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ORIGINAL ARTICLE

Randomized phase II study of cisplatin and 5-FU continuous infusion (PF) versus cisplatin, UFT and vinorelbine (UFTVP) as induction chemotherapy in locally advanced squamous cell head and neck cancer (LA-SCHNC)

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Abstract
Objectives We conducted a multicentric randomized phase II trial comparing 5-FU continuous infusion (PF) and cisplatin, UFT and vinorelbine (UFTVP) as induction chemotherapy (IC) in locally advanced squamous cell head and neck cancer (LA-SCHNC). Primary objective was complete response (CR) to IC and overall survival (OS) was a secondary objective.

Materials and methods PF: cisplatin 100 mg/m^2 i.v. Day 1 (D1) and 5-FU 1,000 mg/m^2 per day i.v. continous infusion D1–D5, every 21 days. UFTVP: cisplatin 100 mg/m^2 i.v. D1; UFT 200 mg/m^2 per day p.o. D1–D21 and vinorelbine 25 mg/m^2 i.v. D1 and D8, every 21 days. Four IC courses were planned in both arms.
Results A total of 206 patients (pts) were included (PF/UFTVP: 99/107): oral cavity: 8%/10%, oropharynx: 20%/25%, hypopharynx: 17%/14%, larynx: 54%/50%. Stage (TNM, 2002): III: 41%/35%, IVA: 23%/27%, IVB: 35%/38%. Complete response to IC: PF:36%/UFTVP:31% (*P*: no significative (NS)). G 3–4 toxicity (PF/UFTVP): neutropenia: 52%/72%; febrile neutropenia: 3%/20% ($P < 0.001$); anaemia:1%/14% ($P < 0.001$); trombocytopenia: 5%/0% ($P = 0.02$); mucositis: 15%/7% ($P < 0.001$). Deaths during IC: 2(2%)/3(3%). IC with UFTVP was associated with a favourable OS in the Cox analysis (actuarial 5 year OS: 49% vs. 34%; HR: 0.67, 95% CI: 0.47–0.95, *P*: 0.03).
Conclusions Although clinical response is equal in both arms, overall survival (Cox) is better in the UFTVP arm. Febrile neutropenia and anaemia were more frequent with UFTVP while mucositis and trombocytopenia were more severe with PF.

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Introduction

The roles of induction chemotherapy (IC) and combined chemo-radiotherapy (CT/RT) in the treatment of locally advanced squamous cell head and neck cancer (LA-SCHNC) have rapidly evolved over the past decade. In resectable disease, survival results are poor and surgery usually has considerable long-term consequences [1]. Multidisciplinary approaches have been explored in an attempt to decrease treatment morbidity and improve survival.

These approaches mainly include IC or induction CT/RT in order to achieve organ preservation. Randomized trials have shown that IC followed by definitive RT allows larynx preservation in two out of three patients with resectable locally advanced disease of the larynx and hypopharynx. This is accomplished without compromising overall survival in comparison with surgically treated patients [2–4]. Nevertheless, OS remains in the range of 40–50% [2–7]. Nearly half of LA-SCHNC patients have non-resectable disease. Results of RT alone in these patients are poor (5 year overall survival under 30%) [1]. In these patients, sequential or concomitant CT/RT were superior in terms of survival when they were compared with RT alone [8–11]. The IC treatment used in most of the above-mentioned studies has been PF: cisplatin 100 mg/m^2 i.v. on day 1 and 5-Fluorouracil (5-FU) 1,000 mg/m^2 continuous intravenous infusion from day 1 through 5, every 21 days [12]. This regimen has moderate haematological toxicity allowing a third drug to be added.

The interest of IC has been importantly improving in the last 2 years due to the positive results of various Phase III trials that have compared PF with new induction regimens adding a third drug to PF [13–18]. Moreover, different groups have explored the role of induction chemotherapy followed by concomitant chemo-radiotherapy with interesting results [19, 20]. Vinorelbine has promising activity in SCHNC [21] and the toxic profile of its combination with PF appears reasonable. In a phase II trial conducted by an Italian group, vinorelbine plus PF showed good activity with acceptable toxicity in metastatic and/or recurrent SCHNC [22]. UFT (uracil–ftegafur) is an oral fluoropirimidine with pharmaco-kinetic properties resembling those of a 5-FU continuous infusion with the advantage of being orally administered and has been used alone or in combination with cisplatin in patients with SCHNC with interesting results [23, 24]. In a previous Phase II trial, we explored the combination of cisplatin, vinorelbine and UFT (UFTVP) as IC in LA-SCHNC with promising results [25] (CR of 54%). We report here the results of a randomized phase II trial comparing PF with UFTVP as induction chemotherapy in LA-SCHNC.

