standardized. The treatment was individually tailored to the patient's tumor classification and performance status. Overall, the total number of courses used for EC varied from 1 to 17 (median 5). The median course duration was 5 days. Our main and current regimen consisted of cis-platinum (25 mg/m²/day) and 5-fluorouracil (1g/m²/day) delivered daily via an implanted venous (subclavian vein) access device (Baxter Health Care Corp, Deerfield IL, USA). Over time other agents, as depicted in Table 3, were also used. The total dosage of the drugs delivered varied in each patient. Neither taxanes, nor long-term maintenance therapy such as with 13-cis-retinoic acid, were used. The dosages were adjusted to tolerance. Antiemetics and oral hyperhydration (2 liters/day) were used routinely during the treatment course. Induction chemotherapy was administered with 15-21 days hiatus between courses with the ultimate interval being determined by toxicity. Clinical examination, blood counts and serum chemistry performed 15 days after each course allowed for analysis of the cumulative toxicity (Table 4) according to the Eastern Cooperative Oncology Group criteria.²¹ Follow-up time was the time from first appointment in our department for index SCC until the date of last contact or death. Median follow-up time was 5 years and three months. Ninety-nine patients were followed for a mean duration of 3 years or until death. Thirty-four patients had more than 10-years of follow-up; one patient was followed for 19 years.

For this study, we defined successful modulation of local therapy was considered when after EC (i) in patients with unresectable tumor a conservation or non-conservation treatment could be performed, (ii) in patients requiring total laryngectomy or composite resection a conservation surgical approach or radiation therapy could be rendered, or (iii) when a patient initially amenable to conservation surgical approach or radiation therapy achieved local control with EC alone. Unsuccessful modulation of local therapy was defined as a patient who was amenable to conservation therapy prior to EC, but underwent total laryngectomy or composite transmandibular resection or when a patient with any resectable tumor prior to EC became unresectable afterwards.

The variables under analysis are listed in Table 5 and 6. The data were summarized using standard descriptive statistics and frequency tabulations. Associations between categorical variables were assessed by cross-tabulation, chi-square test, or Fisher's exact test, and either Wilcoxon's rank-sum tests or Kruskal-Wallis tests were performed to assess the differences between patients' clinical characteristics with respect to continuous variables.²² The distribution of overall survival (OS) is defined as from time of the initiation of EC to death; time to local recurrence is defined as from time of the initiation of EC to local recurrence; and time to nodal recurrence is defined as from time of the initiation of EC to nodal

recurrence. The distribution of OS, local recurrence-free survival or nodal recurrence-free survival was estimated by the Kaplan-Meier method. Log-rank test was performed to test the difference in survival between groups. Regression analyses of survival data based on the Cox proportional hazards model were conducted on survival data. Assumption of proportional hazards was examined for each variable.²³ No violations were detected. P-values less than 0.05 were considered statistically significant. All tests were two-sided. All analyses were conducted in SAS 9.1 (SAS, Institute Inc., Cary, NC) and S-PLUS (Insightful Corp.).

Results

Survival

The 1-, 3- and 5-year Kaplan-Meier actuarial survival estimate was 95.8%, 72.8% and 61.2%, respectively. Over the course of this longitudinal study, 77 (54.2%) deaths were recorded. The causes of death were metachronous second primary tumors (27 patients), intercurrent disease (21 patients), local recurrence (10 patients), distant metastasis (8 patients) and nodal recurrence (4 patients). In the remaining 7 patients, the cause of death was unknown, but there was no evidence of the primary cancer at the time of death.

Table 5 demonstrates the clinical parameters associated with diminished survival. Patients with tumors arising from the glottic larynx had improved overall survival compared to patients with tumors arising in epiglottic and hypopharynx ($p < .0001$, Figure 1). There was a significant statistical decrease in survival in patients who were not initially staged as N0 ($p = .0032$) and this was especially true when patients staged N0 were compared to those staged N2 and N3 ($p = 0.0051$ and 0.0135 , respectively; Figure 2). Medical comorbidity played a significant role in overall survival; when compared to patients who had a Charlson comorbidity index of 0 or 1, patients who had a Charlson comorbidity index of 2 or greater had worse overall survival ($p < .0001$, Figure 3).

