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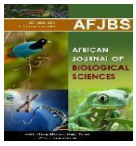

Role of Induction Chemotherapy in Radical Treatment of Locally Advanced Tongue Cancer

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Abstract

Thisprospective studywas conductedfrom October 2015 to November 2019 at the National Cancer Institute of Egypt, evaluating the benefit of applying induction chemotherapy to the management of patients with locally advanced resectableoral tongue squamous cell carcinoma (SCCOT). Sixty-five patients aged 30-71 years with clinical T2-3N0-2M0 SCCOT were planned to receive at least 2 cycles of induction chemotherapy(IC) with docetaxel, cisplatin, and fluorouracil (TPF) protocol then according to their responses being followed by radical concurrent chemoradiation therapy in case of complete response (CR) otherwise surgery then adjuvant radiation therapy. Fifty-two patients received the planned protocol, the outcome was compared to another historical retrospectively matching group, including 52 adult patients who were offered upfront surgery +/- adjuvant radiation or chemoradiation therapy based on their pathological risks.54 (83.1%) patientsout of the 65 IC group had acceptableclinicalresponses, with 40% achieving CR.There wasa 94.2 % total response rate in the fifty-two patients who followed the planned protocol. After a median follow-up of 33 months, there was no significant statistical difference in OS (P=0.620) or DFS (P=0.407) compared to historical upfront surgery.CRin the IC group was associated with superior OS thannon-CR(P=0.031).And a better OS with post-inductionCCRT thanpost-inductionSurgery (P=0.068).Survival and recurrence rate for stage III & IVASCCOT after TPFinduction chemotherapy isnon-inferior to upfrontsurgery, witha higher rate of organ preservation.Additionally, CR is associated with better survival and could be used to predict patient outcomes.

Keywords: Oral tongue SCC, Induction chemotherapy, Surgery, Radiotherapy.

Introduction

Headandnecksquamouscellcarcinoma (HNSCC), especially in advanced and metastatic settings,is considereda major healthproblem not only for its sluggish response even with modern advanced modalities but also because of its association with high cosmetic, functional,and psychological burdens.Low and middle-income countries suffer much as they have 67%& and 82% ofglobal new casesandmortality,respectively (1).Oral cancer is the most common site for head and neck tumors and sixths worldwide, with 378,000 new cases and 178,000 deaths worldwide in 2020(2).Surgery is generally preferred for most cases, especially early stage (3),Because of Its aggressiveness and high tendency for locoregional recurrence,additional postoperative radiation therapy with or without chemotherapy is needed.Definitive RT, concurrent chemoradiotherapy, and sequential therapyare typically reserved for patients who are medically inoperable or who have unresectable diseases (4).Efficacy and success of cancer management in general and oral cancer in specific are measuredby survival improvement mainly.Local response and function preservation are also important and play a role.From this point of view,Induction chemotherapy (IC) has been investigated as a possible strategy to downstage locally advanced head and neck cancers, hopping to provide either the chance for organ preservation or the opportunitytoremovethelesionscompletely with added invitro chemotherapy response assessment guiding the postoperative adjuvant management with subsequent increases in progression-free survival and overall survival (5). IC has proven to have a rule in controlling micrometastases, reducing distant failure rate, and increasing organ preservation in locally advanced HNSCC(6).

The cisplatinandfluorouracillong infusion (PF)protocol achieved higher complete response rates with better survival than other short infusion protocols. It was thefirst to be used in that field. (7). Addition of docetaxel (TPF) associated with improvedoveralland progression-free survival in 2 phase III trials.And reducedlocoregionalfailure anddistantfailurewhen compared with PF in a meta-analysis (8), (9).In oral malignancies, tongue SCC (especially anterior 2/3) isthemostcommonintraoralmalignancywith an alarming increased incidence globally.It is a big challenge to managea case with tongue cancer.It is a highly vascular organ with a high tendency for invasion and distant metastases added to decreased quality of life.Advanced-stage tongue SCC hasthe poorestoutcome, with less than 50% five-year survival rates (10). According to the 2015 cancer registry,in Egypt, the incidence rate of oral cancer is approximate ranges from 1.4 to 2 per 100.000 persons (11)which was raised more in 2020 to 3.17 per 100.000 persons with 1319 new cases (12). These figures, plus the limited studies evaluating the outcome of induction chemotherapy in oral cancers and no one specifically targeted tongue cancer, made us search more into this special malignancy, hoping to help in finding the best possible management.

Aim of the study:

To evaluate prospectively the benefits of adding induction chemotherapy with docetaxel, cisplatin, and fluorouracil (TPF) protocol in stage III & resectable IVA oral tongue SCC on tongue preservation rate, recurrence-free rate, overallsurvivals, and safety profile.And to compare all these results to the data that came from patients offered standard upfront surgery retrospectively.