Patients and methods

The present study was conducted between June 1997 and November 2001 in the Universitary Hospital *Marqués de Valdecilla* in Santander and in the Universitary Hospital *Lozano Blesa* in Zaragoza (Spain). The protocol was approved by the Research Ethics Committee of both institutions.

Included patients had histological diagnosis of SCHNC and locally advanced disease (TNM, 1997: stage III, IV-A and IV-B). Both, initially resectable and non-resectable patients were included. Other inclusion criteria were: age between 18 and 75 years; ECOG performance status (PS) ≤ 2; measurable disease; no previous chemotherapy or radiotherapy; adequate blood counts defined as an absolute neutrophil count of >1,500/ml, platelet count of >100,000/ml; adequate hepatic and renal functions defined as bilirubin, AST and ALT < 1.5 times the upper normal limit (ULN), alkaline phosphatase < 5× ULN, and a calculated or actual creatinine clearance >60 ml/min; no cardiac disease or other serious concomitant illnesses or medical condition; no previous tumor other than cervical, basal or squamous cell cancer of the skin within 5 years of entry into the study; no psychological or sociological problems that could preclude awareness of the study's implications and requirements. Fully informed written consent was obtained from all patients prior to study recruitment. All patients were evaluated before entry into the study in a multidisciplinary outpatient clinic in order to confirm they fulfilled all inclusion criteria, they did not present any exclusion criteria and to assess stage and resectability. Patients were initially staged according TNM classification of 1997 and they have been staged again using their initial records according to TNM classification of 2002 for the present analysis. Details of all eligible patients were forwarded to the trial office based at Santander Hospital to verify eligibility criteria; they were prospectively registered in the trial and were randomly assigned by an independent office to either PF or UFTVP induction chemotherapy in a 1:1 basis using random permuted blocks. Patients were stratified according to resectability at diagnosis.

Treatment administration was performed in an outpatient basis in UFTVP arm and in an inpatient basis in PF arm. Responses to chemotherapy were assessed by clinical evaluation (including fibroendoscopy) and CT scan. Primary tumor site and lymph node responses were scored separately and the site with lesser response determined overall response. Response was assessed on an intent-to-treat basis and according to the RECIST criteria. Complete response (CR) was defined as the disappearance of all clinically evident tumors. A biopsy was performed of the initially affected zone and needed to be negative for the response to be considered as complete. Partial response (PR) was defined as a reduction of more than 30% of the sum of all the largest diameters of all sites with measurable disease. Partial response of >90% at primary (>90% PR) was defined as greater than 90% reduction of the largest diameter of the primary tumor or when a positive biopsy at the initial zone of the primary was the only evidence of tumor. No response (NR) included stable disease (SD), disease progression (DP), or death occurring while on IC.

Induction UFTVP consisted of cisplatin 100 mg/m^2 i.v. day 1, vinorelbine 25 mg/m^2 i.v. days 1 and 8 and UFT

200 mg/m^2 p.o. days 1 through 21 every 21 days, for four cycles. Haematogram was performed on day 15 and if neutrophils were <500/ml, UFT intake was interrupted until next cycle administration with a 20% dose reduction of the three drugs on following cycles. No prophylactic colony-stimulating factor (CSF) was allowed. The use of Epoietin alfa and oral iron was included in the guidelines in the event of hemoglobin falling below 12 g/dL during IC.

UFTVP was immediately discontinued upon evidence of tumor progression or excessive toxicity. Chemotherapy toxicity was quantified using the common toxicity criteria (CTC) of the National Cancer Institute (NCI). Toxic deaths were those that occurred along the whole treatment or in the following 30 days after treatment completion with independence of the grade of complicity assigned to the treatment by the investigator.