Tumor site and medical comorbidity remained significant in the final multivariate model. Patients with primary tumor arising from the glottic larynx had better overall survival ($p < .0001$; HR (95% C.I.) = 0.2.97 (0.175, 0.505)), compared to patients with primary tumor arising from the epiglottic and hypopharynx. No significant differences were detected for patients with tumor arising from oropharynx or supraglottic larynx when compared to patients with primary tumor arising from epiglottic and hypopharynx. The development of metachronous second primary tumor was associated with reduced survival ($p = .001$). Comparing the patients based on the Charlson comorbidity index, patients who had an index of 2 or greater had worse overall survival than patients with an index of 0 or 1 ($p = .0001$; HR (95% C.I.) = 2.573 (1.597, 4.144)).

Incidence and variables influencing local recurrence

The 1-, 3- and 5-year Kaplan-Meier actuarial local control estimates were 76.1%, 53.7%, and 50.7%, respectively. Sixty-five patients developed local recurrence. As depicted in Table 6, in univariate analysis, several variables were statistically associated with local recurrence free survival. Group stratification B had a significantly higher risk of local recurrence than Group A ($p = .0024$). High number of courses of therapy ($p = .0072$, Figure 4), high total dose of 5-fluorouracil (> 37) ($p = .0014$, Figure 5) were statistically associated with increased rates of local recurrence. The median number of cycles of chemotherapy associated with local control was five and those patients who had more than 5 cycles had an increased risk of local recurrence in the univariate analysis ($p = 0.0072$). In multivariate analysis, only high dose (> 37) of treatment of 5-fluorouracil showed significant effect on local recurrence ($p = 0.0014$, HR (95% C.I.) = 2.470 (1.420, 4.296)).

Consequences of local recurrence

In our series, salvage treatment was performed in 83.1% (54/65) of patients with local recurrence. Of the remaining 11 patients, palliative treatment was offered to 10 patients and the treatment modality for one patient was unknown. The overall final (observed) control rate for patients after salvage post- EC was 93.0%. Final local control after salvage therapy varied from 97.2% in patients with glottic cancer to 88.7 % in patients with tumor originating from other locations (Fisher exact test, $p = .097$). Nodal recurrence was more likely to occur in patients with local recurrence than in patients who achieved local control ($p = 0.0003$, HR (95% CI) = 4.611 (2.025, 10.499)) and the 1-, 3- and 5-year Kaplan-Meier actuarial nodal control estimate remained 100% in patients without local recurrence when compared to 91.8 %, 79.7% and 74.7%, in patients with local recurrence. Patients with local recurrence were more likely to have the progression to distant metastasis ($p = .041$, HR (95% CI) = 4.866 (1.065, 22.235)).

The Effect of EC and Down-modulating the Intensity of Locoregional Therapy

—Table 7 summarizes the impact of EC in modulating the extent of the local and regional (LR) therapy. EC resulted in a successful reduction of the extent of LR therapy in 54.9 % of patients (78/142). This extent of reduction in the treatment varied according to the group classification based on the conventional treatment available prior to the start of induction therapy. 61% (57/93) of patients considered as amenable to a conservative approach (group A) achieved local control after EC without the need for radiation and/or conservation surgery). 72% (31/43) of patients initially amenable to a non conservative surgical approach (Group B) achieved local control (either with EC or with a salvage conservation approach). Of the 6 patients who initially presented with unresectable disease (Group C), 4 had local control with EC and 1 with salvage conservation surgery. On the other hand, 11 (7.7%) patients required more intensive LR therapy (2 patients) or became unresectable (9 patients).

Toxicity

Table 4 documents toxicity associated with the administration of EC. Overall, 30 patients (21.1%) experienced Grade 3 toxicity and two patients had grade 4 toxicity (1.4%). Eight patients (5.6%) reported neurological sequelae: peripheral neuropathy (5), intermittent dysesthesias (3). Eleven patients (7.7%) had central venous catheter related complications. Toxicity and/or chemotherapy-related complications did not lead to death.

