

## INFLUENCE OF BOOST TECHNIQUE (EXTERNAL BEAM RADIOTHERAPY OR BRACHYTHERAPY) ON THE OUTCOME OF PATIENTS WITH CARCINOMA OF THE BASE OF THE TONGUE

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We reviewed 90 patients with squamous cell carcinoma of the base of the tongue. Fifty-three patients were treated with external beam radiotherapy alone (3 T1, 11 T2, 21 T3, and 18 T4 tumors) and thirty-seven patients were treated with external beam radiotherapy plus brachytherapy boost (4 T1, 15 T2, 11 T3, and 7 T4 tumors). For patients with T1, T2 and T3 primaries, the actuarial 3-year local relapse-free survival was 42% following external beam radiotherapy alone and 67% following external beam radiotherapy plus brachytherapy ( $p < 0.05$ ). The actuarial 3-year cause specific survival for these T-stages was 37% for patients treated with external beam radiotherapy alone and 53% for patients treated with external beam radiotherapy plus brachytherapy ( $p = 0.1$ ). In the Cox multivariate analyses restricted patients with T1, T2 and T3 staged tumors, treatment modality was the only predictor for local control but no influence on specific survival was found. The trend towards significant differences in specific survival found in the univariate comparison of both treatment modalities was probably due to the significantly higher number of N-positive patients treated with external beam radiotherapy alone. When all stages were included in the Cox analysis, low hemoglobin level, invasion of deep muscle, number of palpable nodes, and history of weight loss significantly influenced the outcome. Soft tissue necrosis occurred more frequently in patients treated with external beam radiotherapy plus brachytherapy (33% vs. 10%,  $p = 0.52$ ).

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Treatment of squamous cell carcinoma of the base of the tongue is largely dependent on radiotherapy since the posterior third of the tongue is essential for deglutition, phonation and airways protection and surgical treatment usually leaves a functional impairment that is proportional to the extent of the resection required to achieve adequate margins. External beam irradiation alone and external beam irradiation plus brachytherapy boost have been used

to treat these tumours, and there is controversy about which one of these two treatment modalities is the treatment of choice for squamous carcinoma of the base of the tongue.

Since 1964, we have used both treatment modalities for base of tongue carcinomas. We have retrospectively reviewed our series to evaluate by means of a univariate analysis and a multivariate analysis whether one of these treatment modalities achieves higher local control and survival rates.

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### Material and Methods

#### Patients

Between July 1964 and December 1989, one hundred and sixteen patients with histologically proven diagnosis of squamous cell carcinoma of the base of the tongue were

admitted at the Department of Radiation Oncology of Clinica Puerta de Hierro, Madrid, Spain. Those patients with newly diagnosed carcinomas treated at our department with curative intent using external beam radiotherapy alone or external beam radiotherapy plus brachytherapy boost were considered eligible for this study. Ninety patients met these criteria and are included in the analysis. Patients with relapsed carcinomas of the base of the tongue (10 cases), those who were referred to us for implant boost after treatment with external beam irradiation at other institutions (4 cases), those treated with surgery and postoperative irradiation (4 cases) or with brachytherapy alone (7 cases), and one patient with metastasis at presentation who was treated for palliation, were excluded from the analysis. Twenty-one patients with squamous cell carcinoma of the valleculae were not included in this study.

The mean age was 57 years (range, 29 to 86 years), and the male to female ratio 29:1 (87 men and 3 women). Information about smoking history was available in 88 clinical records and about alcohol intake habits in 87 clinical records. None of the women in this series smoked or drank alcohol. Ninety-eight per cent of the men were smokers. Regular alcohol intake was recorded in 89% of male patients. The histological diagnosis was differentiated squamous cell carcinoma in 83 cases (92%), lymphoepithelioma in 2 cases (2%) and undifferentiated squamous cell carcinoma in 5 cases (6%). Information about histopathological grade was available in 55 cases; there were 17 (31%) G1 carcinomas, 15 (27%) G2 carcinomas, 16 (29%) G3 carcinomas and 7 (13%) G4 carcinomas. Each patient's disease was retrospectively restaged according to the unified recommendations of the American Joint Committee on Cancer (1) (AJCC) and International Union Against Cancer (2) (UICC) on the basis of descriptions and drawings made at initial presentation. Patient distribution by T-stage and N-stage is demonstrated in Table 1. There were 4 patients (4%) with stage I disease, 14 patients (16%) with stage II disease, 22 patients (24%) with stage III disease and 50 patients (56%) with stage IV disease.