Organ preservation was intended when a CR or a >90% PR was accomplished at primary site independently of the resectability at diagnosis. If response did not meet the aforementioned criteria, surgery was performed when feasible. Neck dissection was intended immediately after recovery from last course of IC when patients had cervical nodes >3 cm at diagnosis and for all residual nodes following RT.

Radiotherapy was administered to patients who achieved a CR or a >90% PR at primary site and for those who had non-resectable residual disease after IC. It was administered 5 days/week in daily 1.8 Gy fractions to the primary site and neck. Dose to the primary site was >65 Gy. Dose to involved neck disease was 60 Gy. A minimum of 45 Gy was bilaterally delivered to clinically uninvolved neck and supraclavicular regions. There were three consecutive cohorts of patients according to the concomitant use of chemotherapy during definitive radiotherapy: cohort 1 (1997–1998): UFT 250 mg/m^2 p.o. daily; cohort 2 (1998–2000): cisplatin 30 mg/m^2 i.v. weekly and UFT 150 mg/m^2 p.o. daily; Cohort 3 (2000–2001): docetaxel 25 mg/m^2 i.v. weekly. When primary tumor site resections were performed after chemotherapy, post-operative RT consisted of a minimum of 60 Gy to tumor bed regions.

In case of persistent or relapsed disease, salvage surgery was performed if feasible. Overall survival (OS) was calculated from the time of entry into the study until death time. Survival with primary site preservation (SPP) was defined as time from entry into the study until resection of primary site or death. Loco-regional control (LRC) was defined as time from entry into the study until loco-regional progression unsuitable to be controlled with surgery, radiotherapy or chemotherapy. Time to systemic failure (TSF) was defined as time from entry into the study until systemic progression.

The study was designed to test which of the two different induction regimens resulted in higher complete response (CR) rate. The expected CR rates of PF and UFTVP schedules were 30 and 50%, respectively. The sample size was calculated to detect a difference of 20% with an 80% power and a bilateral significance level (alpha) of 0.05; therefore, 206 patients (pts) were needed.

All analyses were performed on an intention-to-treat basis. All reported *P*-values were two-sided and *P* values of <0.05 were statistically significant. A Chi-square analysis was used to detect statistical differences in proportions. Survival curves were generated by Kaplan–Meier method. Log-rank test (lrk) was used to compare the different subgroups curves. A multivariate analysis was also performed: a logistic regression for CR rates and a Cox proportional hazard regression for OS. Analysis was performed using SPSS package version 8 (SPSS Inc., Chicago, IL).

Results

Patient's characteristics

Between June 1997 and November 2001, 206 patients (pts) were included (PF/UFTVP: 99/107). Their characteristics and disease extent are summarized in Table 1 and were well balanced between the two arms of the study.

Response to induction chemotherapy

All patients were evaluable for response. Overall response was complete in 36% of patients in the PF arm and in 31% in the UFTVP arm (*P*: no significative (NS)) and partial in 45 and 47%, respectively.

Toxicity of induction chemotherapy

All patients received at least one course of induction chemotherapy and were evaluable for toxicity. Maximum toxicity per patient is shown in Table 2. UFTVP produced significantly more neutropenia, febrile neutropenia and anaemia whereas PF produced more thrombocytopenia, emesis, mucositis and alopecia. Neurotoxicity was equally frequent in both arms. Two pts (2%) died during induction chemotherapy in the PF arm, and 3 pts (3%) in the UFTVP arm (*P*: NS).

Loco-regional treatment (Table 3)

No loco-regional treatment was administered in 7% of the patients in the PF arm and in 6% of the patients in the UFTVP arm (*P*: NS). After induction chemotherapy, 75 patients (76%) in the PF arm and 77 patients (72%) in the UFTVP arm were treated with radiotherapy (*P*: NS). Concomitant use of chemotherapy during RT is summarized in Table 3 and there were no significant differences between the two arms of the study. Surgical resection of primary tumor was performed in 24% of the patients in the PF arm