Patient and methods

After local IRB approval, this study was designed atthe National Cancer Institute, CairoUniversity outpatient clinic.The study included two comparing arms (groups).The firstgrouphadsixty-five new cases with oral tongue SCC recruited prospectively to receive IC (TPF) protocol.Recruitment of patients was donein the period between October 2015 till

November 2019.The second group included fifty-twocontrolcases with the same disease criteria.The control caseswere collectedretrospectivelyfrommedical files for patientswho underwentupfront surgery during the period between 2010 and 2015.Theprospective arm was newly diagnosed adult fit patientswithpathologically confirmedlocallyadvancedresectable(T2> 3cm – T3, N0-2,M0) oral tongue SCC.The stagingwas assessed based on (TNM) classification of the AJCC 7th edition, so upon very advanced and metastatic diseases were excluded.The decision for patients is based on MDT from senior staff in different specialties.

They receivedinductionchemotherapy (TPF-IC) withdocetaxel 75 mg/m2 IV day 1, cisplatin 75 mg/m2 IVday 1, followedby continuous infusion of fluorouracil 750 mg/m2 day1 through day 5 to be repeated every 3 weeks.Regular monitoring and recording of patient tolerability and toxicity to chemotherapy was done.ICwasgiven foratleast twoanda maximum of 4 cycles before clinical response assessment.Response assessment was through clinical examination and local MRI and/or PET-CT based on RECIST criteria.In completely responding patients,radical concomitantchemoradiotherapy by IMRT simultaneous integrated boost technique.Doses of 70, 60, and 54 Gy (over 33 daily fractions, 5 fractions/week) were prescribedto the primarytumor, high-riskandlow-risknodal regions, respectively, with weekly cisplatin 30-40mg/㎡.On the other hand, if no complete response clinically and radiologically, patients were enrolled for surgery and postoperative radiotherapy.Regarding patients who underwent surgery, surgical resection consisted of glossectomy at the primary tumor site with the intent of complete resection of the original tumor and a neck dissection which was at minimum, ipsilateral selective neck dissection.Aftertheendoftreatment, patientswereonfollow-upclinicallyandradiologicallyevery 3 monthsinthefirst 2 years, thenevery 6 monthsthereafter.Duringthe COVID-19 era, follow-upwas doneaccordingtothe patient's new complaint according to the local policy of NCI.

Statistical analysis:

The data was analyzed using SPSS version 24.Continuousnormallydistributedvariables wererepresentedasmean ± standarddeviation, whereasnon-normally distributedvariableswererepresentedasmedianwithrange.Categoricalvariables were represented as frequencies and percentages, and p-values < 0.05 were used to denote statistical significance.Survival analysis was done using the Kaplan-Meier method.A comparison betweentwo survival curves was done using the log-rank test.The difference between the groups was considered statistically significant when the P-value was < 0.05.All tests were 2-tailed.Multivariate analysis to obviate the effect of confounder was done by the Cox regression hazard model.

Results

Initially,sixty-five adult patients were enrolled to receive induction TPF; unfortunately, onlyfifty-twofollowed the planned study protocol.They were compared to another fifty-two cases in the control group.The dropped 13 patients in the IC group were asfollows:two patients refused to undergo surgery after induction chemotherapy, one patient was not fit for surgery, one patient received only one cycle of induction chemotherapy then underwent surgery because of acute renal failure, 2 patients lost follow up after IC,2 patients received CCRT despite no CR, 4 patients lost follow upafter IC for a while and came with irresectable disease, and One patient was irresectable after IC.The dropped patients were excluded from the comparative analysis.Age inthe IC group ranged between 30-71 years, with a median of 49 years.Nearly the sameas the control group, the range was between 27-75 years, but with a higher median of 53 years.While apparent female predominancewas thirty-one patients (59.6%) in the control group, gender was

equal in the IC group; twenty-sevenpatients (51.9%) weremen.Both age and gender were statisticallynon-significant.

The IC group hada higher TNM staging with borderline significant difference (P=0.065) as more than half ofthe patients presented with stage III disease 34 patients (65.4%), (28.8%)15 patientswith stage IVA disease, and only 3 patients (5.8%) had stage II disease.However, stage III was also predominant in the historical group 69.2% (36 patients), stage II came second with 17.3% (9 patients), and stage IVA inseven patients.The clinical nodal status significantly differed between the two groups (P=0.006). IC group had higher N1&N2 disease in 78.8% of its patients, while 50% of control group patients had no palpable nodes N0. Grade I& II differentiated diseases were predominant in both groups, althoughthey represented higher in the IC group, 88.5%versus 78.9% inthe control group.Grade III tumors were higher in the historical group, 21.1%, compared to 11.6% in the IC group, but there was no statistical significance for such representation (P= 0.170).The full description is illustrated in table(1) and figure (1,2).

