

A Randomised Trial of Neoadjuvant Chemotherapy in Locally Advanced Oral Cancers

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Abstract: India accounts for more than one-fourth of the world's burden of oral cancers. 48% of these cancers present in late stages requiring multimodality treatment with both surgery and radiation therapy and have a very poor prognosis with 5-year survival rates of 30- 40%. A randomized, single centre study aimed at comparing the activity and toxicity of two chemotherapy regimens [5-Fluorouracil +Platin (PF regimen) versus Taxol + Platin (TP regimen)] in the neoadjuvant setting for patients with resectable squamous cell cancer of the oral cavity. Treatment was administered 3 weekly for three courses. Response assessment was done after each cycle. Patients with partial response underwent surgery. Adjuvant therapy was based on pathological status. Those who had complete response during chemotherapy received RT alone without any surgery. Patients with static or progressive disease were given radical chemoRT. Primary efficacy parameter was response rate. Secondary end points were overall survival and disease-free survival. A total of 40 patients (60% males and 40% females) with median age of 48 years were studied. All patients completed the study and there were no significant toxicities requiring discontinuation. Two patients on each arm (10%) had complete response. Partial response rates were significantly different [8 patients (40%) in the TParm and only one patient (5%) in the PF arm ($p=0.54$)]. 9 patients(45%) had progression in the PF arm and 4 patients progressed in the TParm (20%) which was significant ($p=0.59$). Static disease was not significantly different ; 8 cases in the PFarm(40%) and 6 cases in the TP arm(15%). The study concluded that paclitaxel/cisplatin combination chemotherapy yields significantly better response rates than 5FU/cisplatin. However, the response rates are inferior to standard three drug regimens currently recommended and preoperative chemotherapy in locally advanced resectable squamous cell carcinoma of the oral cavity is ineffective in reducing tumour volume and stage of the disease.

Keywords: Oral Cancer, Neoadjuvant chemotherapy, Locally advanced oral cancer

1. Introduction

Around 5, 00,000 cases of cancer of the head and neck are diagnosed annually around the world and every year 1, 27,000 people die because oral cancer alone [1]. Oral cancer ranks among the top three cancers in India and accounts for more than one-fourth of the world's burden [2]. Half of these cancers present in late stages requiring multimodality treatment with both surgery and radiation therapy and have dismal 5-year survival rates of 30- 40%.

2. Aim of the Study

- 1) To assess the efficacy of neoadjuvant chemotherapy in locally advanced resectable squamous cell cancers of the oral cavity
- 2) To compare the efficacy and toxicities of two different two drug regimens: Cisplatin and 5-Fluorouracil (PF regimen) and Paclitaxel and Cisplatin (TP regimen)

The potential benefits of neoadjuvant chemotherapy are:

- a) Reduces size of tumour
- b) Renders tumour operable without radiotherapy
- c) Reduces extent of surgery/radiotherapy with better functional and cosmetic outcome
- d) Allows radiotherapy to be kept in reserve as salvage therapy for recurrence
- e) Eradicates micrometastases

3. Patients and Methods

Eligibility and Random Assignment:

Patients with histologically confirmed non metastatic locally advanced resectable squamous cell carcinoma of the oral cavity were included in the study.

Pretreatment evaluation included

- 1) History
- 2) Physical examination
- 3) Biopsy
- 4) Complete blood analysis
- 5) Chest X-ray
- 6) Tumour imaging with CECT of head and neck

Inclusion criteria:

- 1) Age 18-70 years
- 2) WHO performance status ≤ 2
- 3) Stages III and IVA (T3,N0-N2 and T4a,N0-N2)
- 4) Normal haematologic and renal function. Hb $\geq 10g$; adequate bone marrow reserve (total count $\geq 4,000/\mu l$, platelet count $\geq 10,000/\mu l$); normal blood urea and creatinine.
- 5) A normal chest X-ray
- 6) No masticator space, or pterygoid muscle, or infratemporal or skull base involvement on CECT

Exclusion criteria

- 1) Histology other than invasive squamous cell carcinoma
- 2) Metastasis
- 3) Recurrent/Residual disease/second primary cancers
- 4) Patients who received any prior treatment for the disease
- 5) Medical illness(es) precluding full study participation

Neoadjuvant Chemotherapy Regimens

PF regimen: 5-Fluorouracil 500mg/m² as a 3-hour infusion on Days 1& 2. Premedication of Dexamethasone 8 mg; Ondansetron 8 mg and Ranitidine 150 mg intravenously 30 minutes was given before treatment delivery. Cisplatin 75 mg/m² was administered on Days 1& 2 as a 60-minute infusion after prehydration with 1 litre of normal saline. Hydration with 5% Dextrose solution during 24 hours was infused simultaneously.