Table 1 Patients' characteristics

	PF (%)	UFTVP (%)
Number of patients	99	107
Median age (years)	56	60
PS (ECOG)		
0	19	18
1	78	86
2	2	3
Location		
Oral cavity	8	10
Oropharynx	20	25
Hypopharynx	17	14
Supraglottis	41	29
Glottis	13	21
Stage (TNM 2002)		
III	41	35
IVA	23	27
IVB	35	38
T4-A (TNM 2002)	10	9
T4-B (TNM 2002)	30	30
N+	61	60
Resectability at diagnosis	60	61
TALK score (alcoholism, T4, albumin < 4, IK < 80)		
0	28	27
1–2	61	67
3–4	11	6
Initial haemoglobin < 14 g/dl	40	42
Histological grade		
1–2	24	24
3	26	27
X	49	49

and in 29% of the patients in the UFTVP arm. Neck dissection was done in 30% of patients in both arms.

Mortality rate during radiotherapy and surgery was 2 and 2%, respectively in the PF arm and 1 and 1% in the UFTVP arm.

At the end of the whole treatment, 79% of patients were rendered disease free (67% with primary preservation) in the PF arm and 84% of patients were rendered disease free (59% with primary preservation) in the UFTVP arm (P = NS).

Failure and survival

Median follow-up is 64 months (range 33–89 months). Seventy-nine patients (39%) are alive without disease and 128 patients have died: 101(80%) as a result of their head and neck cancer (11 pts from the treatment and 90 pts from head and neck tumor progression) and 27 patients from other causes.

Table 2 Toxicity of induction chemotherapy (maximum toxicity per patient)

	PF (%)	UFTVP (%)	P
>80% planned			
Cisplatin	84	80	NS
5-FU/UFT	77	46	<0.05
Vinorelbine		70	
Haematological toxicity			
Neutropenia G 3,4	52	72	<0.05
Febrile neutropenia	3	20	<0.05
Anaemia G3–4	1	14	<0.05
Thrombocytop.G3–4	5	0	<0.05
Emesis G3–4	15	6	<0.05
Mucositis			
G1–2	37	17	<0.05
G3–4	15	7	<0.05
Alopecia G1–2	50	21	<0.05
Neurotoxicity G1–2	17	21	Pins
Toxic deaths	2 patients (2%)	3 patients (3%)	NS

Table 3 Loco-regional treatment after induction chemotherapy

	PF 99 pts (%)	UFTVP 107 pts (%)	P
Definitive radiotherapy	68	65	NS
RT alone	24	12	NS
RT/UFT	21	24	NS
RT/cisplatin–UFT	13	17	NS
RT/docetaxel	10	12	NS
RT followed by surgery of residual disease	7	6	NS
RT alone	3	3	NS
RT/UFT	0	1	NS
RT/cisplatin–UFT	3	0	NS
RT/docetaxel	1	2	NS
Surgery and adjuvant RT (alone)	17	23	NS
No loco-regional treatment	6	5	NS

As shown in Fig. 1, 5-year actuarial overall survival was 34% in the PF arm and 49% in the UFTVP arm (lrk $P = 0.08$), 5-year actuarial survival with primary site preservation was 27% in the PF arm and 37% in the UFTVP arm (lrk $P = 0.62$), and 5-year actuarial loco-regional control were 45% in the PF arm and 60% in the UFTVP arm (lrk $P = 0.03$). Time to systemic failure was (PF vs. UFTVP): 88 vs. 88% (lrk $P = 0.97$).

In the Cox analysis the only variables associated with a favourable prognosis for overall survival were IC with UFTVP (HR: 0.67, 95% CI: 0.47–0.95, P: 0.03), complete response to IC (HR: 0.53, 95% CI: 0.35–0.8, P: 0.002),

