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Comparative Study Between Gemcitabine Plus Cisplatin and Docetaxel Plus Fluorouracil Plus Cisplatin as Induction Chemotherapy in Unresectable Locally Advanced Head and Neck Cancer Patients in Terms of PFS and OS at 1 Year Follow Up

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Abstract

Background: Head and Neck Squamous Cell Carcinoma (HNSCC) represents a major global health burden, accounting for approximately 800,000 new cases and 330,000 deaths annually. A substantial proportion of patients present with Locally Advanced Disease (LAHNSCC), many of whom are considered unresectable due to technical limitations, advanced tumor stage, or anticipated poor functional outcomes. Concurrent Chemoradiotherapy (CRT) remains the standard of care; however, distant metastasis continues to be a leading cause of treatment failure. Induction Chemotherapy (IC) has been explored as a strategy to improve systemic control and facilitate organ preservation. The Docetaxel, Cisplatin, and Fluorouracil (DPF) regimen has demonstrated superior survival outcomes compared to the doublet cisplatin-fluorouracil (PF), as shown in the MACH-NC meta-analysis, but is associated with significant toxicity.

Aim: This study aimed to assess and compare Progression-Free Survival (PFS) and Overall Survival (OS) between the two study arms over a one-year follow-up period

Patients and methods: This randomized controlled clinical trial was conducted at the Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Suez Canal University, to compare the efficacy and toxicity of two induction chemotherapy regimens-GP) and DPF-in patients with unresectable LAHNSCC. A total of 25 eligible patients were randomized into two equal groups, each receiving three cycles of the assigned induction regimen followed by radical treatment with concurrent chemoradiotherapy or surgery with adjuvant CCRT. All patients were evaluated clinically and radiologically. Performance status was assessed and showed improvement or stabilization in most patients in the GP arm, whereas it declined in several patients in the DPF arm due to higher toxicity.

Results: The study found that patients treated with GP had higher overall and progression-free survival rates compared to those receiving the DPF regimen. Kaplan-Meier survival analysis showed a statistically significant improvement in both Overall Survival (OS) and Progression-Free Survival (PFS) in the GP group.

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Conclusion: The use of gemcitabine with cisplatin as an efficient and more tolerable induction chemotherapy regimen for unresectable LAHNSCC is supported by strong comparative data, according to the study's findings. The GP regimen provides a more practical approach with obvious benefits in actual clinical settings, even if DPF is still a relevant standard with intensive support care infrastructure.

Keywords: Induction chemotherapy; DPF regimen; GP regimen.

Introduction

Worldwide, head and neck squamous-cell carcinoma accounts for around 800,000 new cases, 330,000 deaths, and 5% of newly diagnosed malignancies. Most of them have Head and Neck Squamous Cell Carcinoma (LAHNSCC), which is locoregionally progressed [1].

Because the phrase «unresectable» is difficult to define, more than 50% of cases with LAHNSCC are not appropriate for radical resection (unresectable illness). It is thus widely thought to be appropriate in many instances, such as those that are technically unresectable, have an advanced tumor stage, have a poor predicted surgical result, or have a poor functional prognosis after surgery [2].

Patients with HNSCC have recently seen acceptable local and regional management thanks to advancements in Radiation (RT) technology. The primary cause of mortality and a significant treatment problem is still distant metastases. Induction Chemotherapy (IC) is thought to be crucial for preserving organs and reducing distant metastases. Despite decades of study, the utility of IC is still being studied. But enough data has been gathered to show that DPF (docetaxel, cisplatin, and fluorouracil) is better than the chemotherapeutic doublet PF (cisplatin and fluorouracil) [3].

Induction DPF improved OS over PF (HR 0.72; 95% CI 0.63-0.83) and Progression Free Survival (PFS) (HR 0.78; 95% CI, 0.69-0.87), according to the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC). For unresectable LA-HNSCC, CRT is the standard of therapy; however, IC followed by (C) RT is an alternative [4].

However, treatment-related adverse effects are more frequent with the triplet regimen. Given that repeated chemotherapy cycles are necessary, tolerability becomes a significant challenge for patients. Therefore, there is a pressing need for an induction chemotherapy regimen that is both effective and better tolerated [5].