TP regimen: Paclitaxel 175 mg/m² as a 3hour infusion on Day 1. Premedication to reduce the risk of hypersensitivity: Hydrocortisone 100mg intravenously 60 minutes before and chlorpheniramine 10 mg, Ondansetron 8 mg and Ranitidine 150 mg intravenously 30 minutes before treatment delivery. Cisplatin 75 mg/m² on Day 2 as a 60-minute infusion after prehydration with 1 litre of normal saline. Hydration with 5% Dextrose solution during 24 hours was infused simultaneously.

In both arms, treatment was administered every 3 weeks for a total of three courses.

Treatment Modifications:

Complete Blood Counts were performed 3 weekly or more often if toxicity occurred; evaluation of renal function was repeated before each cycle. Treatment administration was based on evaluation of hemoglobin and blood cell counts before the start of each cycle. Treatment was administered only if the Hemoglobin was more than 10g/dl, Total WBC Count was more than 4000/RL and the platelet count more than 100,000/RL. Treatment was delayed week to week until minimum hematologic parameters are met. After two consecutive treatment delays, on the basis of physician judgment, treatment was either discontinued or continued. Delays were not permitted other than for documented toxicity.

Response assessment:

Response assessment was done using RECIST 1.1 criteria. Complete response was the disappearance of all known disease and malignant nodes <10mm in short axis diameter. Partial response was 30% decrease in the sum of longest diameters of measurable target lesion and no evidence of disease progression. Progression was defined as 20% increase in sum of longest diameters, with minimum absolute increase of 5mm, taking as reference the smallest sum in the study; or appearance of new lesions. Stable disease was non-partial response; non-progressive disease.

Toxicity Assessment:

Toxicity was graded according to Common toxicity criteria for adverse effects of the National Cancer Institute version 4.

Treatment after Neoadjuvant Chemotherapy

Tumor response was assessed clinically and by CT after three courses and all patients with partial response underwent surgery as appropriate. Patients, who had complete response, underwent consolidation of response with EBRT. Patients who had static or progressive disease received 50Gy EBRT after which they were reassessed, and if found operable, underwent surgery. If considered inoperable, they received radical chemoradiotherapy.

Surgical management:

Patients who had residual primary tumour underwent wide excision or composite resection with reconstruction. Those who had no residual primary, but had residual nodal disease underwent radical neck dissection and received post operative radiotherapy.

Follow up:

Patients were monitored for assessment of disease status 1 month after the end of treatment and every month thereafter for the first year and three monthly thereafter. During each visit complete physical examination was performed, and Chest X-rays performed annually. Computed tomography scans were carried out when appropriate.

Statistical Methods:

This was a randomized, single centre study aimed at comparing the activity and toxicity of Fluorouracil +Platin versus Taxol + Platin in the neoadjuvant setting for patients with resectable squamous cell cancer of the oral cavity. Randomization was done using permuted block method. The primary efficacy parameter was the response rates. Secondary end points were overall survival and disease-free survival.

Statistical analysis was performed using SPSS version 16.

The chi-square and t-tests were used when appropriate to compare patient characteristics, responses and toxicity. Influence of clinical, pathological and therapeutic factors on outcome was assessed using a multivariate analysis with a Cox regression model.

4. Case Analysis and Results

From September 2011 to January 2014, a total of 40 patients with locally advanced resectable squamous cell carcinoma of the oral cavity fulfilled the criteria for inclusion in this study.

Patient demographics:

Age:

A total of 40 patients were enrolled. Median age was 48 years (range 31-68 years). None were in the 20-30 age group, 9 were between 31-40 years, 10 were in the 41-50 age group, 16 in the 51-60 age group and 5 were between 61-70 years.

Sex distribution:

60% of the cases were male (n=24) and the remaining 40% were female (n=16).