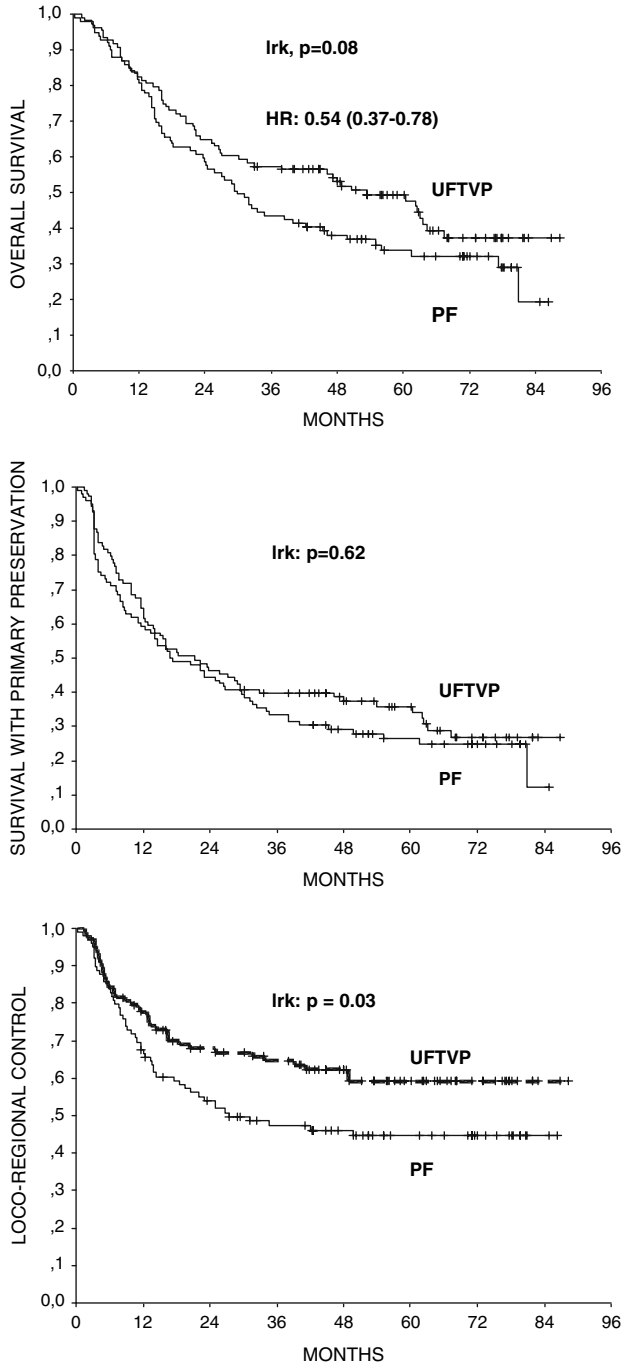

Fig. 1 Overall survival, survival with primary preservation and loco-regional control

stage III (TNM 2002) (HR: 0.54, 95% CI: 0.35–0.83, *P*: 0.04), alcohol intake <120 g/day (HR: 0.65, 95% CI: 0.45–0.93, *P*: 0.02), haemoglobin at the end of induction chemotherapy >10 g/dl (HR: 0.56, 95% CI: 0.34–0.91, *P*: 0.02), >80% of theoretical total doses of 5-FU/UFT administered (HR: 0.62, 95% CI: 0.43–0.91, *P*: 0.01) and no oral cavity location (HR: 0.44, 95% CI: 0.26–0.75, *P*: 0.003).

A subgroup analysis of OS in each treatment arm is shown in Table 4. Concerning stage (TNM-2002) a significant difference in favor of UFTVP was observed in stage III and a nearly significant difference in stage IV-B with no difference in stage IV-A. Five-year actuarial overall survival (OS), survival with primary preservation (SPP), loco-regional control (LRC), and time to systemic failure (TSF) according to stage (TNM 2002) are shown in Table 5 and in Fig. 2. Concerning loco-regional control, again a statistically significant difference in favor of UFTVP was seen in stage III and stage IV-B whereas there were no differences in stage IV-A.

A subgroup analysis of OS of each treatment arm according to the concomitant chemotherapy received during radiotherapy was performed (Fig. 3). A no statistically significant trend toward higher overall survival was observed in the UFTVP arm when RT alone (5-year actuarial OS: UFTVP: 46% vs. PF: 38%, lrk: $P = 0.8$), RT concomitant with UFT (5-year actuarial OS: UFTVP: 60% vs. PF: 55%, lrk: $P = 0.61$) or RT concomitant with docetaxel

Table 4 Subgroup analysis of overall survival (OS)