In cases of respectable locally advanced laryngeal and hypopharyngeal cancer, CRT is the standard of treatment for preserving organs; however, IC followed by (chemo)radiotherapy is another option. This could be more beneficial in maintaining laryngeal function than CRT alone, even if it might not be as successful in managing locoregional illness [6].

For more than half a century, attempts have been made to preserve the larynx. Due to the poor local control and survival rates of RT alone, surgery followed by CRT has become a common practice. However, a number of treatments aimed at preserving the larynx have been developed since surgical laryngectomy has major detrimental effects on function, appearance, and psychological well-being [6].

In patients with incurable LA-HNSCC, CRT and IC followed by CRT have been compared in six sizable randomized controlled studies to far. However, because of the poor trial design, analytic techniques, and patient recruitment, no firm conclusions have been drawn, and despite the promise of IC, the standard of treatment is still CRT [2].

DPF is the usual treatment for IC. Regarding whether RT should be used alone or in combination with other medications during induction of DPF, there is no established protocol. Due of induction DPF's high toxicity, a new IC that is both less toxic and yet effective is needed. Both the usage of novel medications and combinations of current treatments are continuously being tested [6].

GP was used as induction chemotherapy for NPC, and it outperformed conventional treatment in terms of response rate and toxicity profile reduction. Therefore, instead of focusing on nasopharyngeal cancer, we will compare GP and DPF in our research in terms of effectiveness and toxicity as extrapolation to other head and neck malignancies.

Aim: This study aimed to assess and compare Progression-Free Survival (PFS) and Overall Survival (OS) between the two study arms over a one-year follow-up period.

Patients and methods: This comparative clinical study, Randomized Controlled Trial (RCT), phase 3 trial, open label, was held in the Department of Clinical Oncology and Nuclear Medicine at faculty of Medicine, Suez Canal University. The study was conducted through two groups:

Group A: Unresectable LAHNSCC patients receiving gemcitabine plus cisplatin.

Group B: Unresectable LAHNSCC patients with receiving docetaxel plus fluorouracil plus cisplatin.

Inclusion criteria

1) Adult patients (aged between 18-70 years old).
2) Patients pathologically confirmed to have HNSCC.
3) Patients with locally advanced unresectable disease including laryngeal carcinoma, hypopharyngeal carcinoma, oropharyngeal carcinoma, oral cavity cancers and head and neck of unknown origin.
4) Naïve patients who do not receive any treatment either chemo or radiotherapy before randomization).

Exclusive criteria

1) Patients with performance status (ECOG >2)
2) Patients with distant metastatic disease.
3) Patients with calculated creatinine clearance less than 45 ml / min.
4) Patients with moderate to severe hearing loss.

Methods of data collection

The study included two groups and the following data will be collected for each subject in the patients group:

Group A: Unresectable LAHNSCC patients receiving gemcitabine in dose plus cisplatin (1000 mg/m^2 gemcitabine on Day 1 and 8, 100 mg/m^2 cisplatin on Day 1, each for three cycles every 3 weeks)

Group B: Unresectable LAHNSCC patients with receiving docetaxel plus fluorouracil plus cisplatin (75 mg/m^2 docetaxel on Day 1, 75 mg/m^2 cisplatin on Day 1 and 750 mg/m^2/day 5-FU on 5 consecutive days, each for three cycles every 3 weeks)

Each group received 3 cycles of each regimen and assessment of disease progression and comparing the acute toxicity of each regimen during receiving cycles and during receiving radiation therapy baseline assessment included:

A. Detailed medical history including age, sex, residence, performance using ECOG-PS score, educational level of the patient, smoking history.

B. Data related to the disease including primary manifestations of the disease, pathology of primary disease, staging of the disease (TNM), co morbidities The above data was collected from patients' filling records in the Clinical Oncology Department.