Discussion

Since 1981, at the University of Paris V, we have systemically studied the use of platin-based induction chemotherapy for patients with cancers of the larynx and pharynx. For selected patients who achieved CCR after platin-based induction chemotherapy, neither radiation nor conservation laryngopharyngeal surgery was performed. Instead these patients went on to receive additional cycles of chemotherapy and were observed. Many were cured. These small pilot studies ^{7, 8} suggested the feasibility of using “exclusive chemotherapy” to achieve durable, long-term local-regional control without diminishing overall survival.⁷ Since then, two other group have explored this approach and documented similar results in patients classified as N0-1.^{24, 25}

We present the results of 142 patients with SCC of the larynx and pharynx treated with EC during the years 1981-2004. This large cohort represents 26.8% of the patients who achieved a CCR after platin-based induction chemotherapy regimen during the same period at our institution.

Although all the patients whom we studied had SCC originating from the larynx or pharynx, and were treated with a platin-fluorouracil based regimen, the study population was diverse in terms of tumor site, T and N staging, medical comorbidity, chemotherapy regimen and duration of treatment. Yet despite of this heterogeneity, we were able to analyze a large number of patients over a long duration of follow-up. 98.6% of these patients were followed for a mean duration of 3 years and 35 patients for more than 10 years. The size of the study and this lengthy duration of follow-up provide a unique opportunity to determine clinical parameters that are significantly correlated to local control and/or survival after EC.

In our series, the rates of survival achieved at 1-, 3- and 5-year were 94.5%, 71.5% and 60.2%. The main cause of death was metachronous second primary tumors and intercurrent disease, which were much more common than local recurrence, distant metastasis and/or nodal recurrence. Definitive the use of surgery and radiation therapy was tailored for patients with residual disease after maximally cytoreductive therapy. Such approach might diminish acute and long-term swallowing, airway and speech dysfunction, which is commonly seen with concurrent chemoradiation.²⁶ Finally, as in previous studies from our department^{7, 8} and other institutions^{24, 25} the toxicity of EC was tolerable and did not result in death (Table 4).

With this large cohort, we were able to identify (Table 5), several clinical variables that are associated with diminished survival. Patients with tumors arising from the glottic larynx had improved overall survival compared to patients with tumors arising in other sites ($p < .0001$). There was a significant decrease in survival noted in patients not staged initially as N0 ($p = .01$) and this trend was especially true when N0 patients were compared to the few N3 patients ($p < .001$). There was also a significant decline in survival ($p = .0007$) noted when the Charlson comorbidity index²⁰ increased from 0 to 5. The development of metachronous second primary tumor was associated with reduced survival ($p = .001$) Take together, these data suggest that, the best patients for EC are those with tumors originating from the glottic larynx, classified as N0 and with low medical comorbidity status. This notion drawn from our univariate analysis is reinforced by the multivariate analysis performed which found that primary tumor arising outside the glottic larynx and Charlson comorbidity index²⁰ score above 1 were associated with a statistically significant reduction in survival. (Table 5) The N staging did not appear in the multivariate analysis due to the fact that very few patients were not staged as N0. Also, if this approach is used in patients with non glottic tumors classified as N0 we believe that the neck should be treated up-front since nodal failure ($p = .002$) and subsequent development of distant metastasis ($p = .004$) were significantly associated with diminished survival.

Two clinical parameters were associated with diminished local recurrence free survival (Table 6): patients who received a total dose of 5-FU greater than 37gm and those receiving greater than 5 cycles. This notion is a major finding when we compare the results achieved in the current report and the ones from our prior reports^{7, 8}, in which multivariate analysis was not performed. These two findings suggest that in certain individuals there is a threshold dose past which further systemic therapy is likely not effective, both in terms of the amount of 5-FU given and in extending the number of cycles past five. These limitations of EC should be carefully considered in the design of future trials examining this approach.

Overall, sixty patients developed a local recurrence after EC in the current series. Using the Kaplan-Meier²⁷ actuarial life table method, a 73.5%, 53.3% and 50.3%, 1-, 3- and 5-year actuarial local control estimates was achieved in our series with no local recurrence noted after the fifth year. For each group A-C, local control after EC alone is inferior to what is described in the literature and accepted as standard of care. Yet, when local recurrence developed, salvage treatment was possible in 83.3% of cases, resulting in an overall

observed 85.6% local control rate. But salvage treatment after EC was quite effective in many patients and very much within the standard of care—and especially for patients with tumors of the glottic larynx. In fact, we found that final local control for patients with glottic cancer (96%) was significantly ($p = .0001$) better compared to patients with tumor originating from other locations 71%. This finding suggests that further studies using EC must employ extremely rigorous and close follow up before this approach is widely implemented.

