Induction Chemotherapy and Sequential Concomitant Chemo-radiation in Locally Advanced Head and Neck Cancers: How Induction-phase Intensity and Treatment Breaks May Impact on Clinical Outcomes

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Abstract. *Aim: The purpose of the study was to assess outcomes of locally advanced head and neck (LAHNC) treated with induction chemotherapy (ICT) and subsequent concurrent chemo-radiation. Patients and Methods: A total of 71 LAHNC patients were treated with 2-3 cycles of docetaxel, cisplatin and 5-fluorouracil as induction chemotherapy and subsequent concurrent chemoradiation with weekly cisplatin or carboplatin. Definitive radiotherapy was delivered with intensity-modulated radiation and a simultaneous integrated boost approach up to a total dose of 70 Gy in 35 fractions to the macroscopic primary and nodal disease. Results: Actuarial 2-year OS, CSS, DFS, MFS, LC were 55.3% (95%CI=39.3-68.6), 58.6% (95%CI=41.9-72), 60.5% (95%CI=47.3-71.4), 87.3% (95%CI=76.2-93.5) and 74.7% (95%CI=61.5-83.9), respectively. On multivariate analysis undergoing to 3 vs. 2 cycles of TPF (HR=22.31; 95%CI=2.68-185.66; p=0.004) and radiotherapy treatment break >4 days (HR=1.28; 95%CI=1.06-1.55; p=0.01) negatively affected cancer-specific survival (CSS) with statistical significance. Achieving complete remission after ICT had a statistically significant impact on CSS (HR=0.9; 95%CI=0.01-0.54; p=0.009). Patients undergoing ICT with 3 cycles had more frequently treatment breaks compared to those submitted to 2 cycles (HR=1.36; 95%CI=1.06-1.73; p=0.01), and had statistically significant longer treatment break time (5.9+1.8 vs. 3+0.36; p=0.02). Conclusion: A shorter ICT phase may be a better option enhancing patients' tolerance during concurrent chemo-radiation and affecting clinical outcomes.*

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Key Words:Induction chemotherapy, head and neck cancer, concomitant chemo-radiation, treatment breaks, intensity-modulated radiotherapy.

The majority of patients affected with head and neck cancer (HNC) present with loco-regionally advanced disease (1). Combination therapy including comprehensive surgery, radiotherapy (RT) and chemotherapy (CT) are considered well-established treatment modalities (2). Whenever clinical context present with unresectable disease or patients are candidate for larynx-preservation approaches, or primary tumor involves specific head and neck sub-sites, the integration of RT and CT is a standard option (3). The addition of CT in HNC has been evaluated in the MACH-NC meta-analysis that confirmed a 4.5% overall survival (OS) benefit at 5 years for all-timing CT, specifically given as concurrent, induction or adjuvant strategy for locally advanced HNC (4). The most prominent benefit was found with concurrent CT and RT, that is considered the gold-standard (4). Induction chemotherapy (ICT) administered prior to loco-regional definitive therapy still plays a controversial role, since no established consensus is reached at present regarding its utilization (5). ICT is considered an effective approach to provide down-sizing and down-staging of locally advanced disease, potentially reducing toxicity in the definitive phase and a selection tool to divide patients into prognostic categories according to objective response to neoadjuvant treatment (1).