C. Periodic clinical examination to assess patient clinically (cervical Lymph node examinations, cranial nerve examinations, assessment of swallowing, speech assessment, nutritional status and complete physical examination of chest and abdomen to exclude distant metastasis clinically), and acute toxicity of treatment in form of mucositis, myelosuppression, hepatotoxicity and nephrotoxicity and neurotoxicity

D. Radiological evaluation with MRI head and neck with contrast before starting cycles of chemotherapy regimen and after 3 cycles to assess if there is disease progression or regression

E. Assessment of distant metastasis: restaging by PET/CT or Conventional CTs according to availability

Data management: Data was collected and coded then was entered as a spread sheet using Microsoft excel for windows office 2019. Data analysis using Statistical Package of Social Science (SPSS) software program version 21.0 for analysis. Data was presented as tables and graphs; we used t-test to compare between quantitative data expressed as mean and standard deviation. Chi-square test was used to compare between the qualitative data expressed as number and percent. P value was considered as significant when $p<0.05$.

Results

The present study was designed as a randomized controlled clinical trial that included 25 adult patients with unresectable, Locally Advanced Head and Neck Squamous Cell Carcinoma (LAHNSCC) who attended the Clinical Oncology Department at Suez Canal University Hospital, Ismailia.

The patients were randomly assigned into two groups:

- **Group A:** Patients who fulfilled the inclusion criteria and received the Gemcitabine Plus cisplatin (GP) regimen.
- **Group B:** Patients who fulfilled the inclusion criteria and received the docetaxel, cisplatin, and 5-fluorouracil (DPF) regimen.

The demographic details of the surveyed group are shown in (Table 1), which provide crucial information on the cohort's makeup. The gender distribution shows that groups A and B have a noticeable male majority (66.7% and 61.5%, respectively). Group A's age distribution spans from 39 to 70 years, with an average age of 57.75±10.97 years, whereas Group B's age distribution spans from 33 to 66 years, with an average age of 51.46±11.0 years. Regarding age and sex, no statistically significant difference between the two groups under study was found. (p=0.166, FEP=1.00, respectively). Eighty-three percent of group A patients and 61.5% of group B patients had low-risk comorbidities. This difference was negligible (FEP=0.378) by Charlton comorbidity score. Before therapy, 69.2% of group B patients had performance level I, whereas 50% of group A patients had performance status II, which was statistically insignificant (MCP=0.315). In group B, 61.5% of patients had their dose reduced by 20%. We detected no statistically significant difference in dose reduction between the two groups (FEP=0.320). In group B, 53.8% of patients had oral cavity cancer, whereas 50% in group A had laryngeal cancer.

Table 1: Comparison between the two studied groups according to baseline patient, tumor and treatment characteristics.

Parameter	Group A (n=12) (GP)	Group B (n=13) (DPF)	p-value
Sex			
Male	8 (66.7%)	8 (61.5%)	^{FE}p= 1.000
Female	4 (33.3%)	5 (38.5%)	
Age			
Mean ± SD	57.75±10.97	51.46±11.00	0.166
Performance Status (ECOG)			
I	5 (41.7%)	9 (69.2%)	^{MC}p= 0.315
II	6 (50.0%)	4 (30.8%)	
III	1 (8.3%)	0 (0.0%)	
Comorbidities (Charlton Comorbidity Index)			
Low risk	10 (83.3%)	8 (61.5%)	^{FE}p=0.378
High risk	2 (16.7%)	5 (38.5%)	
Primary tumor site			
Oral cavity	3 (25.0%)	7 (53.8%)	MCp= 0.404
Hypopharynx	2 (16.7%)	1 (7.7%)	
Unknown origin	1 (8.3%)	0 (0.0%)	
Larynx	6 (50.0%)	5 (38.5%)	

FET: Fisher Exact Test; MC: Monte Carlo Test; p: p value for comparing the two studied groups.

(Table 2) 41.7% of cases in group A either got partial or complete response, while 30.8% of patients in group B had progression and 23.1% of those either got partial response or did not complete the treatment. No statistically significant variation was identified among the two studied groups (MCp=0.114).

Table 2: Comparison between the two studied groups according to baseline patient, tumor and treatment characteristics.

	Group A(GP)		Group B(DPF)		p
	No.	%	No.	%	
RR after radical TTT	(n = 10)		(n = 9)		MCp= 0.026*
Complete response	5	50.0	1	11.1	
Partial response	5	50.0	3	33.3	
Stationary	0	0.0	1	11.1	
Progression	0	0.0	4	44.4	

MC: Monte Carlo Test; FE: Fisher Exact Test; p: p value for comparing between the two studied groups; *: Statistically significant at p≤0.05; #: 2 more cases died (DPF).