	5 year OS (%) (PF vs. UFTVP)	*P* (lrk)	HR (95% CI)
Resectability at diagnosis			
Yes	45 vs. 56	0.42	NS
No	21 vs. 40	0.07	NS
Stage (TNM 2002)			
III	48 vs. 70	0.03	0.26 (0.11–0.6)
IV-A	30 vs. 42	0.8	NS
IV-B	20 vs. 36	0.10	NS
Nodal status			
N0	47 vs. 65	0.08	NS
N+	24 vs. 37	0.35	NS
T			
T < 4	34 vs. 60	0.03	NS
T4-A	50 vs. 50	0.68	NS
T4-B	22 vs. 42	0.07	NS
Response to induction chemotherapy			
CR	53 vs. 68	0.18	NS
No CR	25 vs. 43	0.09	NS
Concomitant chemo/RT			
Yes	39 vs. 60	0.06	0.52 (0.31–0.88)
No	38 vs. 45	0.8	NS
Location			
Oral cavity	20 vs. 20	0.9	NS
Oropharynx	22 vs. 58	0.04	NS
Hypopharynx	29 vs. 43	0.26	NS
Supraglottis	40 vs. 50	0.43	NS
Glottis	52 vs. 57	0.77	NS

Table 5 Five-year actuarial overall survival (OS), survival with primary site preservation (SPP), loco-regional control (LRC) and time to systemic failure (TSF) according to stage (TNM 2002) and induction chemotherapy

	Stage III			Stage IV-A			Stage IV-B		
	PF 41 pts	UFTVP 38 pts	Lrk *P*	PF 23 pts	UFTVP 29 pts	Lrk *P*	PF 35 pts	UFTVP 41 pts	Lrk *P*
5-year OS (%)	48	70	0.03	30	42	0.8	20	36	0.10
5-year SPP (%)	38	52	0.31	16	25	0.50	22	32	0.39
5-year LRC (%)	62	87	0.03	48	48	0.93	22	43	0.04
5-year TSF (%)	97	97	0.98	73	77	0.70	87	84	0.87

(5-year actuarial OS: UFTVP: 60% vs. PF: 55%, lrk: $P = 0.83$) were administered after induction chemotherapy. This difference reached statistical significance in the subgroup of patients who were treated with RT concomitant with cisplatin-UFT (5-year actuarial OS: UFTVP: 40% vs. PF: 10%, lrk: $P = 0.01$).

Discussion

In the meta-analysis published in 2000 [26], chemotherapy only added a small benefit to loco-regional treatment in terms of OS (HR: 0.90, 95% CI: 0.85–0.94; absolute survival benefit of 4% at 5 years). This meta-analysis suggests that this benefit was higher with concomitant CT/RT (HR: 0.81, $P < 0.0001$, absolute survival benefit of 8% at 5 years) than with sequential chemotherapy and RT (HR: 0.95, $P > 0.05$, absolute survival benefit of 2% at 5 years). In a phase III study conducted by the Head and Neck Intergroup in the United States in patients with resectable locally advanced squamous cell carcinoma of larynx [27], organ preservation was achieved more frequently with concurrent CT/RT than with IC (84 vs. 72%). Nevertheless, OS was equal for both arms and RT was administered without concomitant chemotherapy in the IC arm.

Despite these results, many investigators think IC is an interesting approach because it could serve to identify and select patients with resistant disease who need surgery to achieve local control without taking the risks of the toxicity implied in CT/RT. Moreover, surgery performed following chemotherapy alone has less morbidity than CT/RT patients. The interest of IC has been importantly improving in the last two years due to the positive results of various phase III trials that have compared PF with new induction regimens adding a taxane to PF. The combination of docetaxel, cisplatin and 5-FU (TPF) had shown interesting activity as induction chemotherapy in LA-SCHNC in different phase II trials [28–31]. The results of three phase III trials comparing TPF with PF as induction therapy in LA-SCHNC have been recently presented: In the EORTC-24971/TAX-323 trial a total number of 358 patients with non-resectable LA-SCHNC were included and a significant improvement in OS (lrk: $P = 0.01$; HR: 0.73) was observed in the TPF arm [13]. In the TAX-324, (501 LA-SCHNC patients, 35% non-resectable), TPF was also superior to PF in OS (lrk: $P = 0.005$; HR: 0.7) [14]. In the GORTEC-2000-01, (205 patients with resectable tumors of larynx or hypopharynx), TPF was superior to PF in larynx preservation (lrk: $P = 0.03$) and nearly superior in OS (lrk: $P = 0.09$) [15].