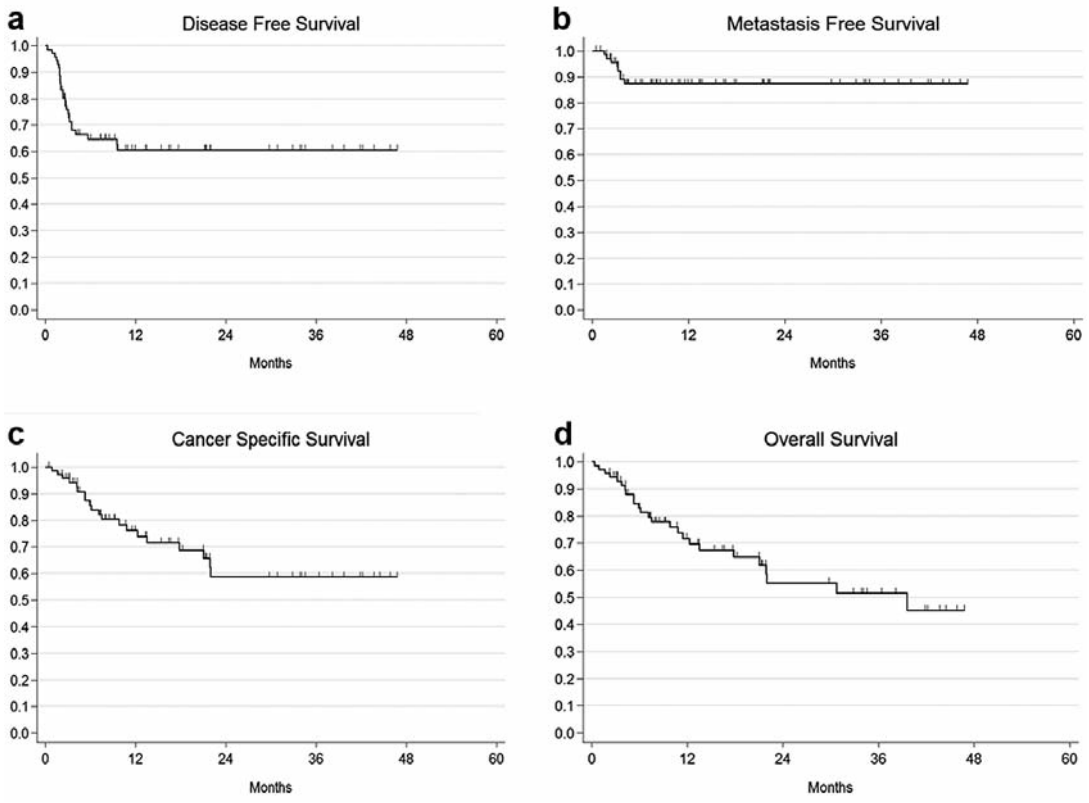

Figure 1. *Overall, cancer-specific, disease-free and metastasis-free survival curves.*

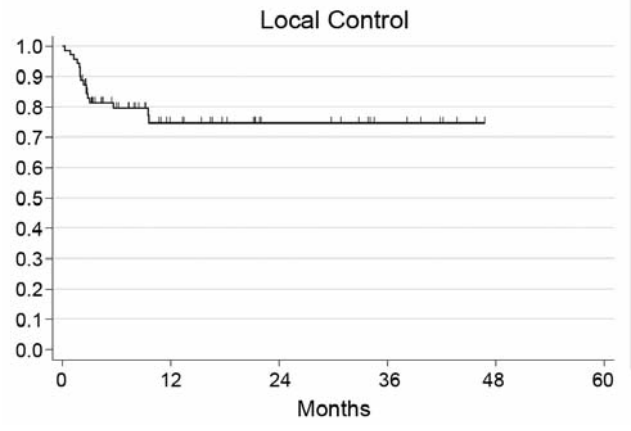

Figure 2. *Actuarial local control.*

Adjunctively, distant metastatic spread may be lowered by the systemic effect provided by ICT (5). We herein present retrospective clinical results of a consecutive case series of locally advanced HNC patients, treated with ICT and subsequent definitive (chemo)radiotherapy in a single-institution tertiary referral University Hospital.

Materials and Methods

Study population. Patients investigated were treated between May 2010 and January 2014 at the Radiaton Oncology Department of the University of Torino, Turin, Italy, for HNC of biopsy-proven squamous histology. Collected clinical information were retrieved from the Medical Records System of our Institutional Hospital and subsequently analyzed. Data undergoing analysis included demographics, primary tumor site, nodal status, staging, chemotherapy and radiotherapy characteristics, treatment response based on clinical examination and radiologic findings, site of recurrence, cause of death and time to recurrence and death.

Treatment characteristics. Patients underwent ICT before definitive treatment that included concomitant RT-CT. Response to ICT was assessed in all patients before definitive treatment using clinical examination, endoscopic investigation and CT or MR imaging.

Chemotherapy. ICT consisted of 2-3 cycles of TPF regimen given as docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 intravenously on day 1 and 5-fluorouracil 1,000 mg/m^2 on days 1-4 with continuous infusion. The choice between 2 or 3 TPF cycle was mainly driven by clinical decision focusing on patient's tolerance to ICT phase. During the concomitant RT-CT phase, patients underwent weekly cisplatin 30-35 mg/m^2 or weekly carboplatin AUC 2 based on tolerance to ICT phase.

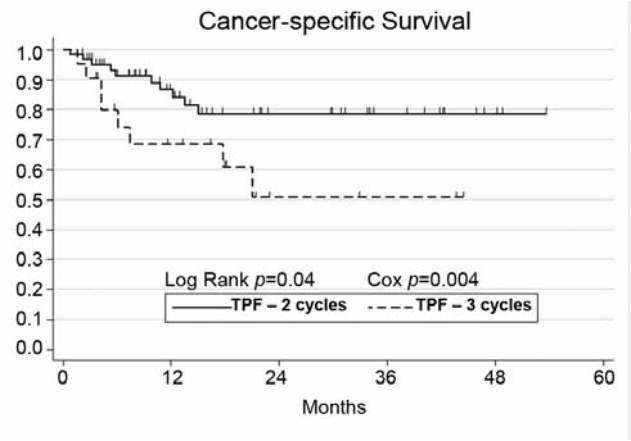

Figure 3. *Cancer-specific survival according to induction chemotherapy length*.