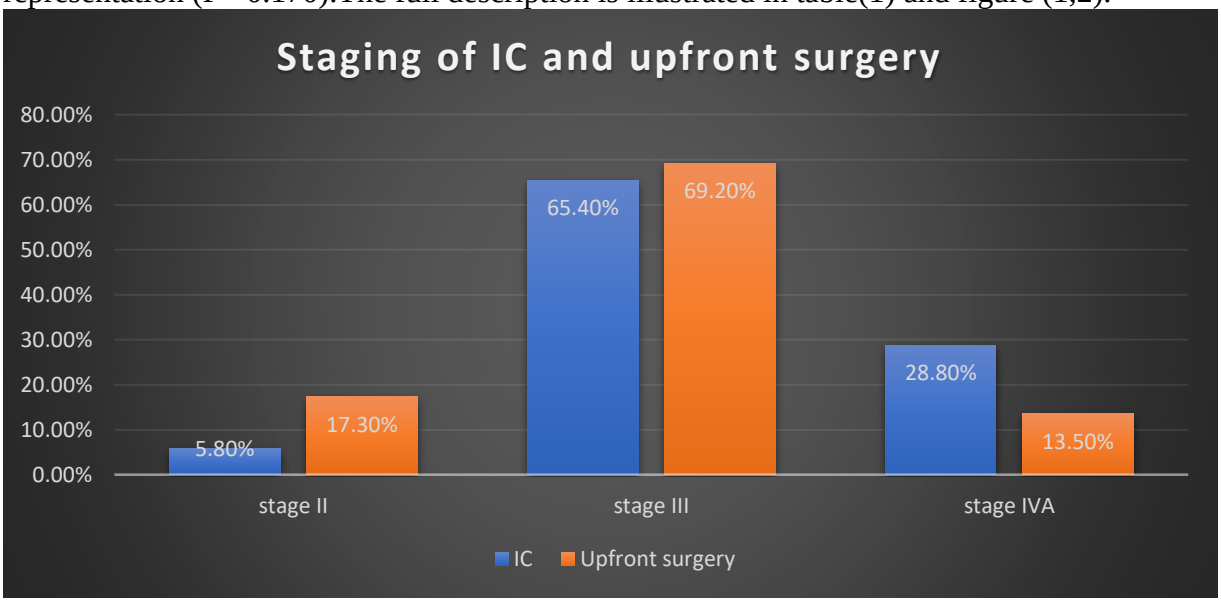

Figure 1: staging of induction chemotherapy and upfront surgery groups.

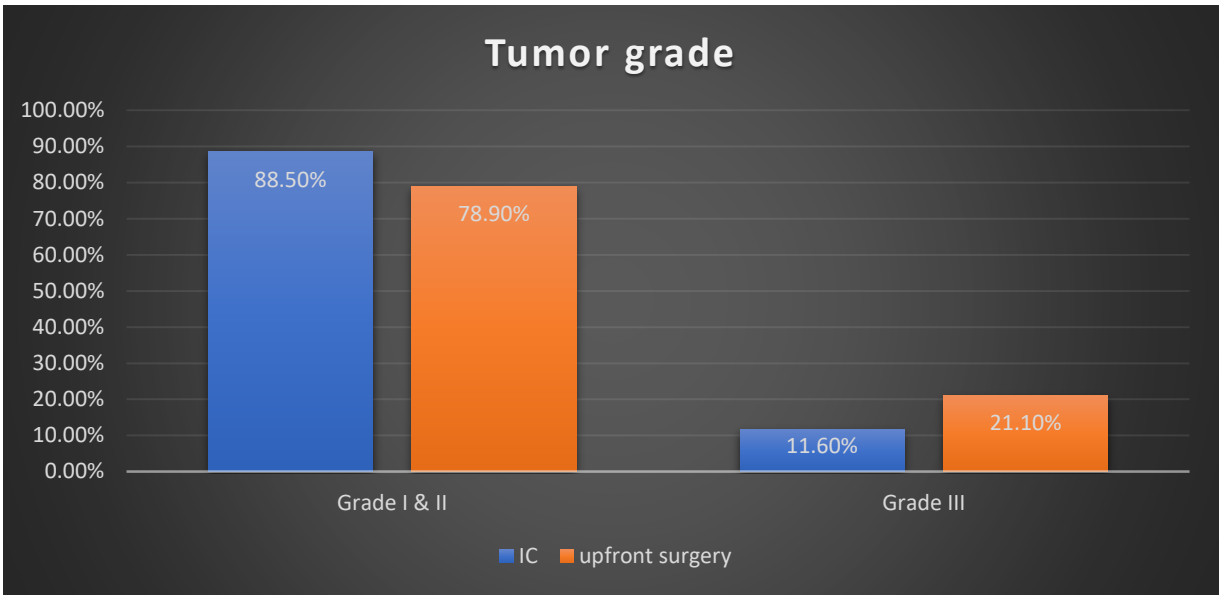

Figure 2: tumor grade

Table 1: Demographic characteristics of patients who received induction chemotherapy and historical upfront surgery.