**Table 1**

*T and N stages distribution in 90 patients (AJCC and UICC unified TNM system (1, 2))*

	N0	N1	N2	N3	Total
T1	4	1	1	1	7
T2	14	4	5	3	26
T3	12	5	12	3	32
T4	8	5	11	1	25
Total	38	15	29	8	90

Overall stage: 4 stage I, 14 stage II, 22 stage III and 50 stage IV cases.

### Treatment

All eligible patients in this series were treated with curative intent; however, this being a retrospective study, treatment policies varied slightly over this period. Our treatment policy has been to treat the primary tumor with radiotherapy alone, using one of two differentiated treatment strategies: either external beam radiotherapy to the primary and the neck followed by a boost to the primary using external beam irradiation, or external beam irradiation to the primary and the neck followed by a interstitial brachytherapy implant using  $^{192}\text{Ir}$  wire. Our treatment policy was to treat T1, T2 and T3 tumors with either of the two treatment schemes mentioned above. T4-staged tumors were treated in most cases with external beam radiotherapy alone. A few patients were treated with surgery plus postoperative irradiation and a small group of patients, most of them with previous irradiation to the head and neck, was treated with interstitial brachytherapy alone. These patients are not included in this report.

*External beam radiotherapy alone.* External beam irradiation was delivered with megavoltage equipment and individualized techniques. External beam irradiation to the primary and the neck was delivered through two opposing lateral fields and, in most cases, a lower neck anterior field for the initial 50 Gy. After 42 to 45 Gy tumor dose, the lateral portals were reduced to spare the spinal cord. After 50 Gy tumor dose, an ipsilateral or two lateral reduced portals were used to deliver a boost dose to the primary tumor with a suitable margin. Differentially weighted fields were used for lateralized tumors. Out of 53 patients treated with external beam radiotherapy alone, 47 patients were treated using a conventional fractionation schedule, 4 patients using a hyperfractionated schedule, and in two patients treated with once-a-day irradiation the dose per fraction was 1.5 Gy. The median total tumor dose was 70 Gy (range 59.40 to 82 Gy). Three patients had T1 primaries, 11 had T2, 21 had T3, and 18 had T4 primaries. The distribution by N-stage was: 17 N0, 8 N1, 21 N2, and 7 N3. The overall stage was stage I in one patient, stage II in 3 cases, stage III in 11 cases, and stage IV in 37 patients. One patient had previously received external beam radiotherapy to the head and neck region and another patient had had an oral cavity tumor that had been treated with interstitial brachytherapy.

*External beam radiotherapy plus brachytherapy boost.* Patients treated with external beam radiotherapy plus brachytherapy boost were initially irradiated with external beam using identical techniques as those described for the initial part of the treatment with external beam radiotherapy alone. After two to three weeks' rest, an interstitial implant was performed using  $^{192}\text{Ir}$  wire. The  $^{192}\text{Ir}$  wires were implanted using the guide gutter technique (35 patients) or the plastic tube loop technique (2 patients). These interstitial brachytherapy techniques, developed at

French institutions, have been extensively described elsewhere (3–6). The doses delivered with external beam radiotherapy varied from 40 Gy to 54 Gy, with a median dose of 50 Gy; and those delivered by interstitial implant varied from 14.44 Gy to 48.9 Gy, with a median dose of 30 Gy. The total tumor doses ranged from 66.76 to 91.92 Gy, with a median dose of 78.38 Gy. Since 1982, computer dosimetry using the implant anteroposterior and lateral radiographs has been used and all interstitial implants performed prior to 1982 have been recalculated using computer dosimetry and the implant radiographs. The minimum target absorbed doses have been used for dose prescription in brachytherapy. Thirty-seven patients were treated with external beam radiotherapy plus brachytherapy. Four patients had T1 primaries, 15 had T2, 11 had T3, and 7 had T4 primaries. The distribution by N-stage was: 21 N0, 7 N1, 8 N2, and 1 N3. The overall stage was stage I in three cases, stage II in 10 cases, stage III in 11 cases, and stage IV in 13 patients.