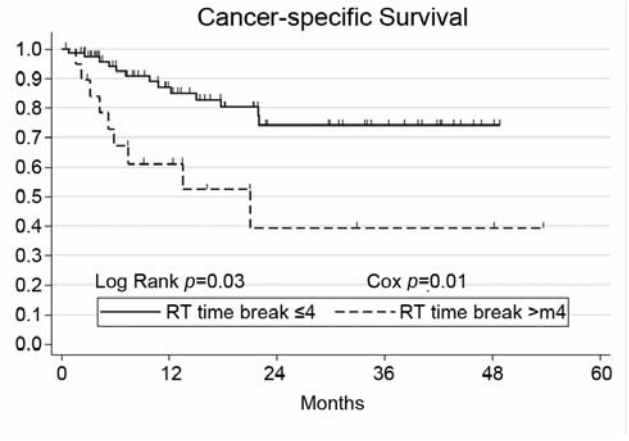

Figure 4. *Cancer-specific survival according to treatment breaks*.

Table I. *Patients' characteristics*.

	N (%)
Age	
<50 years	14 (20)
>50 years	57 (80)
Mean (yrs)	58
Sex	
Male	55 (78)
Female	16 (22)
Smoking	
Yes	43 (61)
No	28 (49)
Regular alcohol intake	
Yes	50 (70)
No	21 (30)
Hypertension	
Yes	9 (17)
No	62 (83)
Diabetes	
Yes	10 (12)
No	72 (88)
ECOG PS	
1	45 (63)
2	26 (37)
CCI score	
Mean	1.5
CCI < 2	57 (80)
CCI > 2	14 (20)
Age adjusted CCI score	
Mean	3
CCI < 2	40 (56)
CCI > 2	31 (44)
Diabetes	
Yes	10 (14)
No	61 (86)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; CCI, Charlson Comorbidity Index.

Radiotherapy. Definitive CT-RT began, usually, 3 weeks after the end of ICT program. Intensity-modulated radiation therapy (IMRT) was administered on a daily basis over 5 days a week using conventional fractionation. A total dose of 70 Gy (2 Gy daily) was prescribed to macroscopic primary and nodal disease. Up to 63 Gy (1.8 Gy daily) were given to prophylactic nodal volumes considered as intermediate-risk of microscopic spread (10-20%) and 54.25 Gy (1.55 Gy daily) for volumes considered as low-risk of dissemination (5-10%), as suggested by recent Italian guidelines (6). Treatment was delivered in 35 fractions over 7 weeks employing a simultaneous integrated boost (SIB) approach, a frequent option in HNC and other oncological contexts (7-9). IMRT employed volumetric arc-therapy (VMAT) (Elekta, Stockholm, Sweden) on Elekta Synergy and was computed on Elekta Monaco treatment planning system (version 3.2), that allows for optimization through biological cost-functions for both planning target volume (PTV) and organs at risk (OARs). Three main function (Poisson statistics cell-kill model, serial and parallel complication models) and 2 beam arrangements (single arc starting from 180° or dual-arc) were used. Dose distribution was optimized so that the 95% of all 3 PTVs received at least 95% or 93% at least 99% of the prescription dose, minimizing hot-spots occurrence (*i.e.* D_{max}<107% of prescribed dose). Dose constraints for OARs were set to D_{1cc}<54 Gy for temporal lobes, posterior fossa, brainstem, optic nerves and chiasm; D_{1cc}<50 Gy for spine's planning reference volume (PRV), D_{1cc}<45 Gy for spine and retina, D_{mean}<5 Gy for lens, D_{mean}<35 Gy for cochlea, D_{mean}<26 Gy for parotid gland volume sum and V30<50% for single parotid gland, D_{mean}<45 Gy for larynx and oral cavity, D_{mean}<52 Gy for submandibular glands, D5cc<70 Gy for mandibular bone and temporo-mandibular joints. The image-guided RT protocol comprised a daily kilovoltage CBCT during the first five fractions and a weekly CBCT thereafter, with an eventual new simulation session for displacements >5 mm.