(Table 3) and (Figure 1) showed baseline performance status was comparable between the two groups, with no statistically significant difference (MCp = 0.315), although Group A had a higher proportion of PS II (50%) and Group B predominantly PS I (69.2%). Following treatment, a significant deterioration in performance status was observed in Group B, with no patients remaining PS I and the majority shifting to poorer status (45.5% PS IV, 27.3% PS III, 18.3% PS II). In contrast, Group A maintained better functional outcomes, with 40% of patients remaining PS I and 50% PS II. Overall, post-treatment performance status was significantly better in Group A compared to Group B (MCp = 0.008), suggesting improved tolerability of the regimen used in Group A.

Table 3: Comparison between the two studied groups according to Performance Status (PS) post radical treatment according to ECOG.

PS	Group A (GP) (n = 10)		Group B (DPF) (n = 9)		^{MC}p
	No.	%	No.	%	
Post					
I	4	40.0	0	0.0	0.008*
II	5	50.0	2	22.2	
III	1	10.0	2	22.2	
IV	0	0.0	5	45.5	
MH (p_0)	10.500 (0.739)		22.500* (0.003*)		

MC: Monte Carlo Test; MH: Marginal Homogeneity Test; p: p value for comparing the two studied groups; p0: p value for comparing between Pre and Post; *: Statistically significant at p≤0.05.

Table 4: Kaplan-Meier survival curve for overall Survival.

	Total No.	No. of Events	Mean (Months)	Median (Months)	% End of study	Log rank	
						χ^2	p
Group A (GP)	12	2	11.08	-	83.3%	4.701*	0.030*
Group B (DPF)	13	8	8.923	12.00	38.5%		

As shown in (Table 5) and (Figure 3), Group A demonstrated a significantly prolonged progression-free survival compared to Group B, with a mean PFS of 10.58 months versus 7.31 months, and 83.3% of patients in Group A remaining progression-free at study end versus only 38.5% in Group B. The log-rank test (χ^2=4.567, p=0.033) confirms the statistical significance of this difference, with earlier and more frequent events observed in Group B (8/13 events) compared to Group A (2/12 events), reflecting superior disease control and treatment durability in Group A.

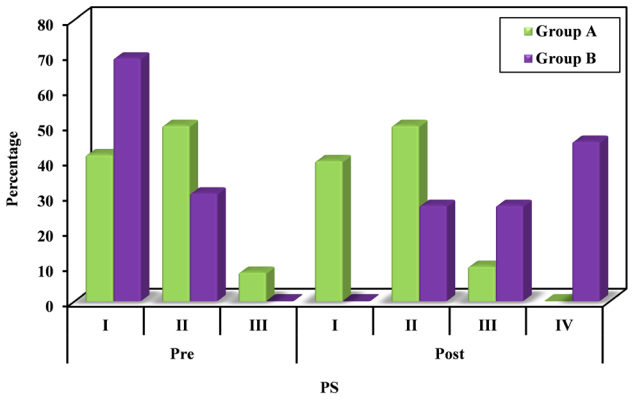

Figure 1: Comparison between the two studied groups according to PS before and post radical treatment.

The Kaplan-Meier analysis of overall survival (Figure 3) demonstrated a statistically significant difference between the two groups (p=0.030) with Group A showing a higher survival rate at 12 months (83.3%) compared to Group B (38.5%). Group A also had fewer death events (2 vs. 8) and a longer mean survival duration (11.08 vs. 8.92 months) as explained in (Table 4) and (Figure 2).

