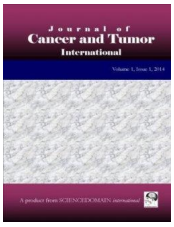

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Induction Chemotherapy as a Predictor for Definitive Treatment in Bulky Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A Schedule More Suited to Sub Himalayan Region

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Authors' contributions

This work was carried out in collaboration between all authors. Author VN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SB and MG managed the analysis of the study. Authors MP and DSP managed the literature searches. Authors MA and SS provided critical intellectual inputs. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: Use of induction chemotherapy (IC) as a predictor for definitive treatment in bulky locally advanced head and neck cancer (LA HNSCC) patients, who are not feasible for any upfront radical treatment in sub-Himalayan population.
Materials and Methods: 33 patients (stage IVA and IVB, T4, N3) LA HNSCC were treated with induction chemotherapy (TP) from April 2013 to August 2015. All patients were considered inoperable or not feasible for upfront radical treatment and Eastern Cooperative Oncology Group (ECOG) Performance status was ≤ 2.

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All patients were reviewed at multidisciplinary tumor board and considered for initial 3 cycles of induction chemotherapy in view of bulky stage IV LAHNSCC. Subsequent Radical (CTRT or Sx → CT RT) or palliative treatment was decided by tumor board after response assessment of NACT. The Statistical Package for the Social Sciences software (SPSS version 16.0) was used for analysis. The response rate, toxicity (accordance with CTCAE *vs*. 4.02), completion rate of radical treatment post NACT and overall survival was reported.

Results: Median follow up was 22 months (18-26 months). After 3 cycles of IC, 20 patients (60.66%) underwent radical treatment and remaining 13 patients (39.33%) were treated with palliative treatment. Overall grade 2-3 toxicity was seen in 12 patients. No toxicity related mortality was noted. The completion rate of radical treatment post IC was 93.5%. The median OS was 18 month ((95% CI 9.00 to 31.00). Total 16 Patients are alive, in which 11 is disease free. Twelve patients expired and 5 patients were lost to follow up.

Conclusion: Our present experience suggests that neoadjuvant chemotherapy with doublet regime is reasonably well tolerated and feasible in limited resource setting of patients with locally advanced disease who are not fit for upfront radical treatment.

Keywords: Locally advanced head and neck cancer; neoadjuvant chemotherapy; radiotherapy; predictor for definitive treatment in head and neck cancer.

1. INTRODUCTION

Head and neck cancers are the most common cancer in India [1-3]. There is a higher incidence of HNSCC in developing countries like India. Tobacco usage is considered to be a risk factor for the development of HNSCC. Advanced loco-regional disease, defined either as non-metastatic Stage III or Stage IV, is the most frequent clinical situation which appears in 60% of the diagnosed patients. For loco-regional disease an acceptable treatment option is based on surgery and/or radiotherapy (RT). On the other hand, in the treatment of inoperable, loco-regionally advanced HNSCC the principal treatment in most institutions is combined-modality treatment with chemo-radiotherapy (CRT) if the patient is medically fit. This approach has become the standard treatment for most patients. The 5-year survival rates of multimodal chemo-radiotherapy are below 20%, with a median survival of 12 months or less [1-3]. Although the role of induction chemotherapy is still investigational, sequential treatment with induction chemotherapy followed by radical treatment for HNSCC has been shown to decrease the risk of distant metastases as a first site of tumor recurrence and may lead to favourable functional outcomes [3,4].

Induction chemotherapy with TPF has gained popularity because of better disease response and possible survival benefit over other combinations that were used earlier [5]. However, the debate on survival benefit still continues. Recent studies reveal no significant benefit in OS with sequential chemoradiation following induction chemotherapy as opposed to concurrent chemoradiation alone for locally advanced head and neck cancer [5,6,7]. Although TPF is widely used as the combination of choice for neoadjuvant chemotherapy in head and neck cancers, the incidence of toxicities remains considerable and the supportive treatment required is often resource intensive.

In our Sub-Himalayan population, the patients who are planned for neoadjuvant chemotherapy face many issues. Most common cited issue is financial difficulties despite of availability of extremely subsidised treatment. Another common problem is that the patients prefer traditional healers. But the most important issue is due to logistic reasons. This is due to the fact that many patients travel from hilly terrain, which often gets subjected to natural difficulties such as landslides and blockade of roads due to snow during winters. Indeed, being the only Cancer Centre in the Garhwal region, patients have to travel for long distances and across difficult terrain for treatment.