Response and toxicity evaluation. After ICT, patients underwent assessment of tumor response with fiber-optic endoscopic examination and radiological evaluation (CT and/or MRI). Macroscopic disease was identified, measured and followed-up for quantitative comparison according to Response Evaluation Criteria In Solid Tumors (RECIST) indications (10). We defined as complete response (CR) the total clearance of all macroscopic primary and nodal lesions. Partial

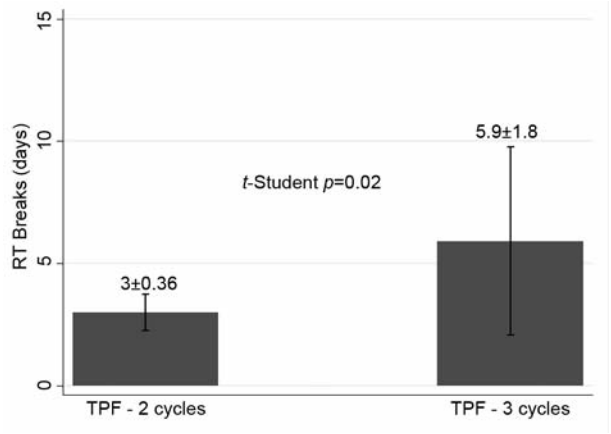

Figure 5. *Mean treatment break length according to induction chemotherapy.*

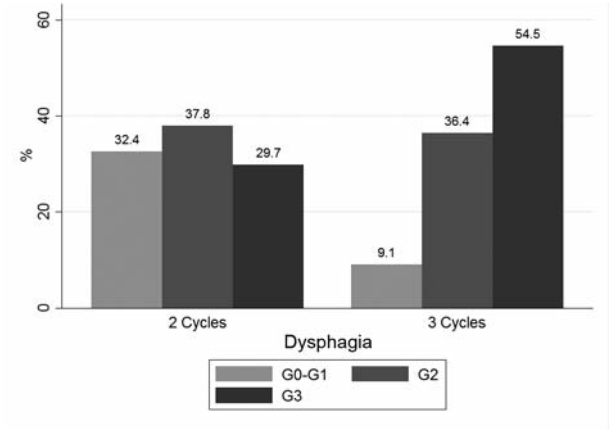

Figure 6. *Rate of acute dysphagia.*

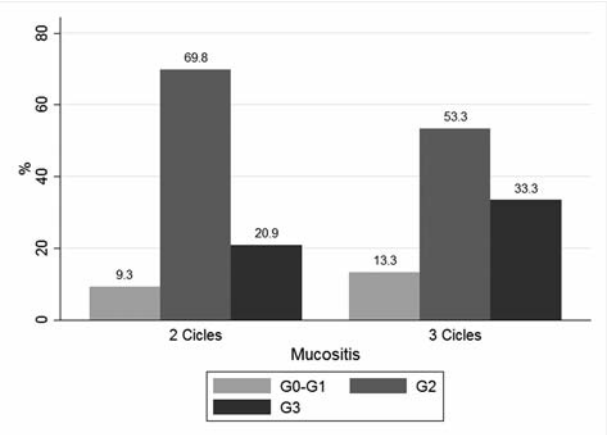

Figure 7. *Rate of acute mucositis.*

response (PR) was considered as a 30% decrease in the sum of longest diameter among target lesions compared to baseline imaging. Progressive disease (PD) was defined as a minimum 20% increase in the sum of longest diameter of target lesions or as the appearance of new lesions. Stable disease (SD) comprehended all cases which could not be allocated neither to PR or PD. Acute toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0) (11). Mucositis, skin toxicity, weight loss, dysphagia and xerostomia were chosen as main toxicity end-points.

Statistical analysis. Disease persistence or recurrence was defined as loco-regional if occurring within the head and neck region and systemic if arising elsewhere. Local and regional failures were taken into account for local control (LC). Death of disease was defined as death due to disease and taken into account for cancer-specific survival (CSS). Death due to cause was considered for OS. All failures and cancer-related deaths were considered for disease-free survival (DFS). Failures in sites other than the head and neck region were taken into account for distant metastasis-free survival (MFS). Survival curves and actuarial rates of relapse were calculated using Kaplan-Meier method. The significance of clinical prognostic factors with respect to DFS, MFS and CSS was assessed by log-rank test on univariate analysis. Multivariate analysis was performed using stepwise Cox proportional hazard regression models and related to OS, CSS and DFS. Student's *t*-test was employed to compare mean values and Fisher's exact test for categorical data. Comparison between patients submitted to 2 *vs*. 3 TPF cycles was undertaken with logistic regression analysis. Odds ratios (ORs) were calculated and presented with their 95% confidence interval. A p-value <0.05 was considered significant. Variables considered either as continuous or categorical were: age, hypertension, diabetes, Charlson Comorbidity Index (CCI), tumor site and subsite, T and N stage, grading, number of cycles of TPF chemotherapy, RT duration, treatment breaks during RT, time between biopsy and chemotherapy or radiotherapy start (days), time between start of CT and start of RT. Stata Statistical Software, version 13.1 (Stata Corporation, College Station, TX, USA) was employed for the present analysis.