Tumour characteristics:

Only squamous cell carcinomas of the oral cavity were included in this trial. Of the 40 patients, 10 had grade I tumour, 14 were grade II and 16 were grade III.

Table 1:

Subsite involvement:

Buccal mucosa was the most frequently subsite accounting for almost half the study group with 19 cases (47.5%). Tongue was the next common subsite with 7 cases (17.5%). Alveolus was involved in 15% (6 cases), lip and retromolar trigone each accounted for 7.5% of cases (n=3) and floor of mouth was the least common with only 2 cases (5%).

Table 2.

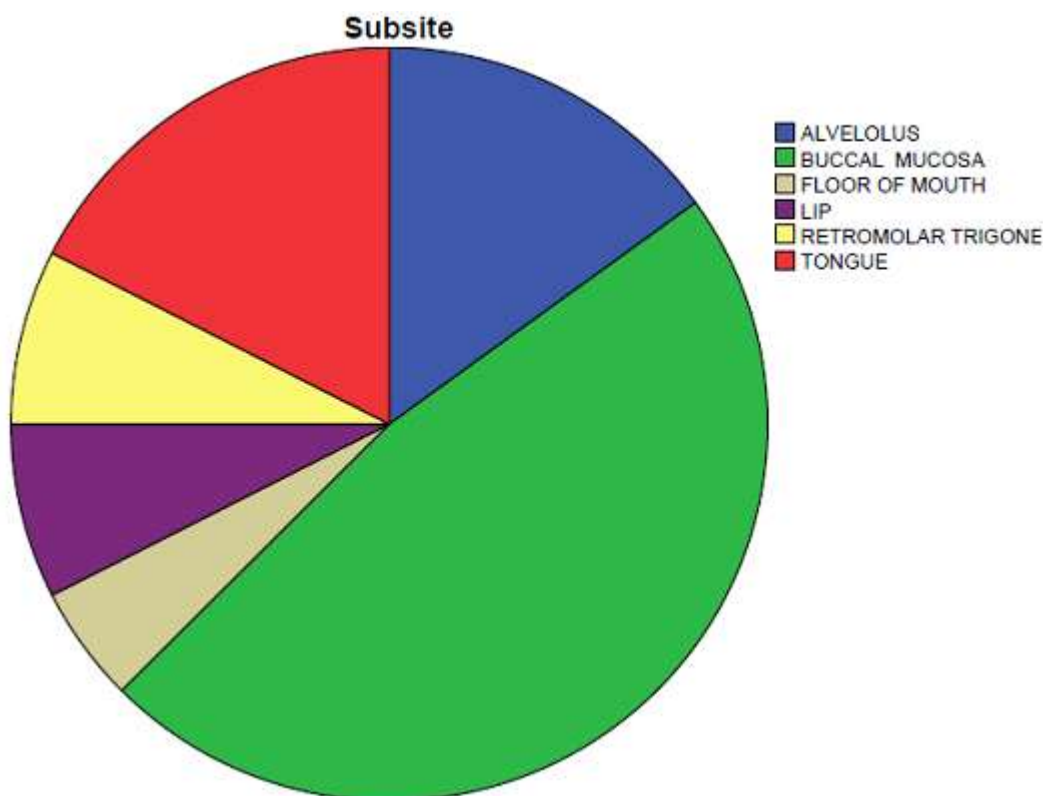


Figure 1

The TP arm had more cases of buccal mucosa; all other subsites were evenly distributed between the two arms.

Table 3

Subsite	PF Arm	TP Arm	Total
Buccal mucosa	6	13	19
Tongue	4	3	7
Alveolus	4	2	6
Retromolar trigone	2	1	3
Lip	2	1	3
Floor of mouth	2	0	2

Stage at presentation:

Table 4

Stage grouping	No. of cases	Percent
T3N0M0	3	25%
T3N1M0	7	
T3N2bM0	5	75%
T3N2cM0	2	
T4aN0M0	1	
T4aN1M0	6	
T4aN1M0	2	
T4aN2aM0	1	
T4aN2bM0	10	
T4aN2cM0	3	

25% of cases were Stage III at presentation and 75% cases were Stage IVa disease.