Characteristics	Total n (104)	IC n (52)	Historical controls n (52)	P value
Gender				
Females	56(53.9%)	25(48.1%)	31(59.6%)	0.238
Males	48(46.1%)	27(51.9%)	21(40.4%)	
Age at diagnosis				
<=40	22(21.2%)	10(19.2%)	12(23.1%)	0.631
> 40	82(78.8%)	42(80.8%)	40(76.9%)	
Clinical T				
T2	23(22.1%)	11(21.2%)	12(23.1%)	0.813
T3	81(77.9%)	41(78.8%)	40(76.9%)	
Clinical N				
N0	37(35.6%)	11(21.2%)	26(50.0%)	0.006
N1	45(42.3%)	26(50.0%)	19(36.5%)	
N2	22(21.2%)	15(28.8%)	7(13.5%)	
Clinical Stage				
II	12(11.5%)	3(5.8%)	9(17.3%)	
III	70(67.3%)	34(65.4%)	36(69.2%)	0.065
IVA	22(21.2%)	15(28.8%)	7(13.5%)	
Smoking				
Yes	39(37.5%)	18(34.6%)	21(40.4%)	0.551
No	65(62.5%)	34(65.4%)	31(59.6%)	
Pathologic grade				

GI and GII	87(83.7%)	46(88.5%)	41(78.9%)	0.170
G III	17(16.3%)	6(11.6%)	11(21.1%)	

As we mentioned, 65 patients were included in the study and received induction TPF, but 52 completed the planned protocol,either radical CCRT or Surgery with adjuvant radioor chemoradiotherapy.Twenty-six patients (40%) out of the 65 (100%) patients reached complete response (CR) and partial response (PR) in 43.1% of them (28 patients). (figure 3).

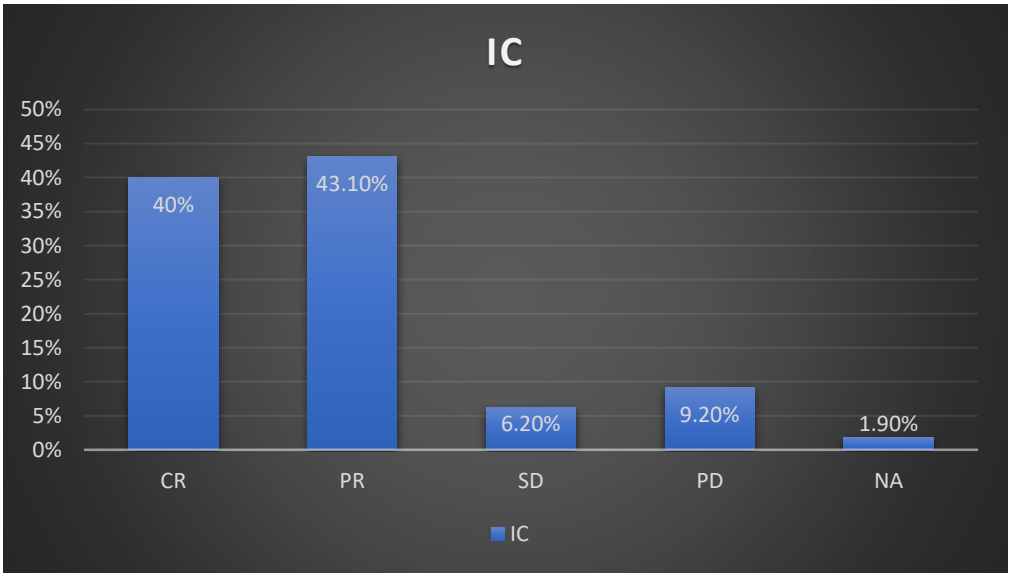

Figure 3: response to induction chemotherapy in intention to treatment.

Final descriptive and comparative analysis was done after excluding the patientswho did not follow the study protocol for the remaining 52 patients.In the fifty-tow patients,CR was 50% (26 patients), PR was 44.2% (23 patients), 3.9% (2 patients)achievedprogressivedisease (PD), and 1.9%(1 patient) achieved stable disease (SD). (figure 4)

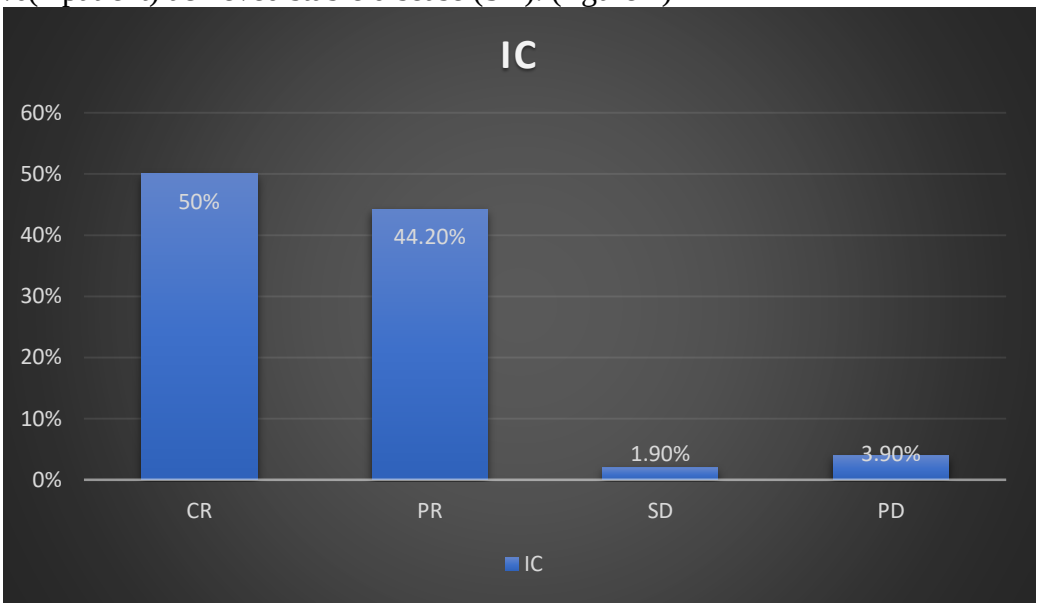

Figure 4: response to induction chemotherapy in per protocol group.