Results

Clinical characteristics. The 71 patients included in the present retrospective analysis had baseline characteristics as detailed in Table I. The majority of patients were older than 50 (80%), male (78%), smoking (61%), with regular alcohol intake (70%) and ECOG PS=1 (63%). Patients had a mean Charlson Comorbidity Index (CCI) of 1.5 and a mean age-adjusted CCI of 3. Main comorbid conditions were hypertension (17%) and diabetes (12%). Patients were affected by squamous cell carcinoma mainly located within the oropharynx (54%), with a cT4 primary tumor stage (41%), cN2b/cN2c nodal stage (60%) and a IVA global stage (59%). Most tumors (43%) were poorly differentiated (G3) and HPV-negative (56%), according to p16 immunohistochemical determination. Mean time between biopsy and ICT start was 41 days (range=21-63). Mean time between ICT conclusion and definitive RT-CT start was 21 days (range=19-32). Mean RT duration was 52,4 days (range=46-84). The mean overall treatment time (ICT+RT-CT phases) was 106 days (range=90-207). Most of the patients received 2 cycles of TPF (74%) as ICT. Up to 6 (SD: +1) weekly cycles of concurrent CT were administered on average (Table II).

Table II. *Disease characteristics*.

Tumor characteristics	N (%)
Site	
Oropharynx	38 (54)
Oral cavity	17 (24)
Hypopharynx	12 (17)
Larynx	4 (5)
Primarytumour stage	
cT1	5 (7)
cT2	21 (30)
cT3	16 (22)
cT4	29 (41)
Nodal stage	
cN0	9 (12)
cN1	7 (10)
cN2a	4 (6)
cN2b	21 (30)
cN2c	21 (30)
cN3	9 (12)
Global stage	
III	17 (24)
IVA	42 (59)
IVB	12 (17)
Grading	
G1	7 (10)
G2	15 (21)
G3	30 (43)
Not available	19 (26)
HPV status	
Positive	10 (14)
Negative	40 (56)
NA	21 (30)

Table III. *Clinical characteristics according to length of induction chemotherapy.*

	TPF - 2 cycles *vs*. 3 cycles		
Clinicalparameter	OR	95% CI	*p*-Value
Median age	0.94	0.87-1.02	0.167
T4 *vs* T1-T3	2.38	0.71-7.89	0.156
T3-T4 *vs* T1-T2	1.58	0.34-7.23	0.554
N3 *vs* N0-N2	0.27	0.03-2.16	0.213
N2c-N3 *vs* N0-N2b	0.22	0.04-1.10	0.066
Stage IVB *vs* III/IVA	0.62	0.23-1.62	0.327
Stage IVB-IVA *vs* III	0.52	0.17-1.75	0.296
CCI > 2	0.66	0.40-1.10	0.101
Grading (G3)	2.30	0.79-6.70	0.125
Hypertension	0.5	0.97-2.64	0.42
Diabetes	1.2	0.21-6.94	0.84
CR rate	2.66	0.13-2.42	0.49
CR+PR rate	0.56	0.13-2.42	0.44
HPV positivity (p16)	0.97	0.89-1.02	0.175
RT breaks > 4 days	1.36	1.06-1.73	0.01

CCI: Charlson Comorbidity Index; CR: complete remission; PR: partial remission; RT: radiotherapy.