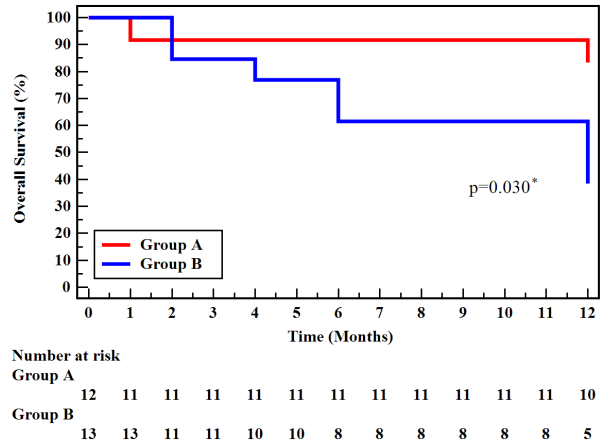

Figure 2: Kaplan-Meier survival curve for overall survival.

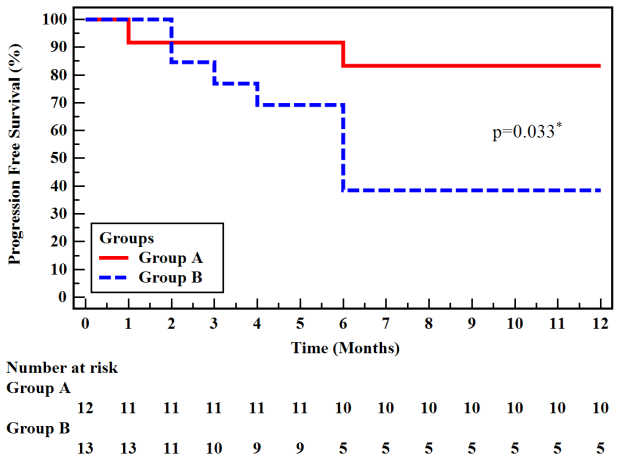

Figure 3: Kaplan-Meier survival curve for progression free survival.

Table 5: Kaplan-Meier survival curve for progression free survival.

	Total No.	No. of Events	Mean (Months)	Median (Months)	% End of study	Log rank	
						χ^2	p
Group A (GP)	12	2	10.58	-	83.3%	4.567*	0.033*
Group B (DPF)	13	8	7.308	6.00	38.5%		

Discussion

In patients with incurable LAHNSCC, this comparative trial assessed the safety and effectiveness of two IC regimens: Gemcitabine plus Cisplatin (GP, Group A) vs Docetaxel, Cisplatin, and 5-Fluorouracil (DPF, Group B). The findings provide crucial information for treatment planning by illuminating significant clinical differences across the regimens in terms of response rates, toxicity profiles, and post-treatment outcomes. Our results raise doubts about DPF's universal advantage and raise the possibility that GP is a safer but equally effective substitute.

Tumor subsite distribution and patient demographics age, sex, comorbidities, and performance status were among the clinical and demographic factors that were statistically similar across the two research groups. Nonetheless, a notable differential in the location of tumor subsites was seen between the two therapy groups. Oral cavity cancers were significantly more frequent in the DPF group (53.8%) than in the GP group (only 25%), and laryngeal malignancies were more prevalent in the GP group (50% vs. 38% in DPF) (p=0.037).

The majority of patients in both groups (92.3% in DPF and 83.3% in GP) had stage IVA disease at presentation, with no statistically significant difference (FEp=0.593). The majority of patients with LAHNSCC were presented at an advanced, incurable stage because of delayed symptom detection or restricted access to specialist treatment, which is consistent with results from many significant studies [7].

The function of IC in LAHNSCC is still up for discussion. Due to significant Western studies like TAX 324 and TAX 323 that showed better progression-free and OS outcomes than PF regimens, the DPF regimen has historically been regarded as the standard [8]. This predominance is challenged by new evidence, such as our present research, which demonstrates significant clinical and radiological responses with the combination of GP regimens.

Group A (GP) had a clinical regression rate of 83.3% in our study, which was considerably greater than the DPF group's (Group B) 51.1% (p=0.002). This pattern was supported by radiological evaluations, which similarly favored GP in both partial and full responses. This improved tumor response challenges accepted wisdom that favors DPF and calls into question whether it can be applied universally to a wide range of patient types [7], who carried out a retrospective analysis in India, provide support for this paradigm shift. They discovered that non-DPF regimens, such as gemcitabine–cisplatin and paclitaxel-cisplatin, produced comparable overall response rates and survival outcomes, with better tolerability in unresectable oral cavity cancers. According to these results, the intensive DPF regimen could not always provide a significant therapeutic benefit in certain subgroups, especially in LMICs where treatment is complicated by patient comorbidities, delayed diagnosis, and a lack of supporting care infrastructure.