Indeed, despite these promising results, the use of EC should not be considered as a standard of care for the treatment of patients with HNC. Multi-institutional prospective study of EC must be performed before such an approach is widely used or advocated. This single-institution experience in a large referral center could be performed where close multidisciplinary follow up is possible. Close observation by the physician for local or regional recurrence and patient's commitment to this regimen is absolutely essential for this approach. Further prospective evaluation in the setting of a clinical trial must be done.

Furthermore, not all head and neck patients are, nor should be, amenable to this EC approach. We wish to highlight the potential advantages of EC, which advocates a purely neoadjuvant approach. With advances in genomic, proteomics, and systems biology, we believe that biomarkers can be found that predict these important outcomes, as has been done in other tobacco-related cancers such as lung cancer²⁸. Future prospective and multicenter trials of EC can be used to select these biomarkers and thus identify which patients are best (or least) suited to receive chemotherapy alone as definitive treatment.

Some may argue that such an approach, in the face of highly effective radiation therapy with or without chemotherapy, is not indicated. But, even in the era of EGFR-targeted therapy^{26, 29}, the mounting toxicity of current therapeutic regimens^{26, 30, 31} suggests that we continue to explore alternative approaches for this challenging disease. For selected patients with laryngopharyngeal carcinoma EC may be worth further consideration, especially for those patients with tumors of the glottic larynx.

Conclusion

We present data that confirms that EC can achieve long-term remission and locoregional control without surgery or radiation in selected patients with laryngopharyngeal SCC. Even for those patients who at first responded to EC and later relapsed, standard salvage therapy was still feasible in a majority of patients. In fact, for this whole cohort, overall survival was comparable to results seen with more standard treatment. Finally, exclusive chemotherapy has permitted us to successfully down-modulate the extent of local and regional therapy while achieving overall survival benefits with a profile of treatment-related toxicity.

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Figure 1. Overall Survival, stratified by site of origin of tumor

Patients are plotted based on the origin of the primary tumor. Tumors of the epilarynx/hypopharynx, glottic larynx, non-glottic larynx and oropharynx are represented by blue, red, black, and orange curves, respectively.

Figure 2. Overall Survival, stratified by N classification

Patients classified by N0, N1, N2, N3 are represented by blue, red, black, and orange curves, respectively.

Figure 3. Overall Survival, by Comorbidity Index

Blue curve indicates Charlson Index 0-1; the red curve represents Charlson Index of ≥ 2

Figure 4. Local Recurrence-free Survival by Courses

Blue curve indicates patients who received 5 courses or less; the red curve represents patients more than five cycles.

Figure 5. Local Recurrence-free Survival by Cumulative Dose of 5-FU. (mg/m²)

Blue curve indicates patients who received a total dose less than 37 mg/m²; the red curve represents patients receiving a total dose equal or above.

Table 1

General data among 146 patients (#: number of patients).

Cohort characteristics	# (%)
Gender	
Male	128 (90.1%)
Female	14 (9.9%)
Age	
Mean age in years	59.3
Range in years	36-80
Age ≥ 70 years	21 (14.8%)
Charlson comorbidity²⁰	
0	63 (44.4%)
1	34 (23.9%)
2	21 (14.8%)
3	10 (7.0%)
4	9 (6.3%)
5	5 (3.5%)
Prior malignancy	16 (11.3%)
Prior head and neck cancer	14 (9.9%)
Prior RT to head and neck	10 (7.0%)

Table 2

TNM staging (UICC 2002).

	N0	N1	N2	N3	Total
T1	33	0	0	1	34
T2	53	5	2	0	60
T3	29	3	1	0	33
T4	8	2	3	2	15
Total	123	10	6	3	142

Table 3

Total dosages of the drugs delivered (mg: milligrams, g: grams).

