Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial

A. Sharma1*, B. K. Mohanti 2, A. Thakar3, S. Bahadur3 & S. Bhasker2

Departments of 1Medical Oncology, 2Radiation Oncology and 3Otorhinolaryngology and Head and Neck Surgery, Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

Background: To know the effectiveness and tolerance of weekly cisplatin added to radiotherapy (RT) in advanced carcinoma of oropharynx and nasopharynx.

Patients and methods: Stage II–IV cancer patients were randomly assigned to either radical RT, 70 Gy/35 fractions over 7 weeks (RT arm), or chemoradiotherapy (CRT), cisplatin 40 mg/m² weekly for seven doses plus RT. Primary end points were (i) the responses, (ii) toxicity profile, and (iii) overall survival (OS) in two groups. Study period was from June 2003 to July 2005.

Results: One hundred and fifty-three patients were randomly allocated to the study, 76 in RT arm and 77 in CRT arm. Seventy-one in each arm completed the planned treatment; complete response (CR): 67.1% versus 80.5% in RT and CRT arms (P = 0.04). Grade III and IV toxicity were 16% and 40% in RT and CRT arms, respectively (P = 0.01). There were frequent treatment interruptions (9.3% versus 28.9%; P = 0.003) and hospitalization (20% versus 40.8%) in the CRT group. OS was superior in the CRT arm (P = 0.02); 27 months [95% confidence interval (CI) 15.2–36.8] for RT versus not reached for CRT. Three-year OS was 42% for RT and 62% for CRT group. CRT and CR were independent prognostic factors.

Conclusion: This trial on Indian head and neck squamous cell carcinoma patients confirms that the use of weekly cisplatin is safe and CRT is superior to RT alone resulting in higher OS.

Key words: chemoradiotherapy, India, nasopharynx, oropharynx

introduction

The head and neck cancers constitute 5% of all cancers worldwide and 15% of all cancers in developing countries [1]. Head and neck squamous cell carcinoma (HNSCC) is one of the commonest cancers in India. Of the 600 000 new head and neck cancer cases diagnosed each year, ~25% are from India [1, 2]. Treatment of early-stage tumors involves surgery, radiotherapy (RT) or occasionally a combination of two [3]. However, advanced stage requires multimodality treatment, which may be surgery with postoperative RT or chemoradiotherapy (CRT). Currently, the preferred schedule is supposed to be concurrent CRT since disease control is achieved with anatomic and physiologic function preservation. Although HNSCC is sensitive to several anticancer drugs, the unresolved issues are whether to use single agent or combination of two or more drugs and whether to deliver chemotherapy in weekly, daily or 3-weekly schedules [4]. A number of trials including meta-analyses were available in the literature giving conflicting results whether addition of chemotherapy definitely leads to improvement in survival at the time this trial was designed in 2003. Also, majority of the trials have taken head and neck cancer as one cancer by clubbing all subsites; however, we know that outcome and response of different subsites are not the same. It is known that concomitant treatment is more toxic than single modality. In the meta-analysis reported in 2000, comparison of local treatment with or without chemotherapy yielded an absolute benefit of 4% in overall survival (OS) at 2 and 5 years in favor of chemotherapy; however, there was much heterogeneity between timings of chemotherapy. When analyzing the data for concomitant CRT, survival benefit was 8% at 5 years. The authors concluded by saying that ‘heterogeneity of data in concomitant setting makes a conclusion difficult’ [3]. An update of this analysis focusing on chemoradiotherapy (with additional 24 trials) reiterated a 4.5% absolute benefit (OS) for
cisplatin 100 mg/m² on days 1, 22, and 43 is considered schedule [11, 12]. Concurrent chemoradiotherapy using
OS 51% versus 31%). In another study, only recurrence-free
disease-free survival (DFS), and locoregional control (3-year
arm in advanced oropharyngeal cancer with regard to OS,
concomitant chemoradiotherapy arm is superior to RT-alone
oropharyngeal cancer only. Calais et al. [9] reported that
randomized trials evaluating CRT versus RT limited to
advanced oropharyngeal cancer to be part of the study, patients were required to have large T2
cancer showed an absolute survival benefit of 6% at 5 years [8].

Compared with cancers of larynx and hypopharynx,
opharyngeal cancer is more common in developing countries
and less amenable to surgery; hence, therapeutic improvement
of available modalities is desirable. There are limited
randomized trials evaluating CRT versus RT limited to
opharyngeal cancer only. Calais et al. [9] reported that
concomitant chemoradiotherapy arm is superior to RT-alone
arm in advanced oropharyngeal cancer with regard to OS,
disease-free survival (DFS), and locoregional control (3-year
OS 51% versus 31%). In another study, only recurrence-free
survival was superior in the concomitant arm [10].

Investigators have used daily- or weekly-based chemotherapy
schedule [11, 12]. Concurrent chemoradiotherapy using
cisplatin 100 mg/m² on days 1, 22, and 43 is considered
standard for locally advanced HNSCC. Whether weekly dose
of 40 mg/m² of cisplatin will be equally effective is to be seen in
prospective setting.

Unfortunately, from India where HNSCC is a common
cancer, there are insufficient data about the feasibility of CRT
practice and its superiority over RT alone. Kumar et al. [13] in
2005 reported phase II data on 95 patients, with a median OS of
12 months and a very high mortality rate of 14% during or
within 30 days of therapy.