Twenty-four (46.2%) patients of the IC group were offered a tongue preservation strategy (figure 5).Theyreceived radical CCRT following induction due to good clinical response. In contrast,twenty-eight(53.8%) patients with a more sluggish response underwent surgical resection, and 16 (57.1%) patients of themreceived PORT due to adverse pathological risks.Clinical response to induction chemotherapy was higher in patients with pathological GI and GII than GIII in the post-induction surgical group with a significant P value (P=0.025).Otherwise, CRisn't affected by other clinicodemographic variables in both subgroups.Further details are in Table (2).

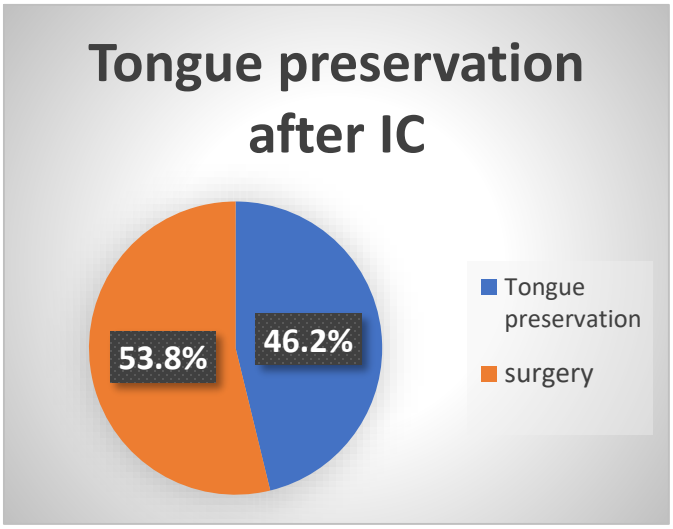

Figure 5: tongue preservation after induction chemotherapy.

Table 2: Demographic characteristics of induction chemotherapy subgroups. (n=52)

Characteristics	Total (52)	CCRT after IC (n=24)	SURGERY after IC (n=28)	P value
Gender				
Females	25	12(50.0%)	13(46.4%)	0.797
Males	27	12(50.0%)	15(53.6%)	
Age at diagnosis				
<=40	10	3(12.5%)	7(25%)	0.254
> 40	42	21(87.5%)	21(75%)	
Clinical T				
T2	11	6(25.0%)	5(17.9%)	.813
T3	41	18(75.0%)	23(82.1%)	
Clinical N				
N0	11	4(16.7%)	7(25.0%)	0.245
N1	26	15(62.5%)	11(39.3%)	
N2	15	5(20.8%)	10(35.7%)	
Clinical stage				
II & III	37	19(79.2%)	18(64.3%)	0.238

IVA	15	5(20.8%)	10(35.7%)	
Smoking				
Yes	18	9(37.5%)	9(32.1%)	0.686
No	34	15(62.5%)	19(67.9%)	
Differentiation				
GI&II	46	24(100.0%)	22(78.6%)	0.025
GIII	6	0(0.0%)	6(21.4%)	

The IC group had significantly lower postoperativepathological T (**P= <0.001**) and a higher negative surgical margin (P=0.002) than the control group. One patient (3.7%) out of 28(100%) had pT3-4A in the IC group versus 35 patients (67.3%) from 52(100%) in the control group.Themargin was negative in 26 patients (96.3%) in the IC group vs33(63.5%) in the control group.Further details about different adverse pathological features in both groups and pathological response to induction chemotherapy in relation to pretreatment parametersare fully described in Table (3).

Table 3: Description of Pathologic Characteristics of Tumors at surgical resection

	Surgery after IC n=28*	Historical control n=52	P value
p (T)			
T1	12(44.4%)	0(0.0%)	<0.001
T2	14(51.9%)	17(32.7%)	
T3 and T4a	1(3.7%)	35(67.3%)	
p (N)			
N0	16(57.1%)	22(42.3%)	0.245
N positive	12(42.9%)	30(57.7%)	
Resection margins			
Negative	26(96.3%)	33(63.5%)	0.002
Positive	1(3.7%)	5(9.6%)	
Close	0(0.0%)	14(26.9%)	

* One case in induction chemotherapy underwent neck dissection only.
IC; induction chemotherapy.