The treatment interruptions that occur because of the toxicity also have a bearing on disease outcomes as the radiobiology of head and neck tumours makes this issue of treatment gaps especially important.

We treated patients with locally advanced HNSCC with bulky nodal disease with induction chemotherapy consisting of 3 weekly paclitaxel and cisplatin followed by “risk-based” definitive treatment consisting of either concomitant chemo

radiotherapy or surgical resection based on the site and stage of disease followed by chemoradiotherapy/radiotherapy. Our hypothesis was that induction chemotherapy with PC regimen followed by risk-based local therapy would achieve long term loco regional and distant disease control with acceptable toxicity.

To the best of our knowledge, there has been no specific study on patients who present with locally advanced squamous cell carcinoma of the head and neck (SCCHN). However, it is noteworthy that in patients receiving treatment for the first time, the response rates of SCCHN to induction chemotherapy ranges from 68% to 72%, among the highest rates for solid tumors [5,6]. If we use induction chemotherapy, it helps in shrinking the tumour with acceptable toxicities and lead to definitive treatment with radical intent, either surgery and/or chemo-radiotherapy. For non-responders the intent of treatment remains only palliation. At our centre, we followed aforesaid approach.

2. METHODS

The treatment plan of patients with locally advanced HNSCC was decided in a multidisciplinary tumor board meeting at our centre. Those patients with locally advanced HNSCC with ECOG performance status ≤2, who were technically unresectable or not feasible for radical treatment, were considered suitable for induction chemotherapy. The induction chemotherapy protocol used at our center is a doublet or triplet regimen consisting of a taxol and a platinum agent with or without 5-fluorouracil.

We retrospectively evaluated, thirty three patients (stage IVA and IVB) of LA HNSCC, who were treated with doublet regimen (PC) induction chemotherapy from April 2013 to July 2015.

Out of 33, 7 patients were in Stage IVA (T4a and N2c) and 26 were in Stage IVB (N3 >6 cm). In all patients ECOG Performance status were ≤ 2.

Patients, who had uncontrolled comorbidities like hypertension, diabetes mellitus, cardiac dysfunction or any other uncontrolled disease were excluded from study.

Subsequent Radical or Palliative treatment was decided by the multidisciplinary tumour board after response assessment of Neoadjuvant chemotherapy.

Work up of the patients included complete blood count, renal biochemistry, chest radiography, dental assessment, CT scan of head and neck and histopathological diagnosis.

2.1 Induction Chemotherapy

All patients were treated with 3 weekly IC (Taxol and Cisplatin) at a dose of Inj Paclitaxel 175 mg/m^2 and Inj. Cisplatin 75 mg/m^2. 31 patients received three cycles of induction chemotherapy. 2 patients received only two cycles of chemotherapy because of poor response.

Toxicity related to chemotherapy was assessed at each visit prior to chemotherapy. Assessment of toxicities were recorded according to CTCAE version 4.02. Delay in planned treatment was noted.

After the completion of therapy, the patients were reassessed clinically and radiologically in the multidisciplinary clinic. Based on the performance status, nutritional status, response to treatment and the status of comorbidities, further treatment could be surgery, radical radiation with or without chemotherapy, palliative chemotherapy or best supportive care alone. Patients, who had >30% response underwent radical treatment that is either surgery or chemoradiotherapy and patients who had < 30% response underwent only palliative treatment.

2.2 Surgery

Surgery included wide local excision along with appropriate neck dissection and reconstruction. All patients underwent preoperative speech and swallowing assessments as well as counselling for nutrition.

2.3 Sequential Chemo Radiation

A total of 90% patients were treated using conventional and 3D-CRT technique. A dose of 66Gy in 33 fractions @ 2Gy per fraction over six and one half weeks by 6 MV Linac was prescribed.

All patients received weekly inj. cisplatin 30 mg per m^2. Weekly complete Blood count and serum creatinine were monitored. All patients were examined every week during the course of chemo-radiation for assessment of toxicity which was assessed according to RTOG acute toxicity criteria. Diet counselling was done prior to radiotherapy. Prophylactic feeding tubes were not placed unless nutritional compromise and/or

dysphagia were identified in baseline assessments.