*Treatment of the neck.* All N0-staged patients received elective irradiation to the neck. Patients with palpable nodes were treated with external beam radiotherapy alone (44 patients), with preoperative radiotherapy and neck dissection (6 patients) or with neck dissection and postoperative irradiation (2 patients). The dose administered to the neck in patients with palpable nodes treatment with external beam irradiation alone ranged from 44 Gy to 79 Gy (median 69.2 Gy).

*Chemotherapy.* Chemotherapy was given to 29 patients with advanced tumors. Seventy-nine per cent of these patients had stage IV disease. Seven patients were given concomitant bleomycin, fourteen patients concomitant tegafur, and one patient was given concomitant methotrexate. Neoadjuvant chemotherapy was given to 7 patients. In one patient treatment consisted of cisplatin, bleomycin, methotrexate, and vincristine; in 4 patients of cisplatin and 5-fluorouracil, in one patient of cisplatin and tegafur, and in another patient treatment consisted of cisplatin and bleomycin. Chemotherapy was given to 23 patients treated with the external beam radiotherapy (43%) and to 6 patients treated with external beam radiotherapy plus brachytherapy (16%).

#### *Follow-up*

Three patients were lost to follow-up. All remaining patients have been followed up for at least two years and 53 patients (59% of cases) have been followed up for at least 5 years.

#### *Statistical methods*

Data were stored and analyzed at the Department of Biostatistics. The statistical software of BMDP was used for data analysis (7, 8). In the present study various

clinical and treatment-related factors were evaluated by means of univariate and multivariate analyses to assess their influence on two endpoints: the probability of controlling the primary tumor (local relapse-free survival) and the probability of escaping death due to cancer or death with cancer (adjusted or cause-specific survival). The clinical factors that were analyzed were age, alcohol intake, smoking habits, T-stage, maximum tumor diameter, N-stage, node fixation, number of palpable nodes, diameter of the largest node, stage, history of weight loss, hemoglobin level, histological grade, and tumor invasion into the extrinsic musculature of the tongue.

The univariate analysis performed to evaluate the influence of the treatment modality used for the primary tumor on local relapse-free survival and adjusted survival was restricted to patients with T1, T2 and T3 staged primary tumors because the number of T4-staged tumors treated with external beam radiotherapy plus brachytherapy was small and currently we do not use this technique to treat T4-staged tumors.

Other treatment-related parameters analyzed were: total dose and total duration of treatments performed with external beam radiotherapy alone, and total radiation dose given to patients treated with external beam radiotherapy plus brachytherapy boost. In the first part of the study all these variables were studied independently by means of univariate analyses to assess their effect on local relapse-free survival and adjusted survival.

Probabilities for local relapse-free survival and adjusted survival were calculated using the Kaplan-Meier method (9), and differences between curves were evaluated by the Mantel-Cox test (10). In the analysis of local relapse-free survival, persistent tumors at the primary site and recurrences of the primary tumor were scored as failures and patients were censored when they remained without evidence of relapse at the primary site at the last recent follow-up or when they died without prior relapse at the primary site. The adjusted survival rate is defined in the American Joint Committee on Cancer manual (11) as the proportion of the initial patient group that escaped death due to cancer if all other causes of death were not operating. Accordingly, in the analysis of adjusted survival, patients were scored as 'dead with disease' when they had cancer at the time of death and were censored when they died of known intercurrent diseases without evidence of tumor recurrence. The three patients eventually lost to follow-up and two patients dead from unknown causes were considered uncensored (relapsed) at the last follow-up date for the local relapse-free survival and the adjusted survival analyses. Statistical significance was considered when the p-value was less than 0.05 but p-values up to 0.10 are also noted. In the second part of the study, those clinical variables with prognostic significance or with a trend toward prognostic significance in the univariate analysis were compared using the regression model of Cox (12).