Drug delivered	No. of patients who received the drug	Total dose delivered mean (range)
Cisplatin	140	695 mg (75mg -1500mg)
Carboplatin	23	1062 mg (28mg -3200mg)
5-Fluorouracil	141	43 g (12g -145g)
Bleomycin sulfate	23	138 mg (37mg - 420mg)
Vepeside	13	724 mg (1mg - 2400mg)
Oncovin	7	5 mg (1mg - 10mg)
Methotrexate	9	396 mg (90mg - 960mg)
VP-16	3	1200 mg (600mg -1800mg)
Thiotepa	3	23 mg (10mg - 30mg)

Table 4
Toxicity according to the Eastern Cooperative Oncologic Group criteria.²¹ (% in parenthesis)

	Renal	Digestive	Mucosal	Otologic	Anemia	Neutropenia	Thrombocytopenia
0	77 (54.2)	77 (54.2)	96 (67.6)	140 (98.6)	107 (75.4)	118 (83.1)	111 (78.2)
1	33 (23.2)	31 (21.8)	18 (12.7)	2 (1.4)	13 (9.2)	9 (6.3)	9 (6.3)
2	27 (19.0)	28 (19.7)	21 (14.8)	0 (0)	18 (12.7)	10 (7.0)	17 (12.0)
3	5 (3.5)	6 (4.2)	7 (4.9)	0 (0)	4 (2.8)	4 (2.8)	4 (2.8)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (0.7)

Table 5

Univariate statistical analysis of survival (mg: milligrams, g: grams, NS: non significant).

Variable		HR	p value	
			univariate	multivariate
Age	Continuous variable	1.03 (1,1.05)	0.03701	0.03701
	Age>=70	1.69 (0.97,2.95)	0.06280	0.06280
Gender	Male	1.56 (0.63,3.87)	0.33671	0.33671
T classification	T4	1.38 (0.62,3.08)	0.43131	0.78898
	T3	0.93 (0.47,1.84)	0.82603	0.78898
	T2	1.01 (0.55,1.82)	0.98432	0.78898
N classification	N3	4.36 (1.36,14.02)	0.01349	0.00318
	N2	3.75 (1.49,9.46)	0.00514	0.00318
CoMorbidity Status	>1	2.83 (1.79,4.5)	0.00001	0.00001
Primary Tumor Site	Larynx Glottic	0.75 (0.31,1.79)	0.51688	0.00003
	Larynx NonGlottic	0.28 (0.17,0.48)	0.00000	0.00003
Treatment Group	C	2.47 (0.98,6.24)	0.05644	0.10755
	B	1.36 (0.84,2.2)	0.21531	0.10755
Total dose of cisplatin	Continuous	1 (1,1)	0.24006	0.24006
Total dose of FU	Continuous	1 (0.99,1.01)	0.70325	0.70325
Cisplatin	>=720	0.78 (0.5,1.23)	0.28813	0.28813
Use of carboplatin	Yes	0.86 (0.43,1.74)	0.67759	0.67759

Note: the group not showing in the table is the reference group for each variable.

Table 6

Univariate Statistical analysis of local recurrence (mg: milligrams, g: grams, NS: non significant).

Variable		HR	p value	
			univariate	univariate
Age	1-year increments	0.98 (0.95,1)	0.09239	0.09239
gender	Male (vs. female)	0.57 (0.28,1.15)	0.11410	0.11410
T	T4	1.89 (0.79,4.5)	0.15035	0.15901
T	T3	1.88 (0.91,3.88)	0.08609	0.15901
T	T2	1.1 (0.55,2.2)	0.77748	0.15901
N	N3	2.19 (0.53,8.99)	0.27710	0.13213
N	N2	2.64 (1.05,6.64)	0.03950	0.13213
N	N1	0.76 (0.24,2.42)	0.63827	0.13213
site	LarynxNonGlottic	1.79 (0.72,4.44)	0.20938	0.15732
site	LarynxGlottic	0.71 (0.41,1.24)	0.23017	0.15732
group	B (compared to A)	2.18 (1.32,3.61)	0.00237	0.00718
Total_dose_cisplatin	One unit increment	1 (1,1)	0.09917	0.09917
cisplatin	Total dose >=720mg	1.28 (0.78,2.1)	0.32894	0.32894
carboplatin	Yes versus No	0.99 (0.5,1.93)	0.96630	0.96630
FU37	Total dose >=37	2.47 (1.42,4.3)	0.00137	0.00137
Number of courses	Greater than 5	2.36 (1.26,4.42)	0.00718	0.00718

Table 7
Positive and negative effects of the modulation performed using EC

	Definitive local control after EC	Local failure after EC : methods of salvage and definitive result		
		Conservative with success	Non conservative with success	Palliative
Group A (93 patients)	57	30	2	4
Group B (43 patients)	17	14	7	5
Group C (6 patients)	4	1	0	1