However,there wasa non-significant recurrence rate difference at a median follow-up of 33.03 months (range 6-76 months). Still, thepercentage of recurrence, either local or locoregional, was higher in the control group compared to IC group 29(55.8%) & 23(44.2%), respectively (p=0.327).There was no significant relation between pre-induction clinicodemographic or pathological variables and recurrence status.More can be seen in Table (4&5).

Table 4: Rate and pattern of recurrence in patients who received induction chemotherapy and historical controls.

	Induction chemotherapy n (52)	Historical controls n (52)	P value
Recurrence			
Yes	23(44.2%)	29(55.8%)	0.327

No	29(55.8%)	23(44.2%)	
Type of recurrence Local	5(21.7%)	10(34.5%)	
Regional	6(26.1%)	13(44.8%)	0.060
Locoregional	12(52.2%)	6(20.7%)	

Table 5: Recurrence and pretreatment demographic and clinical variables in the induction chemotherapy group.

Variable	Total number(n=52)	Recurrence(n=23)		P value
		No	**Rate**	
Gender				
Male Female	27 25	13 10	48.1% 40%	0.554
Age at presentation				
<=40 > 40	10 42	4 19	40% 45.2%	0.764
Clinical T				
T2 T3	11 41	4 19	36.4% 46.3%	0.554
Clinical N				
N0 N1 N2	11 26 15	4 12 7	36.4% 46.2% 46.7%	0.839
Clinical Stage				
Stage II & III Stage IVA	37 15	16 7	43.2% 46.7%	0.822
Smoking				
Yes No	18 34	8 15	44.4% 44.1%	0.982
Complete response by IC				
Yes No	26 26	13 10	50% 38.5%	0.402
Surgery after IC				
Yes No	28 24	11 12	39.35% 50%	0.438
IC cycles				
4 2-3	20 32	12 11	60% 34.38%	0.123

However,no P value, but survival was higher in the IC group.As 2 and 5-year OS was 64.2% &55.4% for the IC group and 62.8% & 44.3% for the control group, respectively.Also,the OS rate was higher for patients with a lower clinical N category (P=0.006), and the median OS at five years was not reached for patients with clinical N0 and N1 at presentation.In the IC group,the complete clinical responders had a higher 5-year OS (p= 0.031).OS was also better in

the radical CCRT-receiving group than in the post-induction surgically treated group (P=0.068).Please see full details in Table(6,7,8,9) and figures (6,7,8,9).

Table 6: Overall survival in patients who received induction chemotherapy and historical controls.

OS	Total	Events	2 years	5 years	median	P value
Total cases	104	55	.635	.484	59.046	-
Group						
IC	52	23	.642	.554	67.467	0.620
Upfront surgery	52	32	.628	.443	43.026	

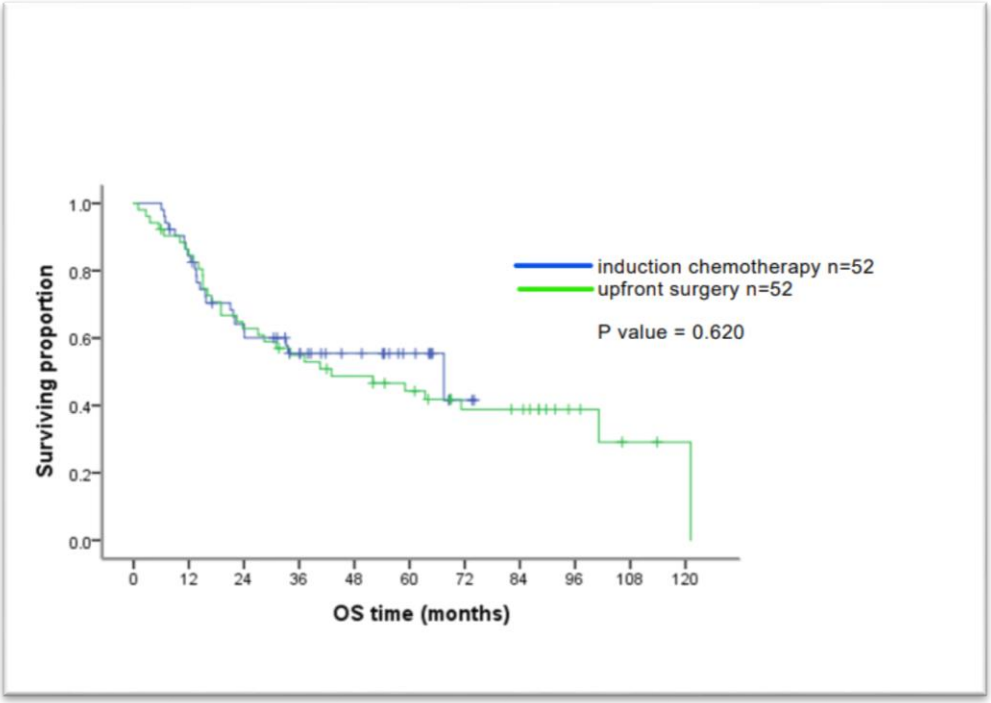

Figure 6: Overall survival in patients who received induction chemotherapy and historical controls.

Table 7 : Overall survival in relation to clinical node status in patients who received induction chemotherapy.