The Statistical Package for the Social Sciences software (SPSS version 16.0) was used for analysis. The demographic details, status of disease, details of the chemotherapy including the toxicity according to the CTCAE version 4.02 (common terminology criteria of adverse events), response rate to NACT (RECIST version 1.1), completion rate of radical intent treatment post induction chemotherapy (IC), progression free survival (PFS) and overall survival (OS) were reported.

Descriptive statistics were calculated to describe the sample characteristics, toxicity, and functional outcomes. Survival distributions were estimated using the Kaplan-Meier method. Statistical differences between paired data were analysed using the nonparametric sign-rank test. Statistical significance was considered with α-level 0.05.

3. RESULTS

Table 1 shows the baseline characteristics of the study subjects. Thirty three patients with previously untreated stage IV SCCHN were enrolled. Median follow up of the patients was 22 months (18-26 months). Site wise distribution was as follows: oral cavity: 14 (42.43%), oropharyngeal- 7(21.21%), laryngopharynx-8(24.24%) and unknown primary with neck secondary UNP-4 (12.12%) respectively. The response rate was assessed in 33 patients after completion of induction chemotherapy. 20 patients (60.60%) had > 30% response, following which they underwent radical treatment and remaining 13 (39.40%) were treated with palliative treatment.

Fig. 1 and Table 2 shows primary site wise and subsite wise response rate. Arm A were treated with palliation (<30% response) and arm B were treated with radical intent (>30% response).

Out of 14 patients with oral cavity cancers, resectability and suitability for surgery could be achieved in 7 patients. However, 3 patients of buccal mucosa cancers underwent surgical resection followed by adjuvant chemo radiotherapy, and rest 4 refused for surgery and were treated with radical chemo radiation.

Thus, the calculated completion rate (Cp) of radical intent treatment was 93.5% as 19 of 20 patients completed radical intent treatment.

Table 1. Baseline characteristics of the study subjects N = 33 (100%)

Baseline characteristic	Result		
Age	Mean: 52.70 years	Range: 30 – 74 years	Median: 54 years
Sex	Male: 31(94%)	Female: 2(6%)	
Performance Status	ECOG PS II: 30 (91%)	ECOG PS III: 3(9%)	
Histology*	WDSCC: 5(15%)	MDSCC: 22(67%)	PDSCC: 6(18%)
Primary Site (Subsite)	**Oral Cavity: 14 (43%)** Buccal Mucosa: 5 Tongue: 6 RMT: 1 Hard Palate: 2 **Oropharynx: 7 (21%)** Tonsil: 3 Base Tongue: 4 **Laryngo Hypopharynx: 8 (24%)** Pyriform Fossa: 5 Supraglottis: 3 **CUPS: 4 (12%)**		
Stage	IV A: 17 (51%)	IV B: 16 (49%)	
Co morbidities	DM : 3		
Radiotherapy Technique	2D: 13 (39.4%)	3DCRT: 19 (57.6%)	IMRT: 1 (3%)

**WD SCC - Well differentiated squamous cell carcinoma*
MDSCC- Moderately differentiated squamous cell carcinoma
PDSCC - Poorly differentiated squamous cell carcinoma

Table 2. Subsite wise response of patients with induction chemotherapy

Primary site (100%)	Subsite	.> 30% Response	<30% Response
Oral cavity (14) (42.4%)	Anterior Tongue	3	3
	Buccal Mucosa	3	2
	Hard Palate	1	1
	Retromolar Trigone	0	1
Oropharynx(7) (21%)	Base of Tongue	3	1
	Ca Tonsil	2	1
Laryngo hypopharynx (8) (24%)	Larynx	2	1
	Pyriform fossa	4	1
CUPS(4)		2	2

3.1 Toxicity

At the end of treatment 12(36%) patients had grade 2 mucositis, 4(12%) patients had grade 3 (9%) mucositis and 2(6%) patients developed grade 2 haematological toxicities in radical treatment group. No toxicity related mortality was seen.

In Arm A, Thirteen patients underwent palliative radiotherapy. Median PFS (Progression Free Survival) in palliative group was 5 months (95% CI 2.6-9.4 months).