Also, we performed another Cox multivariate analysis restricted to patients with T1, T2, and T3 tumors to evaluate the influence of the treatment modality used to treat the primary tumor on the outcome including in the model the clinical variables cited above and the variable 'treatment modality used to treat the primary tumor' (i.e. external beam radiotherapy alone vs external beam radiotherapy plus brachytherapy boost). These Cox multivariate analyses were performed in relation to two major end points: local relapse-free survival and adjusted survival.

Complications were retrospectively graded according to severity. Soft tissue necroses were graded as mild if they healed with conservative management within six months, as moderate if healing required more than six months of conservative management, and as severe if they required hospitalization or surgical treatment. Osseous necroses were graded as: grade 1 = periosteal exposure; grade 2 = limited osteolysis; grade 3 = formation of sequestrum; grade 4 = any osseous necrosis with fracture or requiring hospitalization or surgical treatment. Trismus was scored as presence or absence of this complication. The  $\chi^2$  test with the Yates correction was used for comparisons of proportions in the evaluation of complication rates and to compare the T-stage distribution of the treatment groups.

## Results

### General outcome

Out of 90 patients, 24 (27%) remained alive at the closing date of the study, 45 (50%) had died of tumor related causes, 8 (9%) had died of intercurrent diseases, 8 (9%) of second cancer, 2 patients (2%) had died from unknown causes, and 3 patients (3%) had been lost to follow-up.

Forty-eight patients relapsed. Of these 48 relapses, 28 (58%) were isolated local recurrences, 4 (8%) isolated nodal recurrences, 2 (4%) isolated distant failures, 6 (12%) primary and nodal failures, 2 (4%) primary and distant failures, 4 (8%) nodal and distant failures, 2 (4%) local, nodal and distant failures. Ninety-five per cent of local relapses and all nodal recurrences appeared within two years following treatment. The actuarial 3-year local relapse-free survival was 83% for T1, 57% for T2, 43% for T3 and 49% for T4. The actuarial three-year adjusted survival was 83% for stage I, 36% for stage II, 42% for stage III and 42% for stage IV.

### Univariate analysis

The clinical factors associated to statistically significant differences in the univariate analysis are summarized in Table 2. Hemoglobin level lower than 120 g/l and presence of tumor invasion into the extrinsic musculature of the tongue were associated to statistically significant differences in both the probability of local relapse-free survival

**Table 2**  
Univariate analysis of clinical factors

Factor description	No. of patients	Three-year survival rates	
		LRFS	Adjusted survival
T-stage			
T1	7	83%	83%
T2	26	57%	36%
T3	32	43%	42%
T4	25	49%	42%
		pNS	pNS
N-stage			
N0	38	59%	58%
N1	15	48%	50%
N2	29	47%	30%
N3	8	20%	15%
		p = 0.06	p < 0.003
Stage			
I	4	67%	67%
II	14	57%	54%
III	22	53%	51%
IV	50	42%	37%
		pNS	pNS
Invasion of the extrinsic musculature			
No	75	56%	48%
Yes	15	27%	22%
		p < 0.03	p < 0.02
Weight loss			
No	79	53%	46%
Yes	11	36%	24%
		p = 0.10	p = 0.06
Haemoglobin level			
≤ 12 g/dL	10	22.5%	17%
> 12 g/dL	71	52%	45%
		p < 0.03	p < 0.05
Nodal diameter			
< 2 cm	18	42%	27%
2–4 cm	20	57%	54%
> 4 cm	14	31%	16%
		p = 0.06	p < 0.002
No. of nodes			
1	22	45%	52%
2 or 3	19	51%	41%
≥ 4	11	33%	0%
		pNS	p < 0.007

LRFS: Local relapse-free survival. NS: not significant. Differences were not significant in relation to other variables analyzed: age, amount smoked, alcohol intake, tumour diameter, node fixation, and histological grade.

and the probability of adjusted survival. There was a trend towards statistically significant differences in the probability of local relapse-free survival and adjusted survival in relation to weight loss. N-stage, nodal diameter and the number of palpable nodes significantly influenced the probability of adjusted survival.