Stage distribution in the two arms:

Table 5

Stage		Arm			
		PF	Total	TP	Total
T3N0M0	III	0	6	3	4
T3N1M0		6		1	
T3N2bM0	IVa	1	14	4	16
T3N2cM0		2		0	
T4aN0M0		1		0	
T4aN1M0		3		3	
T4aN1M0		2		0	
T4aN2aM0		0		1	
T4aN2bM0		5		5	
T4aN2cM0		0		3	
Total			20		20

The Stages were almost evenly distributed in both trial groups. In the PF arm, 6 cases (30%) were Stage III disease, while 4(20%) were Stage III in the TP arm. 14 cases (70%) were Stage IVa in the PF arm, while 16(80%) were Stage IVa in the TP arm.

Stage distribution in the two arms:

Overall response:

Table 6

Response RECIST	Arm		Total
	PF	TP	
CR	2	2	4
PR	1	8	9
SD	8	6	14
PD	9	4	13
Total	20	20	40

Complete clinical response occurred in 4 cases (10%) while 9 cases (22.5%) had partial response; an overall response to chemotherapy occurring in 32.5% of patients. The disease was static in 14 patients (35%) and 13 patients (32.5%) progressed on treatment.

When response in each arm was compared, complete response rates were even with 2 cases on each arm (10% each). Partial response rates were significantly different with 8 patients (40%) in the paclitaxel/cisplatin arm, and only one patient (5%) achieving partial response in the cisplatin/5FU arm ($p=0.54$). Static disease response was not significantly different between the two arms (8 in the PF arm and 6 in the TP arm). Significant progression occurred in the cisplatin/5FU group with 9 of the 20 patients showing progression during treatment (45%) and 4 had progressive disease in the paclitaxel/cisplatin arm (20%) ($p=0.59$).

Response of tumour to chemotherapy:

Table 7

Subsite	Response	PF Arm	TP Arm	Total
Buccal mucosa	CR	1	3	4
	PR	0	3	3
	SD	4	4	8
	PD	1	3	4
Total		6	13	19
Tongue	CR	0	0	0
	PR	0	2	2
	SD	1	0	1
	PD	3	1	4

Total		4	3	7
Alveolus	CR	0	0	0
	PR	0	1	1
	SD	1	1	2
	PD	3	0	3
Total		4	2	6
Retromolar trigone	CR	0	0	0
	PR	1	0	1
	SD	1	1	2
	PD	0	0	0
Total		2	1	3
Lip	CR	0	0	0
	PR	0	1	1
	SD	1	0	1
	PD	1	0	1
Total		2	1	3
Floor of mouth	CR	1	0	1
	PR	0	0	0
	SD	0	0	0
	PD	1	0	1
Total		2	0	2

Subsite did not affect tumour response to chemotherapy. Buccal mucosa had a trend towards better overall response rate which was not statistically significant ($p=0.9$). Tongue, alveolus, retromolar trigone and lip did not have a single complete response in either arm. The numbers however were too low for assessment of statistical significance.

Response according to Stage of disease:

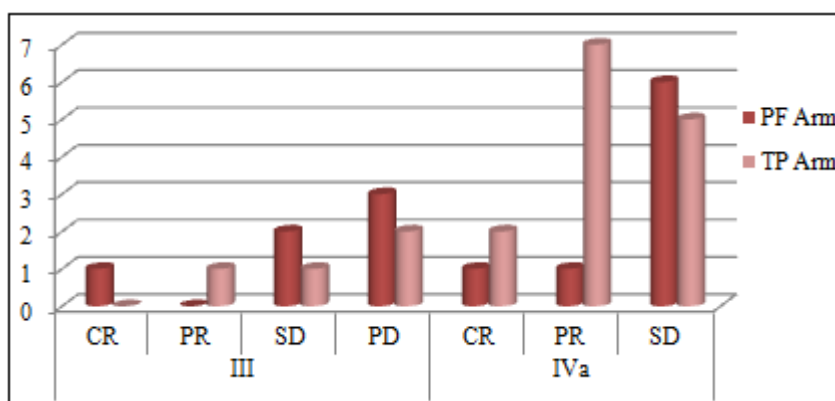


Figure 2

Table 8

Stage	Response	PF Arm	TP Arm	Total
III	CR	1	0	1
	PR	0	1	1
	SD	2	1	3
	PD	3	2	5
Total		6	4	10
IVa	CR	1	2	3
	PR	1	7	8
	SD	6	5	11
	PD	5	3	8
Total		13	17	30

Patients with Stage III disease had a 20% response with 1 patient achieving complete response in the PF arm and one patient in the TP arm showing partial response. 50% of patients in Stage III had progressive disease (5 of 10 patients

progressed on therapy). 3 patients had static disease (33.3%).