OS	Total	Events	2 years	5 years	Median	P value
IC Group	52	23	.642	.554	67.467	-
N0 (ab)	11	4	.727	.636	NR	0.006
N1 (a)	26	8	.711	.664	NR	

N2 (b)	15	11	.467	.311	14.408	

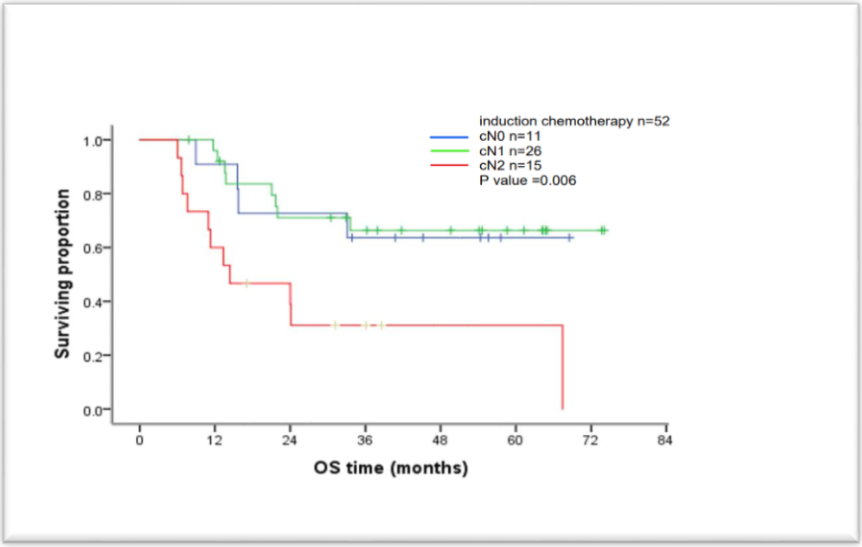

Figure 7 : Overall survival in relation to clinical node status in patients who received induction chemotherapy.

Table 8 : Overall survival in relation to response to induction chemotherapy.

	Total	Events	2 years	5 years	Median	P value
CR after IC						
no	26	15	.522	.397	24.013	0.031
yes	26*	8	.760	.712	67.467	

*Two patients achieved complete response radiologically but unfortunately came late and underwent surgery instead of CCRT.

CR; complete remission, IC; induction chemotherapy

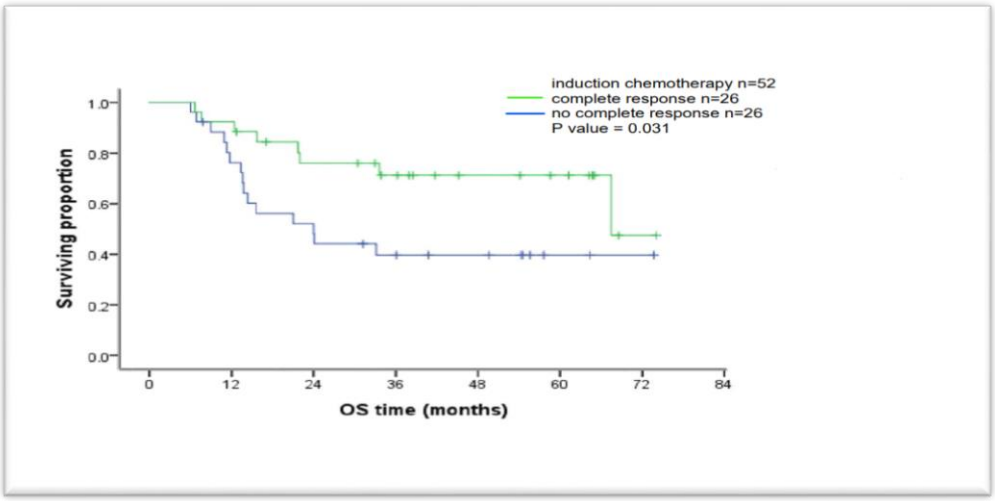

Figure 8 : Overall survival in relation to response to induction chemotherapy.

Table 9: Overall survival in relation to the response and type of treatment after induction chemotherapy.

	Total	Events	2 years	5 years	median	P value
OS						
CR+CCRT	24	8	.746	.696	67.467	0.068
Surgery after IC	28*	15	.546	.425	24.112	

**Two patients achieved complete response radiologically but unfortunately came late and underwent surgery instead of CCRT.*

OS; overall survival, CR; complete remission, IC; induction chemotherapy, CCRT; concurrent chemoradiation