The group of T1, T2 and T3 staged patients treated with external beam radiotherapy and the group of T1, T2 and T3 staged patients treated with external beam radiotherapy

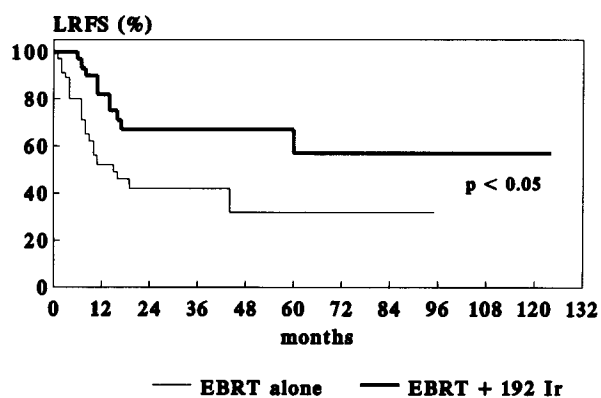


Fig. 1. Actuarial local relapse-free survival of patients with T1, T2, and T3 staged carcinomas according to the treatment modality used to treat the primary tumor. LRFS: local relapse-free survival. EBRT alone: treatment with external beam radiotherapy alone. EBRT + <sup>192</sup>Ir: treatment with external beam radiotherapy plus brachytherapy boost

plus brachytherapy were statistically comparable according to T-stage but the number of patients with palpable nodes was significantly higher in the group of T1, T2 and T3 staged patients treated with external beam radiotherapy alone. The actuarial local relapse-free survival curves according to treatment modality for patients with T1, T2 and T3 tumors are demonstrated in Fig. 1. The actuarial 3-year relapse-free survival was 42% (standard error: 8.7%) for patients treated with external beam radiotherapy alone and 67% (standard error: 9.1%) for patients treated with external beam radiotherapy plus brachytherapy boost. The differences between curves were statistically significant ( $p < 0.05$ ).

The actuarial adjusted survival curves according to treatment modality for patients with T1, T2 and T3 tumors are demonstrated in Fig. 2. The actuarial 3-year survival was 37% for patients treated with external beam

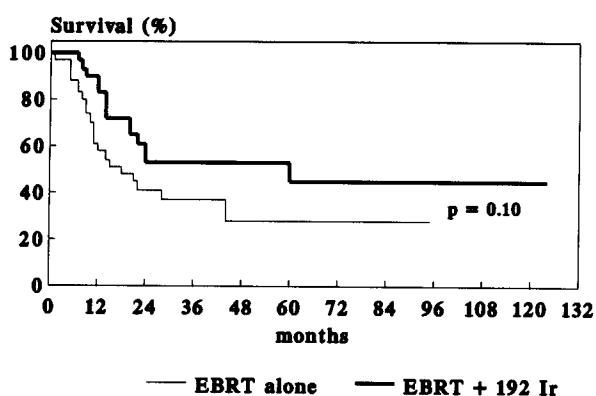


Fig. 2. Actuarial adjusted survival of patients with T1, T2, and T3 staged carcinomas according to the treatment modality used to treat the primary tumor. EBRT alone: treatment with external beam radiotherapy alone. EBRT + <sup>192</sup>Ir: treatment with external beam radiotherapy plus brachytherapy boost.

Table 3

Univariate analysis of treatment related factors

Factors description	No. of patients	3-year actuarial survival rates	
		LRFS	Adjusted survival
Total radiation dose (EBRT alone)			
≤ 6000 cGy	2	50%	50%
6000–7000 cGy	27	44%	36%
> 7000 cGy	24	49%	42%
		pNS	pNS
Treatment duration (EBRT alone)			
≤ 45 days	5	0%	0%
46–55 days	16	67%	59%
> 55 days	32	42%	36%
		p < 0.004	p < 0.006
Total radiation dose (EBRT + <sup>192</sup> Ir)			
≤ 7000 cGy	3	67%	33%
> 7000 cGy	34	58%	52%
		pNS	pNS

LRFS: local relapse-free survival. NS: not significant. EBRT alone: Patients treated with external beam radiotherapy alone. EBRT + <sup>192</sup>Ir: Patients treated with external beam radiotherapy plus brachytherapy boost.

radiotherapy alone and 53% for patients treated with external beam radiotherapy plus brachytherapy boost. There was a trend toward significant differences in adjusted survival according to treatment modality ( $p = 0.1$ ).