Oncological outcomes. The median observation time was 24 months (range=6-50). At the end of ICT, the overall objective response rate (ORR) was 77%, with 67% of patients having a PR and 10% a CR. Remaining 23% had SD. At the end of concomitant RT-CT phase, 48 patients (68%) had a CR, while 15 (22%) had a PR, for a total ORR of 90%. During follow-up a total of 28 patients experienced disease relapse or progression (40%), with loco-regional progression being the most prominent pattern of failure. A total of 23 patients (32%) was dead at the time of last observation, with 18 (25%) cancer-related deaths. Conversely, 48 (68%) patients were alive, with 38 (53) having no evidence of disease. Actuarial 2-year OS, CSS, DFS, MFS, LC were 55.3% (95% CI=39.3-68.6), 58.6% (95% CI=41.9-72) , 60.5% (95% CI=47.3-71.4) , 87.3% (95% CI=76.2-93.5) and 74.7% (95% CI=61.5-83.9), respectively (Figures 1 and 2). Multivariate analysis showed that CCI >2 (HR=1.4; 95% CI=1.04-1.92; p=0.025) and 3 *vs*. 2 cycles of TPF (HR=3.28; 95% CI=0.98-11.1; p=0.05) had a statistically significant influence on LC. Oral cavity primary site (HR=5.49; 95% CI= 1.14-26.46; p=0.034) and CCI>2 (HR=4.06; 95% CI=1.18-13.94; p=0.026) had a statistically significant correlation with MFS. Age adjusted CCI >2 (HR=1.69; 95% CI=1.19-2.42; p=0.004) , 3 *vs*. 2 cycles of TPF (HR=22.31; 95% CI=2.68-185.66; p=0.004), RT treatment break >4 days (HR=1.28; 95% CI=1.06-1.55; p=0.01) and achieving a CR *vs*. no CR (HR=0.9; 95% CI=0.01-0.54; p=0.009) affected CSS with statistical significance (Figures 3 and 4). ICT with 3 *vs*. 2 cycles of TPF (HR=4.30; 95% CI=2.68-9.66; p=0.047) and a RT treatment break >4 days (HR=1.38; 95% CI=0.99-1.93; p=0.05), achieving a CR *vs* no CR (HR=0.03; 95% CI=0.03-0.34; p=0.004) had an impact on OS with statistical significance. We compared patients receiving 3 cycles of TPF as ICT with those receiving 2 in terms of clinical variables with no major differences, except for treatment breaks during RT which were more frequent for patients submitted to 3 TPF cycles (HR=1.36; 95% CI=1.06-1.73; p=0.01), as shown in Table III. Patients treated with 3 TPF cycles had statistically significant longer treatment breaks than those undergoing 2 cycles (5.9+1.8 *vs*. 3+0.36; p=0.02) (Figure 5).

Toxicity profile. During ICT, maximum detected acute toxicity (G3-G4 events) included hematologic toxicity (neutropenia: 65.4%; anemia: 8.2%; thrombocytopenia: 7.8%), nausea (2.1%), vomiting (2.1), diarrhea (3.2%), alopecia (10.5%) and stomatitis (4%). Febrile neutropenia rate was 5%. No major differences were found among patients receiving 2 or 3 TPF cycles. During definitive CT-RT patients experienced G3 dysphagia (35%), G3 mucositis (29,6%), G3 erythema (25%), G3 dysgeusia (10%) and G3 xerostomia (3%). Patients receiving ICT with 3 cycles of TPF had a higher rate of G3 dysphagia (54.5% *vs*. 29.7%) and G3 mucositis (33.3% *vs* 20.9) (Figures 6 and 7). A different timing was observed for recovery from acute toxicity (time between maximum detected acute toxicity during treatment and minimum detected toxicity during follow-up. Mean recovery time was 3.97 months (SD=+3.27) for erythema, 3.96 months for mucositis (SD=+3.16), 7.64 months for dysgeusia (SD=+7.24), 7,35 months for xerostomia (SD=+5.75) and 4.38 months for dysphagia (SD=+3.47) (Figure 8).