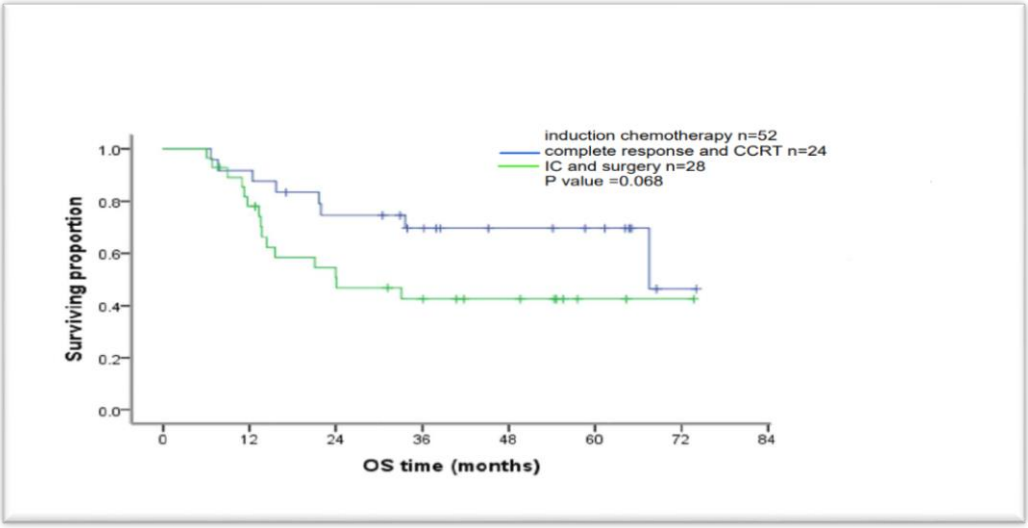

Figure 9: Overall survival in relation to the response and type of treatment after induction chemotherapy.

Two patients experienced acute renal failure grade 4 toxicity during induction chemotherapy, one of them after the first cycle and the other patient after the second cycle.Table number (10) demonstrates the toxic effects associated with induction chemotherapy.

Table 10: Adverse events associated with induction chemotherapy.

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4	
	N	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Anemia	11	16.9	6	9.2	4	6.2	1	1.5
Thrombocytopenia	5	7.7	3	4.6	3	4.6	1	1.5
Leukopenia	10	15.3	8	12.3	3	4.6	-	-
neutropenia	15	23	10	15.3	6	9.2	2	3
Nausea/vomiting	26	40	17	26.1	6	9.2	1	1.5
Diarrhea	5	7.7	2	3	3	4.6	-	-
Oral mucositis	6	9.2	8	12.3	2	3	1	1.5
Peripheral neuropathy	-	-	2	3	2	3	-	-
Renal	2	3	-	-	1	1.5	2	3

DISCUSSION:

With the increased incidence of oral tongue cancer and its subsequent drawbacks,advances in local control and functional preservation are still far from the right way.Optimal decision-making, treatment planning, and posttreatment response assessment need a multidisciplinary approach (13). Globally, there is an increased incidence of oral tongue cancer, especially in females below 40 years (14). This matchedthe gender distribution in our study as nearly 60% of the control group were female; however, there was equal gender distribution in the IC group.In Westerncountries, tobacco smoking and alcohol are the main risk factors for oral cavity SCC with synergistic effects (15).

According to the literature, younger patients < 40 years are associated with more aggressive disease, but no survival difference compared to older ones (16). The recurrence rate in our study wasn't high in younger patients (p=0.764), maybe as most of them were above 40 years, 80.8% in the IC group and 76.9% in the control group.Localized oral SCC stage I and II were reported to be associated with 5 years OS (67 and 51 %, respectively) to surgery.(17, 18). Contrary stage III/IV is associated with a high risk of local recurrence, distant metastases, and lower 5-year OS (39& 27%, respectively) (19). That mandates the usage of Combined modality approaches to optimize the chances for long-term disease control (20, 21). However, there havebeen no survival benefits in most previous randomized trials(22). In recent trials, induction chemotherapy, especially TPF in those stages, achieved surgical and functional preservation of important oral structures like the tongue and mandible (23). There was improved OS (median 5.1 versus 3.3 years) in oropharyngeal carcinoma patients who received 3 cycles of cisplatin and infusion FU induction therapy in one randomized clinical trial compared to definitive locoregionaltreatmentalone (24). The 2021 MACH-NC study also detected a small benefit for cisplatin and (FU) inductionin patients with oropharyngeal cancers versus locoregional therapy(25). According to The EORTC 24971/TAX 323 trial and further meta-analysis evaluating triple therapy, the TPF regimen significantly improvedOS compared with the PF regimen with decreased locoregional recurrence rate(26, 27). With respect to all previously mentioned trials and meta-analyses.However, there were no survival benefits in our study from induction TPF, which is matched with most evidence. Still, the percentage of 5 years OS was higher in the IC group vs.the control group (55.4%& 44.3% respectively).The recurrence rate was also higher in the control group, 55.8% VS 44.2% in the IC group, and the P value was non-significant (p=0.327).CR predicts a better 5-year OS in the IC group (P=0.031).OS was also better in the radical CCRT-receiving group than in the post-induction surgically treated group (P=0.068).

CONCLUSION

However, there has been no full agreement or consensus until now about who will benefit much from using induction chemotherapy in LAHNSCC.TPF protocol is the best choice,with satisfactory resultsand limited toxicity,especially in organ preservation.Trials to integrate immune therapy into the backbone of the induction plan may be a future therapeutic hope for those patients.

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