Among patients with Stage IVa disease, 3 patients (10%) had complete response and 8 patients (27%) had partial response. Eleven patients had static disease (37%); 8 patients progressed on therapy (27%). Only partial response was significantly different between the two trial arms among Stage IV disease. TP arm had significantly higher partial response in Stage IV ($p=0.03$). Overall response to chemotherapy was not significantly related to Stage of the disease.

Response according to subsite

Table 9

<i>Subsite</i>	<i>Response</i>	<i>PF Arm</i>	<i>TP Arm</i>	<i>Total</i>
<u>Buccal mucosa</u>	CR	1	3	4
	PR	0	3	3
	SD	4	4	8
	PD	1	3	4
Total		6	13	19
<u>Tongue</u>	CR	0	0	0
	PR	0	2	2
	SD	1	0	1
	PD	3	1	4
Total		4	3	7
<u>Alveolus</u>	CR	0	0	0
	PR	0	1	1
	SD	1	1	2
	PD	3	0	3
Total		4	2	6
<u>Retromolar trigone</u>	CR	0	0	0
	PR	1	0	1
	SD	1	1	2
	PD	0	0	0
Total		2	1	3
<u>Lip</u>	CR	0	0	0
	PR	0	1	1
	SD	1	0	1
	PD	1	0	1
Total		2	1	3
<u>Floor of mouth</u>	CR	1	0	1
	PR	0	0	0
	SD	0	0	0
	PD	1	0	1
Total		2	0	2

5. Complications and Compliance

There were no major complications necessitating discontinuation of therapy in either arm and all patients completed the protocol.

The commonest adverse effect was vomiting. 12 patients had anorexia, 16 patients had nausea, 28 had vomiting, 4 developed allergic reactions, 19 had decreased haemoglobin, 4 had decreased neutrophil counts and 5 developed neuropathy. Allergic adverse effects were more common in the Paclitaxel and Cisplatin arm. There was no other difference in toxicity profiles among the two groups.

Surgery:

A total of 20 patients in the study group underwent surgery. Nine patients who had partial response underwent surgery with composite resection and myocutaneous pedicled flap reconstruction. Of 27 patients who had static or progressive disease, and received RT, at the end of 50 Gy, 11 patients were found operable, and underwent surgery. 10 patients had resection of both primary tumour and cervical nodes, while one patient underwent modified radical neck dissection only as the primary tumour had complete clinical response. 3 patients developed flap necrosis. Of these one patient was operated post chemo and two patients had received RT prior to surgery; of which one developed metabolic complications and died in the post operative period.

Outcome:

Among the 4 patients who had complete response and consolidation with EBRT, 1 developed contralateral nodal recurrence which was surgically managed.

Of 9 patients who had partial response and underwent surgery, 2 patients defaulted adjuvant RT, developed recurrence and died; 2 developed recurrence following RT, one at the primary tumour site and the other in the contralateral neck, both of which were inoperable.

Of the 14 patients with static disease, 5 patients underwent surgery post RT. Of these, 2 patients developed recurrence, one died and another is alive with disease. Among those found inoperable and who received chemoradiation, 8 patients developed recurrence and 5 died of disease. 6 patients are disease free, 3 of who had prior surgery.

Of 13 patients who progressed on chemotherapy, following RT, 6 patients underwent surgery; 5 developed recurrence and 4 died. Of the remaining 7 patients, all developed recurrence and 3 died of it.

Overall, at the end of the study period, 14 patients died, 10 were alive with recurrent disease and 16 were alive with no clinical evidence of disease.

6. Discussion

Patient characteristics

In this study, patients in both chemotherapy groups were well matched for age and gender and there was no significant effect on the response rates or the adverse effects encountered. Grade and size of the tumour did not have a significant role in the responses or the outcomes.