Discussion

ICT has been historically used in squamous cell HNC with a high objective response rate and a strong correlation between response to neoadjuvant CT and favourable clinical outcome after subsequent RT (1, 12). ICT is thought to provide a substantial advantage in preventing distant relapse, even if the impact on loco-regional control is limited (1). By combining ICT with sequential definitive chemo-radiation, clinical outcome may supposedly be optimized with CT-RT affecting LC and ICT controlling distant spread (5). Neoadjuvant CT is also useful since it is able to select patients according to the magnitude of response to frontline treatment (13). A comprehensive meta-analysis performed by the MACH-NC over 17,346 from 93 randomized trials conducted between 1965 and 2000 showed no improvement in OS for ICT in general, even if a statistically significant 10% reduction in the risk of death (95% CI=0.82-0.99) was observed with the PF regimen over RT alone, translating into a 2.4% (SD=+1.4%) improvement over RT alone in terms of 5-year OS (4). It should be noted, however, that in the same report a 19% statistically significant reduction (95% CI=0.78-0.86) in the risk of death was observed for concomitant RT-CT, translating into an absolute improvement in terms of absolute 5-year OS of 6.5% (SD=+1%), compared to RT alone. In the same meta-analysis, ICT significantly reduced distant metastasis rate (HR=0.73; 95% CI=0.61-0.88; p=0.001), with no influence over loco-regional control. Concomitant CT-RT strongly reduce loco-regional failure (HR=0.74; 95% CI=0.70-0.79; p<0.001), with a less significant improvement in MFS (HR=0.88; 95% CI=0.77-1.00; p=0.04). Our series seems to confirm some of the knowledge available in the medical literature regarding this setting of patients and this treatment approach. Actuarial 2-year DFS and CSS were 60.5% (95% CI=47.3-71.4) and 58.6% (95% CI=41.9-72) with results comparable to the experimental ICT arm (3 TPF cycles)+RT concomitant to weekly carboplatin (AUC 1.5) of the TAX 324 trial which reported a Progression-free survival (PFS) of 53% and to the ICT arm (3 TPF cycles)+RT concomitant to weekly carboplatin (AUC 1.5) or docetaxel (20 mg/m^2) of the PARADIGM trial in which authors observed a 3-year PFS of 65% (14,15). Interestingly, our rate of systemic failures is consistently low with a MFS of 87.3% (95% CI=76.2-93.5), even within a cohort that included up to 41% of T4 and 42% of N2c-N3 disease, which are considered clinical situations more prone to distant spread (16). These data confirm the findings of the MACH-NC meta-analysis where ICT reduced distant metastasis rate and are quite similar to those reported in the TPF-meta-analysis where at 2 year the risk of distant failure was 9.6 % for patients receiving Tax-PF as ICT strategy (17). Moreover, in our study, ICT confirmed its role in 'chemo-selecting' patients between responders and non-responders according to response to the induction phase. In our series, achieving a CR after ICT, had a statistically significant influence on both CSS (HR=0.9; 95% CI=0.01-0.54; p=0.009) and OS (HR=0.03; 95% CI=0.03-0.34; p=0.004), highlighting how response to neoadjuvant chemotherapy may identify a favorable prognostic group that has good clinical results after definitive chemo-radiation. The CR rate after ICT in our cohort was 10%, with other 67% achieving a PR for an ORR up to 77%, after 2 (74%) or 3 (26%) cycles of TPF chemotherapy. These data are similar to those reported in the experimental arm of the TAX 323 trial (CR=8.5%; ORR=68%) which employed 4 TPF cycles as ICT and to results of the experimental arm of TAX 324 trial (CR=17%; ORR=72%) which used 3 TPF cycles (18). This finding seems to underline the fact that adding adjunctive TPF cycles over 2 may not provide additional clinical benefit to these subset of patients. In this sense, theDeCIDE trial, which employed 2 TPF cycles as ICT, had an ORR of 64% and a CR rate of 7%.

Several randomized phase III trials explored the role of ICT in locally advanced HNC. As pointed out by Benasso, 2 main investigational approaches have been employed in these prospective clinical trials: a) testing for a potential benefit in terms of clinical outcome by adding ICT to definitive concurrent chemo-radiation; b) testing for the role of ICT prior to a reduced-intensity radical concomitant chemo-radiation phase in order to enhance patients' tolerance and compliance (13). In the first setting (a), the DeCIDE study was designed as a multicenter randomized phase III trial for advanced nodal (N2-N3) HNC patients to assess whether adding 2 cycles of TPF to concomitant chemo-radiotherapy given with a hyperfractionated schedule (docetaxel, fluouracil and hydroxurea+1.5 Gy twice a day every other week) may decrease MFS and increase OS (16, 19). After a minimum 30-month follow-up time, no statistically significant difference was found in terms of OS, DFS and relapse-free survival (RFS), even if the study was underpowered since it did not reached the planned target for accrual. For instance, the