On the other hand, the studies confirmed that DPF can improve laryngeal preservation and decrease distant metastases. However, both studies also reported high rates of toxicity and treatment-related morbidity, which could counteract any slight improvement in survival, particularly in patients who are already fragile [9].

This opinion was further clarified by a meta-analysis, which found that while DPF lowers the risk of distant metastases, its effect on OS is still negligible as Comparison to Definitive (CRT) without induction [10].

Additionally, despite its potential benefits in tumor downstaging, another trial further muddies the picture by showing no discernible survival benefit of IC (including DPF) prior to concurrent CRT [11].

This disparity calls into doubt the generalizability of DPF, particularly in non-Western communities, and implies that pharmacogenomics, tumor biology, treatment adherence, and supporting care infrastructure may all be important considerations.

Our results further confirm this, indicating that vigorous induction regimens may not necessarily result in improved long-term outcomes since there is no discernible OS benefit with DPF despite increased toxicity.

In our investigation, Group A showed a statistically significant OS advantage over Group B, with a 12-month survival rate of 83.3% against 38.5%. As an induction regimen for LAHNSCC, our results are consistent with and reinforce earlier clinical data indicating the GP regimen's good effectiveness and safety profile. When compared to DPF-based regimens, IC with GP in locally advanced nasopharyngeal cancer shown a significant improvement in survival outcomes and was linked to lower hematologic toxicity in the phase III research [12]. Similarly, a research found that patients treated with DPF had a 3-year OS of around 62%, but at a significant toxicity cost, with grade 3-4 neutropenia occurring in more than 75% of cases [13].

On the other hand, as our cohort showed, GP regimens have continuously shown more favorable toxicity profiles, which may increase treatment compliance and eventually lead to better survival. In addition, a randomized controlled trial conducted in India revealed similar response rates and survival outcomes between GP and DPF regimens, but it also showed that the GP arm experienced significantly fewer dose reductions and lower treatment-related morbidity. This is especially pertinent in our context, where the lack of supportive care infrastructure makes the less toxic regimen more feasible and possibly more effective in real-world situations [14].

The difficulties of providing intensive triplet therapy outside of highly specialized centers are highlighted by the interesting fact that the sharp decline in Group B's survival curve in our study, especially within the first six months, reflects the high early dropout and complication rates observed in DPF-treated arms in previous trials (e.g., TAX 323 and TAX 324).

Our results support the mounting evidence that GP may provide a more favorable toxicity profile and a clinically significant survival advantage, making it a competitive option to DPF in the induction scenario, particularly in settings with limited resources.

Our results showed a statistically significant difference (p=0.033) between the mean PFS of 10.58 months for the GP group and 7.31 months for the DPF group. According to a different study, Gemcitabine-based induction therapy achieved comparable progression-free survival and overall response rates to DPF with a more favorable toxicity profile [15]. This study also showed that GP was especially effective in patients who could not tolerate the aggressive triple-agent DPF regimen. The significant prolongation of PFS suggests that GP provides superior disease control. This conclusion is further supported by the fact that Group A experienced fewer advancement events (2/12) than Group B (8/13). Gemcitabine's radio sensitizing qualities, which improve locoregional control during CRT [14], and its enhanced systemic tolerability, which reduces delays or dosage reductions, are probably the causes of this benefit.

Hitt et al. [16], also demonstrated comparable or superior PFS with less harmful induction protocols, highlighting the significance of striking a balance between tolerability and intensity. DPF, on the other hand, has received substantial validation as a typical IC regimen. Although DPF is still the most successful in terms of tumor response, other doublet regimens like GP may provide a good compromise between effectiveness and tolerability, according to a meta-analysis of induction regimens [6].

Our findings provide clinical support for this assertion, which is particularly pertinent in contexts where treatment-related morbidity is a significant worry. Additionally, a greater proportion of patients in the GP group (83.3%) remained progression-free at the end of the study, compared to 38.5% in the DPF group [17].