In Arm B, twenty patients were treated by definitive treatment after IC. Table 3 depicts status of those patients who were treated with radical intent.

Table 3. Status of radical treated patients

Arm B (n=20) (100%)		
Alive without disease	11 (55%)	
Alive with disease	Local Recurrence	3 (15%)
	Nodal Failure	2 (10%)
	Distant Mets	1 (5%)
Loss in follow up		2 (10%)
Death	1 (5%)	

The median OS was 18 months (95% CI 9.00 to 31.00) (Fig. 2). There was a significant (p=.001) difference in survival in both arms (Fig. 3). Table 4 shows that 16(48%) patients were alive, 12 (36%) patients expired and 5 patients were lost to follow up.

4. DISCUSSION

Locally advanced head and neck squamous cell cancer patients with ECOG performance status of 2 or less, who are unresectable and considered unsuitable for any radical treatment upfront are often treated with palliative radiation alone [8-10]. Such an approach has been reported previously from India and is associated with unsatisfactory survival outcomes.

As the sample size was small, univariate or multivariate analysis was not possible in the above study.

Table 4. Overall status of the study subjects at the time of analysis

Status	Number of patients (N=33)	Percent
Alive without disease	11	33.3
Alive with disease	5	15.2
Death	12	36.4
LOF	5	15.2
Total	33	100.0

Table 5. Table comparing PFS and OS of different palliative RT schedules with present series

Author_Number	PFS	OS
Mohanti [8]	NR	200/400 days*
Ghoshal [9]	3 months	NR
Das [10]	NR	7 months
Corry [23]	3.1 months	5.7 months
Porceddu [24]	3.9 months	6.1 months
Present series	5 months	18 months

**Overall OS not reported. Patients given 20 Gy/5# had 200 days at OS, responding patients treated with more 20Gy/5# had 400 days as OS*

Mohanti et al. [8] reported that 578 patients were treated with a uniform palliative schedule of 20 Gy/5# over 5 days. The median survival was only 200 days. Though all sub-sites in head and neck cancers were included in the study, oropharyngeal cancers were predominant (233 patients, 46%).

Ghosal et al. [9,10], reported the results of QUAD shot therapy from another centre in north India. Fifteen patients were treated with QUAD shot and had good symptom relief but with a median PFS of just 12 weeks.

Agarwal et al. [11] published results of 110 patients treated with an alternative schedule of 40Gy in 16# over 3.1 weeks. Similar to the previous report, the most common subsite was oropharynx (41%). 50% of patients had a KPS (Karnofsky performance status) equal to or above 70 and non T4 disease was present in 22% of patient. In this report, the median local progression free survival was around 1 year. The PFS (including local and distant progression) and OS were not reported. These series from major centres in India shows that palliative radiation is often used for symptom relief when tumours are not considered curative. Interestingly, despite the majority of the tumours belonging to favourable subsites like the oropharynx, good performance status and stage IV A disease, palliative RT was preferred over radical treatment. Though no valid reasons are mentioned by the authors as such, it can be predicted that extensive disease and limited resources may have swayed the decision to use palliative treatment.