Table 3 summarizes the results of the univariate analysis of treatment-related factors. Prolongation of the total duration of the treatment in patients treated with external beam radiotherapy alone was associated to a lower probability of local relapse-free survival and adjusted survival. There were no significant differences in the probability of local relapse-free survival and adjusted survival in relation to the total radiation dose administered to patients treated with external beam radiotherapy alone or the total radiation dose administered to patients treated with external beam radiotherapy plus brachytherapy.

Multivariate analysis

The significant or nearly significant variables obtained previously were analyzed using the Cox proportional hazards model. The model enters those factors that independently influence prognosis in a stepwise fashion, the most significant variable being entered first. In the first multivariate analysis which included all T-stages, hemoglobin level was found to significantly influence the probability of local relapse-free survival. Also, there was a trend toward significance ( $p$ -value higher than 0.05 and lower than 0.1) in relation to invasion of the deep musculature of the tongue. Table 4 gives the coefficients, the standard errors, the  $p$ -values, the relative risks, and the 95% confidence

**Table 4**

*Cox proportional hazards analysis: Independent clinical factors influencing local control*

Factors and subgroups	p-value	Relative risk (e <sup>β</sup> )	Relative risk (95% CI)
Hemoglobin level			
> 120 g/l	0.03	2.5	1.08–5.79
≤ 120 g/l			
Invasion of deep muscle			
No	0.053	2.04	0.98–4.21
Yes			

β: regression coefficient. CI: confidence interval

**Table 5**

*Factors predicting local control in T1, T2 and T3 staged carcinomas of the base of tongue*

Factors and subgroups	p-value	Relative risk (e <sup>β</sup> )	Relative risk (95% CI)
Treatment modality			
EBRT + <sup>192</sup> Ir	0.03	2.33	1.07–5.08
EBRT alone			

β: regression coefficient. CI: confidence interval. EBRT alone: Treatment with external beam radiotherapy alone. EBRT + <sup>192</sup>Ir: treatment with external beam radiotherapy plus brachytherapy.

**Table 6**

*Cox proportional hazards analysis: Independent clinical factors influencing adjusted survival*

Factors and subgroups	p-value	Relative risk (e <sup>β</sup> )	Relative risk (95% CI)
Number of palpable nodes			
≤ 3	0.008	3.10	1.33–7.21
> 3			
Invasion of deep muscle			
No	0.03	2.15	1.07–4.33
Yes			
Weight loss			
No	0.04	2.25	1.03–4.94
Yes			

β: regression coefficient. CI: confidence interval.

intervals of the relative risks for each significant prognostic factor.

The treatment modality used for the primary tumor was the only independent prognosticator for local relapse-free survival in the Cox multivariate analysis restricted to patients with T1, T2 and T3 staged tumors (Table 5). This analysis was performed including in the model those clinical factors with prognostic significance in the univariate analyses and the variable 'treatment modality used to treat the primary tumor'. Three independent variables were

found to significantly influence adjusted survival in the following order: 1) number of palpable nodes, 2) tumor invasion of the extrinsic musculature of the tongue, and 3) weight loss. Table 6 shows the significant variables influencing adjusted survival. Their respective coefficients, standard errors, p-values, relative risks, and 95% confidence intervals of the relative risks are also shown.

The number of palpable nodes was the only independent prognosticator for adjusted survival in the Cox multivariate analysis restricted to patients with T1, T2, and T3 staged tumors treated with external beam irradiation alone or with external beam irradiation plus <sup>192</sup>Ir brachytherapy boost (95% confidence interval of relative risk: 1.91 to 14.8, p = 0.0016). This analysis was performed including in the model those clinical factors with prognostic significance in the univariate analysis and the variable 'treatment modality used to treat the primary tumor'.

#### *Treatment complications*

There was a 6% incidence of trismus, a 20% incidence of soft tissue necrosis and a 5% incidence of bone exposure. There was a 2% incidence of major complications that required surgery. The incidence of mild, moderate, and severe soft tissue necrosis was 10%, 5% and 5% respectively. The incidence of grade 1, grade 2, grade 3, and grade 4 bone necrosis was 2%, 0%, 2%, and 1% respectively.