Paclitaxel, cisplatin and 5-FU was compared with PF as induction therapy in a phase III trial [16] (382 patients; non resectable: 64%): the paclitaxel arm produced higher CR rate (33 vs. 14%, $P < 0.001$) and a trend to longer OS (lrk: $P = 0.06$), this difference being more evident in unresectable disease (lrk: $P = 0.04$).

Our randomized phase II trial explored the role of a new regimen of IC, UFTVP, trying to improve the results of PF in two ways: increasing the number of complete response rates (associated with better survival and organ preservation) by adding vinorelbine, and improving convenience by using oral UFT instead of 5-FU continuous infusion.

According to the main objective of the trial (CR rate to IC) it has been a negative trial because there was no significant difference between the two arms. Nevertheless, although this trial was not designed nor powered to detect a difference in OS (it was only a secondary objective), a better OS in favor of the induction UFTVP arm was seen (5-year OS: PF 34% vs. UFTVP 49%). This difference was only nearly statistically significant in the univariate analysis (lrk, $P = 0.08$) but it was statistically significant in the Cox analysis (HR: 0.67, 95% CI: 0.47–0.95, *P*: 0.03). This better OS in the UFTVP arm appears to be due to a better loco-regional control (5 year LRC: PF 45% vs. UFTVP 60%, lrk $P = 0.03$) which is accomplished without more resections of the primary tumor (5-year SPP: PF 27% vs. UFTVP: 37%, lrk $P = 0.62$). The improvement of OS and LRC was better in stage III and IV-B than in stage IV-A.

Another concern is the role of concomitant CT/RT after induction chemotherapy in LA-SCHNC. Different groups have found interesting results with this approach [19, 20]. Moreover, some phase I/II trials suggest a promising activity with docetaxel and paclitaxel concomitant with radiotherapy in thoracic tumors [32] and in SCHNC