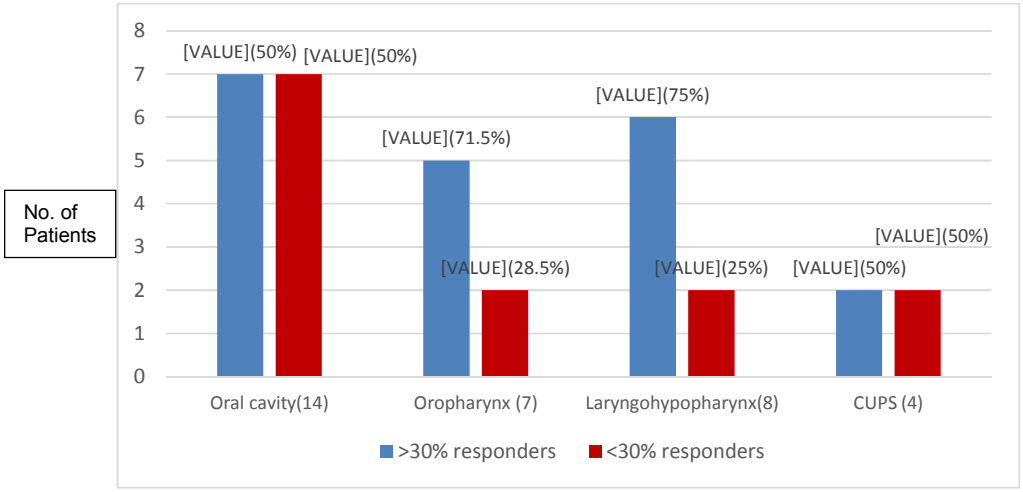

Fig. 1. Primary site- wise response rate of induction chemotherapy

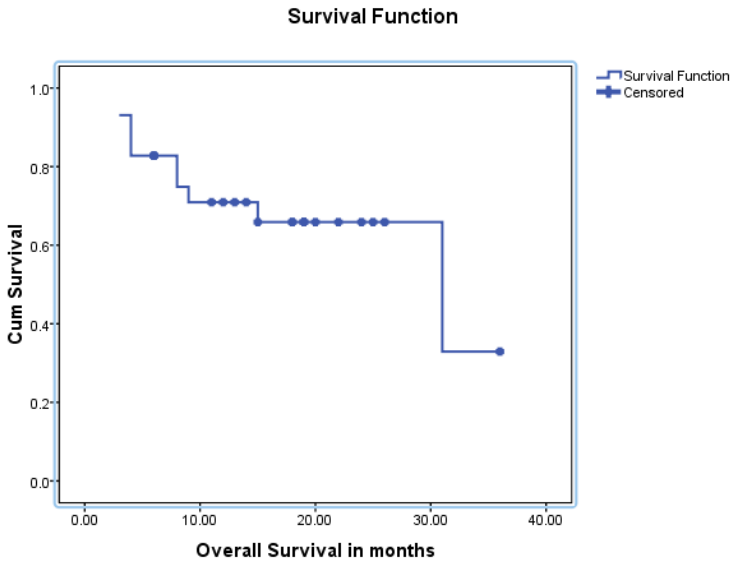

Fig. 2. Kaplan Meier estimate overall survival in all patients

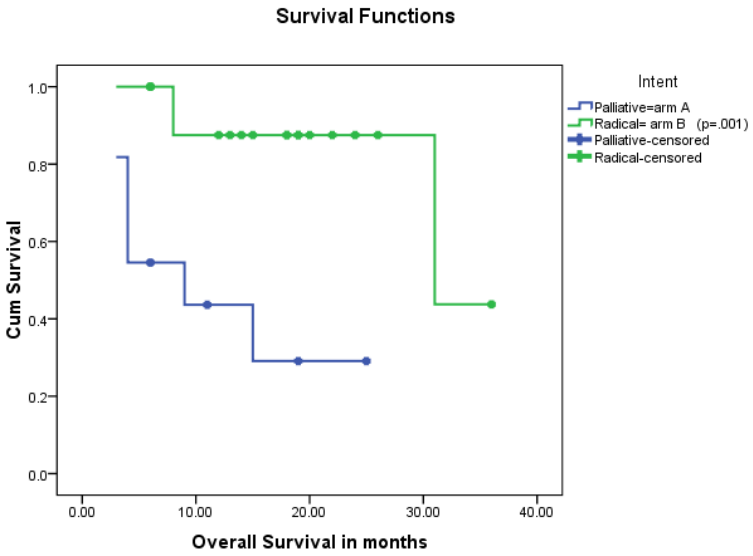

Fig. 3. Kaplan Meier estimate of overall survival in both arms

All the patients had stage IV disease. However, only 30% had stage IVB while 43.16% had non T4 disease (T1-T3). The early results of this phase II trial are favourable with respect to disease control, but also demonstrate encouraging long-term functional outcomes [11,12].

IC is used with the goal of reduction of tumour volume prior to definitive treatment. Other biological advantages include a potential efficacy against systemic micrometastasis. However, prolongation of the overall treatment time is a point against the widespread acceptance of IC as a routine standard of care. Even though survival benefit has not been noted, several studies have demonstrated a benefit in terms of tumour volume reduction and as well as in the reduction of distant metastasis [12,13].