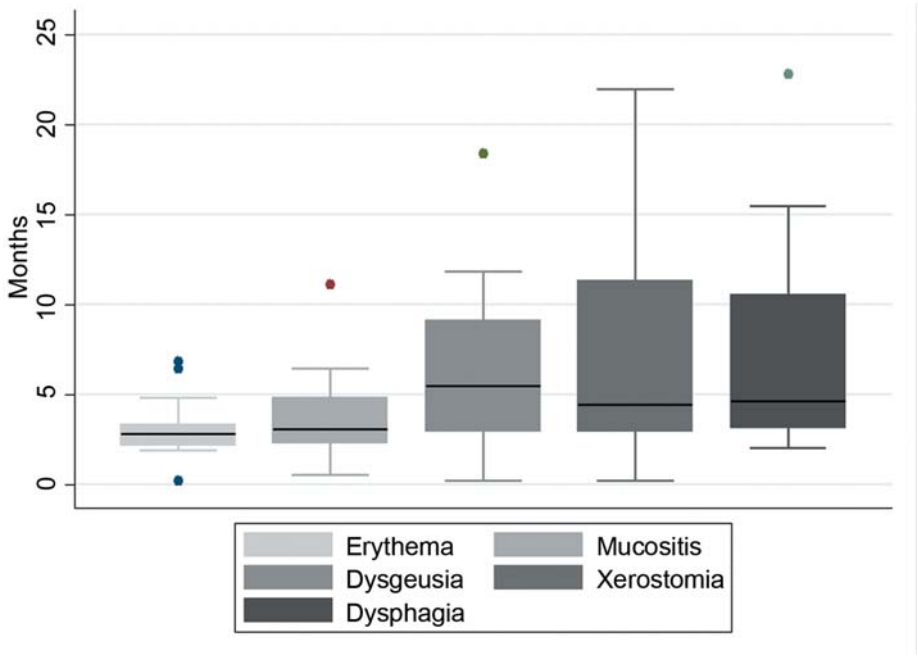

Figure 8. *Timing of release from acute toxicity.*

cumulative 3-year incidence of distant failure was 10% for ICT compared to 19% for concurrent CT-RT (p=0.025), without a consequent translation into improved MFS, RFS and OS. Nevertheless, a trend towards better OS was observed for the subset of patients having N2c or N3 disease at diagnosis (p=0.19). Regarding toxicity, serious adverse effects were most commonly observed in the ICT arm compared to the CT-RT arm (47% *vs*. 28%; p=0.002) (16, 19). Another interesting trial that directly tests upfront chemo-radiation *versus* ICT+sequential CT-RT is the SWOG 0427 trial comparing, in oropharyngeal cancer patients, conventionally fractionated radiotherapy (70 Gy) concurrent to cisplatin (100 mg/m^2 every 3 weeks) to the same regimen preceded by 1-3 course of ICT with TPF. Accrual was terminated and clinical results are awaited. In the second setting (b), the PARADIGM is a multicenter phase III trial investigating 3 cycles of TPF ICT before a tailored definitive RT-CT approach bases on response (70 Gy/35 fractions over 7 weeks concurrently with weekly carboplatin AUC 1.5, for complete responders and 72 Gy over 6 weeks with a concomitant boost approach delivering 1.8 Gy/1.5 Gy fractions concurrently with 4 cycles of weekly docetaxel 20 mg/m^2 for partial responders, stable disease or primary progressive patients) compared to concurrent RT-CT (2 cycles of cisplatin- 100 mg/m^2 concurrent to 72 Gy over 6 weeks in 1.8 Gy/1.5 Gy fractions) (15, 19). After a median follow-up time of 49 months, the 3-year OS was 73% for ICT and 78% for CT-RT (HR:1.09; p=0.77). A higher rate of febrile neutropenia was observed in the ICT arm (15, 19). In the same setting (b), other studies (such as INTERCEPTOR in Italy and a GORTEC trial in France) are investigating the role of target therapy (cetuximab) concomitant to RT after ICT (13). In our study, we found a statistically significant difference in terms of LC (HR=3.28; 95% CI=0.98-11.1; p=0.05), CSS (HR=22.31; 95% CI=2.68-185.66; p=0.004) and OS (HR=4.30; 95% CI=2.68-9.66; p=0.047) between patients submitted to 2 TPF cycles and those submitted to 3 in the ICT phase, with an advantage for a shorter ICT course (Figure 3). After a matched-comparison between these 2 subset of patients, the only significant difference among groups was found for treatment breaks which were more frequently observed in the 3 TPF cycle group (HR=1.36; 95% CI=1.06-1.73; p=0.01) (Table III). On average, the 3 TPF cycle group had statistically significant longer treatment breaks than the 2 cycle group (5.9+1.8 *vs* 3+0.36; p=0.02) (Figure 5). Interestingly, on multivariate analysis treatment breaks >4 days had a statistically significant correlation with CSS (HR:1.28; 95% CI:1.06-1.55; p=0.01) and OS (HR:1.38; 95% CI:0.99-1.93; p=0.05) (Figure 4). Patients submitted to a more intense ICT course (3 TPF cycles) had a higher rate of G3 dysphagia (54.5% *vs* 29.7%) and G3 mucositis (33.3% *vs* 20.9 %) compared to those undergoing to a 'lighter' ICT course. Our study might be considered as a hypothesis generating evidence, even if within a retrospective framework, with a slender sample size and short observation time, that a mildly intense ICT course might be a better option for locally advanced HNC patients prior to definitive chemo-radiation employing IMRT with weekly cisplatin or carboplatin.

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Conflicts of Interest

The Authors declare that they do not have any conflict of interest.

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