Chemotherapy and response

The overall response rate in this study was 32.5% (9 of 40 patients) and this was only similar to the response rate historically achieved with cisplatin as a single agent. The EORTC 24971 trial which compared PF chemotherapy regimen to three drug regimen with addition of Taxol reported overall response rate of 59% for the PF arm and 79% for the TPF arm. In this study, there was a 15% overall response in the PF arm and 50% overall response in the TP arm. Although the response rate of the Taxol, cisplatin arm is significantly better than the PF arm in our study, it is inferior to the response rate reported for the standard induction chemotherapy 3 drug combination of TPF in most trials. Almost all trials which include Taxol in the regimen, add it as the third drug in addition to cisplatin and 5FU, and very few trials of Taxol with cisplatin as a two drug regimen are available for comparison. Docetaxel is the taxane used in all the trials, compared to paclitaxel which was used in our study. Among the trials using paclitaxel and cisplatin, is the retrospective study at the Tata Memorial Hospital, Mumbai, which used this combination as one of four different regimes on 123 patients with borderline resectable tumours of the head and neck [3]. They report a resectability rate of 68% with the three drug regime and 38% with the two drug regime; which was either paclitaxel/cisplatin (70 patients) or docetaxel/cisplatin (17 patients) or paclitaxel/carboplatin (10 patients). However,

the response rates of individual regimes are not mentioned in the analysis.

Toxicity of therapy:

Almost all study trials report tolerable toxicity with the two drug regimen. The three drug regimen is associated with greater response, at the cost of greater toxicity. No major complications occurred in our study and all patients completed the protocol chemotherapy regimen in both arms. Toxicity profile in both arms varied with GI disturbances dominating the PF arm and neuropathy being common in the Taxol arm.

Toxicity of radiotherapy requiring discontinuation or default from therapy occurred during the course of study. Among 27 patients who received radiation therapy for progressive or static disease, 9 patients defaulted therapy due to toxicity, of whom 7 died due to disease progression.

Operative and post operative complications:

Only one patient who underwent surgery following chemotherapy developed flap dehiscence which was resutured. The wound morbidity among patients who underwent radiation prior to surgery was higher; however, only two patients developed major postoperative complications, of which one died.

Recurrence and outcome:

Of 13 patients who had response to chemotherapy, 5 patients developed recurrence after definitive treatment. One patient died of the disease.

Among the non-responders, 22 patients out of 27 developed recurrence after definitive treatment, and 13 died. Recurrences in the non-responders occurred even after they underwent standard treatment protocols of chemoradiation +/- surgery as compared to the responders who remained free of disease. This probably reflects a more aggressive tumour biology in the non-responders which accounts for the poorer outcome.

Progressive disease occurred in 13 patients following induction chemotherapy making one third of potentially resectable tumours inoperable. The unfavourable response rates in resectable oral cavity cancer render this modality of treatment unviable in this group.

7. Literature Review

Ever since the RTOG trial established the efficacy of adding chemotherapy to radiotherapy, resulting in improved outcomes, there has been great interest in the role of chemotherapy in head and neck cancers. Investigation of the role of combined chemoradiation dates back to the 1960s, with early studies exploring the sequential and concurrent use of single agents such as fluorouracil (5FU), bleomycin, cisplatin, methotrexate, and mitomycin. These trials demonstrated poor response to chemotherapy while singling out cisplatin as the most effective single agent with a 25-30% response rate. The historically important Veteran Affairs Laryngeal Cancer Study ultimately demonstrated that induction chemotherapy followed by radiation could achieve organ preservation in SCCHN patients without

compromise in overall survival [4]. Paccagnella et al. from Italy conducted a phase III trial in 2010 on 101 patients to compare concomitant PF plus radiotherapy without induction chemotherapy with TPF induction followed by concomitant PF plus radiotherapy (TPF plus chemoradiotherapy) [5]. In the phase III trial, the primary endpoint was complete response at 6 – 8 weeks after chemoradiotherapy and was achieved by 50% of patients who received TPF plus chemoradiotherapy. This was significantly more than in the chemoradiotherapy alone group (21%; $p = .004$). The median overall survival in the chemoradiotherapy arm was 33.3 months, with a 1-year survival rate of 78%, whereas in the induction chemotherapy plus chemoradiotherapy group the median OS was 39.6 months and the 1-year survival rate was 86%.