However, our study's small sample size and brief median follow-up call for careful interpretation. To confirm these early results, larger randomized controlled trials-like the upcoming phase III studies comparing GP with DPF-will be essential. Our study's significant mortality rate difference between the GP and DPF groups (16.7% vs. 61.5%; p=0.041) highlights the intricate relationship between patient compliance, toxicity, and therapeutic success. Although DPF is thought to be a powerful induction regimen, our research indicates that its high toxicity profile could outweigh any advantages to survival, especially for susceptible groups.

Our study's mortality results contribute to the rising worry that DPF does not improve survival in real-world situations, especially when toxicity monitoring, nutritional treatment, and patient support systems are subpar. better treatment continuity was made possible by the GP regimen's better-balanced toxicity-efficacy profile, which is often the deciding factor in survival outcomes for unresectable LAHNSCC [7].

In conclusion, the GP group had longer mean survival durations and fewer incidents than the DPF group, with both OS and PFS being noticeably superior. These findings are consistent with growing evidence that GP is a more effective and manageable regimen that may provide a clinically significant benefit in practical settings, especially for populations where toxicity control and treatment compliance are significant problems.

Conclusion

The findings of this study suggest that the combination of gemcitabine and cisplatin may represent a more tolerable and potentially effective induction chemotherapy option for patients with unresectable locally advanced head and neck cancer. Compared with the DPF regimen, GP demonstrated favorable survival outcomes with a more manageable toxicity profile. While DPF remains an established standard, particularly in settings with adequate supportive care, the GP regimen may offer a practical alternative, especially in resource-limited clinical environments. Further large-scale studies are warranted to validate these findings.

Abbreviations

5-FU: Fluorouracil; AE: Adverse Event; CCRT: Concomitant Chemoradiotherapy; CI: Confidence Interval; CT: Chemotherapy; DPF: Docetaxel Plus Fluorouracil Plus Cisplatin; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal Growth Factor Receptor; GP: Gemcitabine Plus Cisplatin; HNSCC: Head and Neck Squamous Cell Carcinoma; HPV: Human Papillomavirus; IC: Induction Chemotherapy; IMRT: Intensity-Modulated radiation Therapy; LAHNSCC: Loco-Regionally Locally Advanced Head and Neck Cancer; LRC: Locoregional Control; MACH-NC: Meta-Analysis of Chemotherapy in Head and Neck Cancer; MRI: Magnetic Resonance Imaging; NPC: Nasopharyngeal Cancer; ORR: Objective Response Rate; OS: Overall Survival; OSCC: Oropharyngeal Squamous Cell Carcinoma; PET/CT: Positron Emission Tomography/Computed Tomography; PF: Cisplatin Plus 5-FU; PFS: Progression-Free Survival; PS: Performance Status; RCTs: Randomized Controlled Trials; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; TNM: Tumor/Node/Metastasis; WHO: World Health Organization.

Declarations

Ethical considerations

1. All the procedures of this study will be approved by the Suez Canal University Hospital and family medicine department.
2. Approval from research Ethics Committee, faculty of medicine Suez Canal University will be taken before starting field work.
3. Informed written consent will be obtained from the participants before the start of the study.
4. Explanation of the research aims and procedures will be provided to the participants.
5. The study maneuver and the possible effects and side effects of the drugs will be explained to the participants.
6. Confidentiality will be assured. (Participant's data will be considered confidential and not be used outside this study without participant's approval, coding instead of participants names will be used, both participants and researcher will be blind.
7. Participants have the right to refuse to participate in the study without negative impact up on them and without affection of the medical care provided to them.
8. Participants have the right to withdraw from the study at any time without giving any reason.
9. The researcher phone number and all possible communicating methods will be identified to the participants to return at any

time for any explanation. All participants will be announced by the results of the study.

Conflicts of interest: The authors declare that they have no competing interests.

Research estimated budget in: This research is self-funded.

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Supplementary						Publications	Total
histopathology	drugs/Lab chemicals	Lab-investigations	Software	Material and printing	Others)		
……	50,000	……	5000 for statistical analysis	3000	……	5,000	63,000
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