Patients treated with external beam radiotherapy plus brachytherapy boost had a 33% incidence of soft tissue complications, 11% incidence of bone complications, and one patient out of 36 required surgical treatment. The incidence of mild, moderate, and severe soft tissue necrosis was 17%, 11% and 5% respectively. The incidence of grade 1, grade 2, grade 3, and grade 4 bone necrosis was 5%, 0%, 3%, and 3% respectively. Patients treated with external beam radiotherapy alone had a 10% incidence of soft tissue complications and a 2% incidence of bone complications, and one patient out of 51 required surgical treatment. The incidence of mild, moderate, and severe soft tissue necrosis was 6%, 0% and 4%, respectively. The incidence of grade 3 bone necrosis was 2%, and there were no cases of grade 1, grade 2 and grade 4 necrosis. The incidence of soft tissue necrosis was significantly higher in patients treated with external beam radiotherapy plus <sup>192</sup>Ir brachytherapy boost (p = 0.052). There were no statistically significant differences in the incidence of other complications according to treatment modality. The dose delivered by external beam, the dose delivered by implant and the dose rate did not significantly influence the incidence of complications.

#### **Discussion**

The first step in this study was to evaluate the influence of clinical factors on the probability of local control and

survival. This was followed by another analysis to evaluate whether treatment modality influenced the outcome independently of the clinical prognostic factors identified in the first analysis. In the multivariate analysis, invasion of the deep musculature of the tongue was a prognostic factor for local control and survival but we were unable to demonstrate a relationship between T-stage or tumor diameter and the outcome. These results, which have also been reported by other authors (4, 13, 14), might be due to the difficulty of accurate assessment of the extent of these basically infiltrative lesions by surface measurements. T-stage was a prognosticator for tumor control in some univariate analysis (15, 16) and in two multivariate analyses (17, 18), but not in other (13, 14, 19–21). In the present series, the number of palpable nodes was the strongest predictor of survival. These results are consistent with those of Calais et al. (15) and Foote et al. (22) reporting the predominant influence of lymph node involvement on the probability of survival.

In the present study, some factors which are not related to primary tumor extent or nodal metastasis were predictors for local control and survival. Patients with low hemoglobin level had a higher probability of local relapse. The influence of hemoglobin level on the probability of local control in patients with oropharyngeal carcinoma has been reported by Bentzen et al. (23). Weight loss was an independent predictor for adjusted survival. Similar findings have been reported by Mick et al. in patients with advanced head and neck carcinomas (24).

The role of interstitial brachytherapy boost in the treatment of cancer of the base of the tongue remains controversial (25–28). Most studies in the literature report the experience of a single institution using either external beam irradiation boost or brachytherapy boost but not both techniques. In these reports, the rates of local control achieved with external beam radiotherapy plus brachytherapy boost varied from 80% to 100% for T1 tumors (3, 19, 29–31), from 71% to 100% for T2 tumors (3, 19, 29–31), and from 80% to 90% for T3 tumors (19, 30, 31). The rates of local control achieved with external beam radiotherapy alone ranged from 72% to 100% for T1 tumors, from 55% to 90% for T2 tumors and from 33% to 81% for T3 tumors (14, 15, 32–34). Jaulerry et al. (17) from the Institut Curie reported a five-year actuarial local relapse-free survival of 96% for T1 tumors, 54% for T2 tumors, and 37% for T3 tumors treated with external beam radiotherapy alone. Wang (21) from the Massachusetts General Hospital reported a 5-year actuarial local relapse-free survival of 67% for T1 tumors, 87% for T2 tumors, and 57% for T3 tumors using accelerated hyperfractionated external beam irradiation. Lusinschi et al. (4) from the Institut Gustave-Roussy reported a 5-year local relapse-free survival of 85% for T1 tumors, 50% for T2 tumors, and 69% for T3 tumors treated with external beam radiotherapy plus brachytherapy boost. Although the rates of local control seem to be

slightly superior for patients treated with external beam radiotherapy plus brachytherapy boost, we must underscore that the direct comparison of results from different institutions requires great caution because the methods used for calculation of control rates differ. For example, we have considered those patients lost to follow-up and those who died from unknown causes as locoregional failures. Also, staging accuracy for oropharyngeal tumors varies between physicians (35) and the staging criteria may also differ from one institution to another.