While initial studies were mostly conducted with the use of doublet-IC, recent studies have shown more favourable outcomes with the use of triplet regimens, by the addition of taxol to the usual cisplatin and 5-fluorouracil [14,15].

Oropharyngeal tumors are frequently associated with HPV and such tumours normally have a favourable prognosis [16,17]. Response rates with IC are reportedly as high as 80%, with about half of the responding patients demonstrating complete responses [12,13].

This exploratory study demonstrates the effectiveness and tolerability of induction chemotherapy using TP for LA HNSCC compare to TPF. The response rate of 60% is comparable to the 68-80% response rate observed with TPF in randomized trials and in routine practice [5,6,15]. Interestingly, TP was tolerable (since we did not observe any death due to toxicity); but TAX 323 has reported 83% patients had grade 3 and 4 febrile neutropenia [6].

The prognosis of the nonresponding population was poor. It is due to the rationale that non response to IC often is an indicator of subsequent radioresistance. Reasons include potentially enhanced repair mechanisms against cytotoxic insults such as radiation and chemotherapy. Another reason could be possibly because of a high proportion of dormant cells in the tumour, which could compromise radiosensitivity and chemosensitivity, since cytotoxicity is maximum upon actively dividing cells [12,13,18,19].

We considered the response to induction chemotherapy to be an important prognostic factor which may determine the sequence and timing of further planned definitive therapy: patients with lesser response were treated with palliative treatment. Therefore, on the basis of the evaluation made after induction chemotherapy, we adopted a flexible protocol, based not only on the patient's compliance and general conditions, but mainly on their response to neoadjuvant chemotherapy. A similar but less customized multimodality treatment was followed by Kovacs et al. [20] in a

large series of oral and oropharyngeal cancer patients.

Patil et al. [21] reported 83.3% response rate of TPF regime in 12 patients of inoperable and technically unresectable oral cavity tumors, which had higher response rate as compared to our TP regime. Simultaneously, TPF causes more toxicity, in-patient admissions and supportive care. Administration of such regimens therefore requires greater financial and logistical support. There is little data on the use of TPF in such resource limited settings.

Our results do show some noteworthy features. Despite nearly all the patients having a performance of 2 or less, the tolerance to induction chemotherapy was acceptable. All patients completed the scheduled induction chemotherapy though there was no serious toxicity and no toxicity related death in our study. We believe that improved tolerance and response to chemotherapy could reflect improved nutrition. The response rate of 60.7% noted in our study compares favourably with other published literature. The response rate is especially surprising considering the large proportion of oral cavity tumours and adverse prognostic factors.

In a study conducted by Patil et al. [22] fifteen HNSCC patients with ECOG≥2 underwent weekly induction chemotherapy. The response rate was 66.7%, which was quite similar to our study (60.60%). They have shown resectability of around 47% similarly in our study, the conversion rate to resectability was around 50%. The impact of multimodality treatment was seen in OS with 2 year survival being 34% and the median OS being 16.53 months, which is comparable to our study.

We have reported the conversion rate to resectability was around 50% and similar number of patients received radical intent treatment post-induction therapy. The impact of multimodality treatment was seen in median OS being 18 months. These results are better than the previously reported series [23,24] with palliative radiation as shown in Table 5.

Another similar study by Viana et al. [25] showed that TP regimen proved to be safe and tolerable with low toxicity during the induction phase, permitting CRT based on cisplatin in the majority of patients included. Overall response rate after induction chemotherapy with TP regimen was 82.5% for patients with resectable disease and 55.5% for unresectable disease, which is comparable to our study, which showed 60% response rate in inoperable locally advanced head and neck cancer.

5. LIMITATIONS

Our study has a few limitations. The study was based on a retrospective analysis, and only 33 patients met the inclusion criteria. The primary tumor sites were also heterogeneous and data regarding the human papilloma virus (HPV) status of the patients was not available. The HPV status could have influenced the outcome following non-surgical treatment.

6. CONCLUSION

Our present experience suggests that induction chemotherapy with doublet regime is reasonably well tolerated and is feasible in a limited resource setting in those patients who are not fit for upfront radical treatment. Rather than treating such patients with palliative intent with poor outcome, our approach resulted in radical treatment in 60% of patients.

CONSENT

Written informed consent was taken from all the patients undergoing treatment.

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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