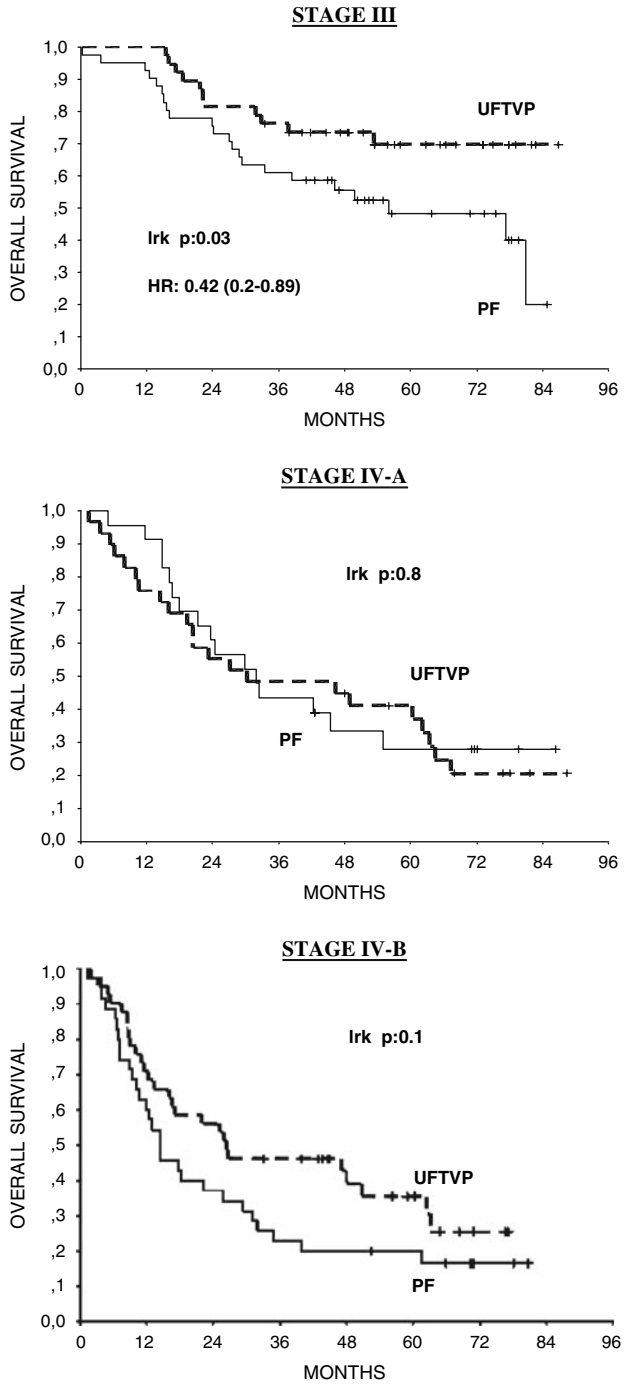

Fig. 2 Overall survival and stage (TNM 2002)

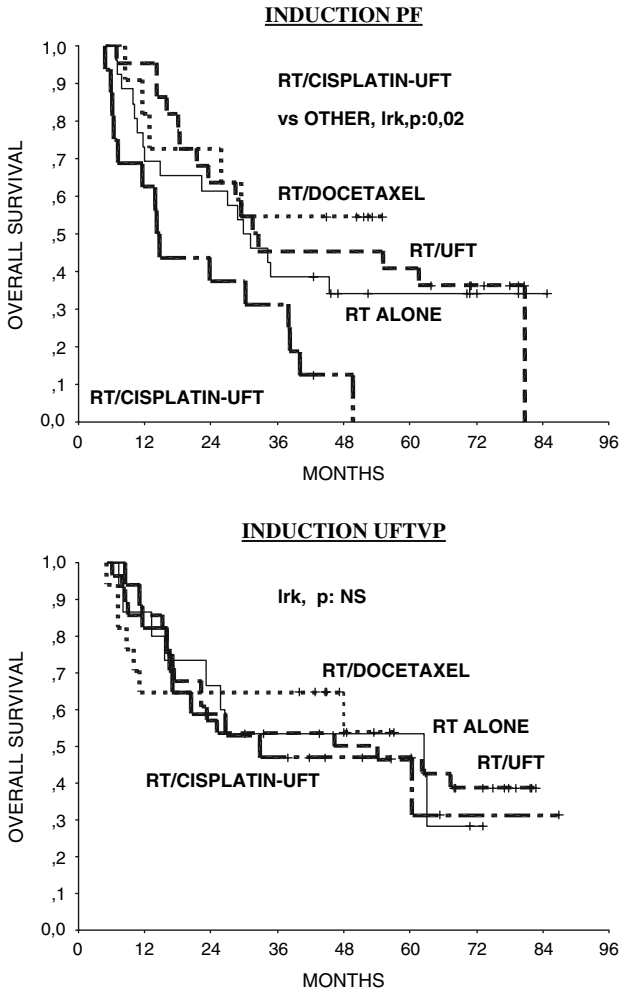

Fig. 3 Overall survival according to the concomitant use of chemotherapy during radiotherapy (only patients treated at primary site with radiotherapy after induction chemotherapy have been considered for this analysis)

[33, 34]. The different regimens of concomitant CT/RT used after IC in this trial, although consecutively used and well balanced between the two arms of the study, might be a problem for long-term results evaluation. The analysis of possible interactions between the type of IC and the type of concomitant CT/RT administered has limited value (subgroup analysis, no randomization, small number of patients, etc.). Nevertheless, we have observed better OS in the UFTVP arm in all the subgroups of patients. This improvement was only a non statistically significant trend in the subgroup of patients treated with RT alone, concomitant RT/UFT or concomitant RT/docetaxel, and it seems to be higher, reaching statistical significance in the subgroup of patients treated with concomitant RT/cisplatin-UFT.

In summary, our findings suggest that although IC with UFTVP obtained similar CR rate than PF, it could be superior in LCR and OS. These results must be considered with caution because OS and LRC were secondary objectives and there is also heterogeneity in loco-regional treatment. Nevertheless, the promising results achieved with induction UFTVP in this trial in terms of efficacy, toxicity and convenience, provides this regimen an interesting role in the treatment of LA-SCHNC and could be investigated in future trials.

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