In the French GETTEC trial (Groupe d'Etude des Tumeurs de la Tête et du Cou), 318 patients with potentially curable oropharyngeal cancers were randomised to receive three cycles of PF induction chemotherapy followed by radiotherapy with or without prior surgery or only locoregional therapy [6]. Median survival was significantly longer in the induction chemotherapy arm (5.1yrs Vs 3.3 yrs). The type of locoregional therapy did not influence the clinical benefits of induction chemotherapy. In 2002, Pignon et al. published their findings from the "Meta-Analysis of Chemotherapy in Head and Neck Cancer study" of 63 randomised control trials on nearly 11,000 patients assessing the survival impact of adding chemotherapy to locoregional treatment in the adjuvant, neoadjuvant settings and as induction chemotherapy [7]. This was the largest study which studied the outcome of chemotherapy in head and neck squamous cell cancers and validated the use of induction chemotherapy in the management of unresectable, locally advanced cancers of the head and neck. They reported an absolute survival benefit of 4% at both 2 years and 5 years with the addition of chemotherapy to locoregional treatment. However, this benefit was statistically significant only with the addition of concomitant chemotherapy to radiotherapy. However, when 16 of the 31 trials using chemotherapy other than 5FU and cisplatin were excluded and analysed, a statistically significant overall survival benefit of 5% at 5 years was observed when induction chemotherapy was added to locoregional treatment [8].

Following the encouraging results showing benefit of induction chemotherapy in unresectable SCCHN, attempts were made to replicate these outcomes in resectable late stage disease. However, most of the studies were small, single institutional trials which were not powered to show small differences.

A meta-analysis of randomized trials (1965–2011) was performed to study the impact of induction chemotherapy on survival, disease control, and toxicity in resectable locally advanced SCCHN by Ma et al. published in the World Journal of Surgical Oncology, 2013 [9]. Fourteen trials analysed data of 2099 patients. Induction chemotherapy followed by locoregional treatment (surgery and/or radiotherapy or chemoradiotherapy) was compared to locoregional treatment alone (surgery and/or radiotherapy or chemoradiotherapy) in 11 RCTs (1,505 patients). Induction

chemotherapy was followed by surgery in non-responders and radiotherapy/chemoradiotherapy was given to responders.

The study did NOT find a significant difference in overall survival between patients treated with and without induction chemotherapy (HR = 1.01, 95% CI 0.88, 1.16, $p = 0.84$); neither was there a significant difference noted according to the protocol of induction chemotherapy, such as cisplatin and 5-fluorouracil (PF), other platin-containing combinations, or multiple agents without platin. There was also no significant difference in long-term (5-year) locoregional recurrence rate between patients treated with or without induction chemotherapy (432 patients, ratio difference = 2%, 95% CI -12%, 16%, $p = 0.76$). However, among the 700 patients who did develop distant metastases, those patients treated with induction chemotherapy had a significantly lower long-term (5-year) rate of distant metastases (8% difference, 95% CI 1%, 16%, $P = 0.02$), when compared to those who were treated without induction chemotherapy. Induction chemotherapy did not improve overall survival, disease-free survival or locoregional control. Toxicity of induction chemotherapy was acceptable for further therapy.

Most of patients receiving PF induction chemotherapy in this study were oral cancer patients; whereas previous studies of induction chemotherapy in HNSCC patients included not only oral cancer, but also oropharyngeal and hypopharyngeal cancer. The study concluded that the efficiency of adding PF agents to standard care may differ between patients with oral cancer, and those with oropharyngeal or hypopharyngeal cancer. The authors summed up that the effect of PF induction chemotherapy may differ among different primary tumour sites, and therefore, the primary tumour site might be considered before adding PF induction chemotherapy; that induction chemotherapy may be more effective in oropharyngeal and hypopharyngeal cancer than in oral cancer.

8. Conclusion

- 1) Preoperative chemotherapy in locally advanced resectable squamous cell carcinoma of the oral cavity was ineffective in reducing the tumour volume and the stage of the disease.
- 2) Paclitaxel with cisplatin combination chemotherapy yielded significantly better response rates than 5FU and cisplatin. However, the response rates were inferior to the standard three drug regimen currently recommended.
- 3) Neoadjuvant chemotherapy did not improve the prognosis and is not recommended in initial management of locally advanced resectable squamous cell carcinoma of the oral cavity.

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