Hoffstetter et al. (36) from the Centre Alexis Vautrin and Housset et al. (37) from the Hôpital Necker compared the results achieved at their institutions using both treatment techniques. In patients with T1 and T2 tumors (36, 37), and also in patients with T3 tumors (36) the local control rates were significantly higher with external beam irradiation plus brachytherapy boost.

In the univariate analysis performed in the present study, the probability of local relapse-free survival of patients with T1, T2 or T3 staged tumors of the base of the tongue treated with external beam radiotherapy plus  $^{192}\text{Ir}$  brachytherapy boost was significantly higher than the probability of local relapse-free survival of patients with tumors of the same stages treated with external beam radiotherapy alone ( $p < 0.05$ ). Differences in the probability of adjusted survival according to treatment modality were not statistically significant ( $p = 0.10$ ). Also, this factor was the only predictor for local control in the multivariate analysis of clinical and treatment related factors restricted to patients with T1, T2 and T3 staged tumors.

Our results support those reported by Hoffstetter et al. (36) and Housset et al. (37) and suggest that when patients are evaluated in a single institution and according to uniform criteria, treatment with external beam radiotherapy plus brachytherapy boost increases the probability of local control. Nevertheless, our study and those referred above are retrospective and we must take into account that these differences might be due to differential bias in the selection of patients for each treatment modality. In particular, the bias in the distribution of N-positive cases could partly explain the differences in local control probability between both treatment groups since N-stage has been shown to significantly influence the probability of local control in several studies (38–42). However, the fact that N-stage did not influence the probability of local control in the multivariate analysis performed in the present study should not be disregarded. Needless to say, only a randomized study would allow to state whether brachytherapy boost brings about a real improvement.

Since the number of palpable nodes was the main predictor for adjusted survival in the multivariate analyses, the trend towards significance in the univariate comparison of both treatment modalities was probably due to the significantly higher number of N-positive cases treated with external beam radiotherapy alone.

The incidence of complications in patients treated with external beam radiotherapy alone in the present series falls within the range reported by institutions that used this treatment technique (14, 32, 34, 43). Also, the rates of complications in patients treated with external beam radiotherapy plus brachytherapy were similar to those reported in the literature (3, 4, 19, 31). The incidence of complications was higher in those patients treated with external beam radiotherapy plus brachytherapy boost. Hoffstetter et al. (36) also reported higher rates of complications for patients treated with external beam radiotherapy plus brachytherapy boost. The increased risk of complications associated with the use of brachytherapy boost is probably related to the use of hairpins to perform most of the implants in the present series. The incidence of complications is probably lower when the implants are performed with the looping techniques (19).

In the univariate analysis, prolongation of treatment time was associated to a lower probability of local relapse-free survival and adjusted survival. The low local control and survival probability achieved in patients whose treatment course was completed in less than 45 days seems paradoxical, but treatments completed in less than 6 weeks and a half were in fact shortened treatment courses which were administered to patients with very advanced tumors that had responded very poorly to treatment. Four of these five patients had tumors whose diameter exceeded five centimeters, and the total dose ranged from 60 to 61 Gy in three cases. The deleterious effect of treatment interruptions has been previously reported for carcinomas of the head and neck (44), for carcinomas of the oropharynx (23, 45, 46), and for carcinomas of the tonsillar region (47, 48).

In the present series tumor dose did not significantly influence the outcome. These results must be interpreted with caution since patients with large tumors, poorly responding tumors and those who required treatment interruptions received higher radiation doses. The chemotherapy schemes used were very heterogeneous, and this precludes a precise evaluation of its influence on the outcome. Accordingly, it is very difficult to decide whether chemotherapy could influence the local control and survival rates achieved in the two groups of patients reported in this series, i.e.: the external beam radiotherapy alone group and the external beam radiotherapy plus brachytherapy group. The most frequently used chemotherapy scheme, concomitant tegafur, did not influence local control or survival in the randomized study conducted at our department (49).

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