At the time of designing this study, we decided to test the
feasibility of CRT in oropharynx and nasopharynx cancer in
a prospective randomized manner. Our study objectives were
based upon the context of significant head and neck cancer
burden in any Indian cancer center, to utilize single-agent
chemotherapy on weekly basis with irradiation, which can be
easily practiced. The subsites selected are the ones where
efficacy of CRT has been established and surgery is usually not
preferred.

patients and methods
study design
A prospective phase II randomized single-center study was conducted at the
Dr BR Ambedkar Institute Rotary Cancer Hospital of All India Institute of
Medical Sciences, New Delhi. Local ethics committee approved the protocol
and the study.

patient population
Patients were eligible for study if they had a confirmed diagnosis of
squamous cell carcinoma of oropharynx or nasopharynx, stage II–IV
(American Joint Committee on Cancer 5th edition, 1997). For stage II
cancer to be part of the study, patients were required to have large T2
lesions. Computed tomography (CT) scan or magnetic resonance imaging
was done when disease extent could not be assessed clinically. Patients
attending head and neck cancer clinic at our center were examined by
a team comprising head and neck surgeons and radiation and medical
oncologists. Those who were otherwise eligible to be taken up for radical RT
were explained about this study. From June 2003 to July 2005, 190 patients
were screened and counseled for the study; of which, 153 randomized
patients received therapy and were analyzed (Figure 1). At the time this
study was planned, cetuximab was not in clinical practice for HNSCC and
hence, control arm chosen was RT alone. Patients were randomly assigned
to one of the treatment arms through computer-generated lots.
Stratification as per primary site was not done. Inclusion criteria also
included Karnofsky performance status (KPS) > 70 and normal
hematological, renal, and liver functions.

treatment
RT arm—radical RT dose of 70 Gy in 35 fractions over 7 weeks (at five
fractions per week; standard fractionation) by using cobalt 60 or linear
accelerator, as per current practice. All patients were treated with parallel-
offered lateral fields and spinal cord was shielded at 44 Gy. Whenever
necessary, CT scan-based three-dimensional conformal RT was utilized in
order to limit dose to surrounding organs such as eye, brain, and
spinal cord. CRT arm—concurrent chemoradiation injection cisplatin
(DDP) 40 mg/m² weekly for seven doses (i.e. days 1, 8, 15, 22, 29, 36, and
43) beginning day 1 of radiation treatment and radical RT 70 Gy in 35
fractions over 7 weeks as in the RT arm. DDP infusion was given along with
antiemetic in saline as per standard practice. Treatment interruptions were
allowed for grade IV neutropenia or thrombocytopenia till recovery or any
other significant toxicity where physicians felt that continuation of
treatment may be detrimental. Patients who developed significant mucositis
resulting in decreased oral intake were given i.v. alimentations along with
Ryle’s tube feeding. Patients were hospitalized for any clinically significant

Figure 1. Consolidated Standards of Reporting Trials diagram. HNSCC,
head and neck squamous cell carcinoma; OPX, oropharynx; NPX,
nasopharynx; RT, radiotherapy.
treatment compliance

Treatment outcome and toxicity are shown in Table 2. Majority of patients were able to complete the planned treatment. Seventy-one patients (93.3%) in the RT group and 71 (92.2%) in the CRT group completed treatment with or without delay. However, there were more frequent treatment interruptions (22; 28.9%) in the CRT arm compared with that (7; 9.3%) in the RT arm. These were statistically significant ($P = 0.003$).


toxicity

Patients who had grade IV myelotoxicity or grade III or IV mucosal toxicity with impaired nutritional intake were admitted for nutritional support. Twelve (16%) patients in the RT-alone arm and 31 (40%) patients in the CRT arm required hospitalization for management of mucosal toxicity and parenteral nutrition ($P = 0.002$). The commonest toxicity seen were mucositis and vomiting. The grade III and IV acute toxicity was documented in 14 (20%) and 30 (40%) patients in the RT versus the CRT arm, respectively ($P = 0.015$). All these were reversible. No patient discontinued treatment because of therapy and there was no toxic death reported during this study and analysis period.


two treatment groups.

Primary:

1. To know if addition of concurrent chemotherapy increases the responses in these patients as compared with RT alone.
2. To know the toxicity profile in the two treatment groups.
3. To know the 3-year OS analysis in the two treatment groups.

Secondary:

Progression-free survival (PFS).

Tumor responses were evaluated as per clinical examination between 4 and 6 weeks of completion of therapy. Adverse reactions were graded as per National Cancer Institute—Common Toxicity Criteria version2.0 (https://webapps.ctep.nci.nih.gov/webobis/ctc/webhelp/Common_Toxicity_Criteria_CTC_v2.htm).

statistical methods

Exact test for contingency tables, Kaplan–Meier estimates for survival, and log-rank tests were used to test for difference in response rates, toxic effects, and survival. We expected a 3-year OS of 60% in the CRT arm and 40% in the RT-alone arm. $P$ values $< 0.05$ were taken as significant. Statistical analysis was done using SPSS 10.0 program.

results

Patients’ baseline characteristics including demographic profiles, stages, etc. are given in Table 1. Both groups were well balanced with regard to age, sex, and clinical stage. However, there was significantly more number of nasopharyngeal cancers in the CRT arm. All efficacy analyses were done on an intent-to-treat basis. More than 90% of the patients had stage III or IV cancer at the time of presentation. Node-positive disease was seen in 72.4% and 77.9%, respectively, in the RT and the CRT group.

Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RT, n (%)</th>
<th>CRT, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>76 (100)</td>
<td>77 (100)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>66</td>
<td>71</td>
<td>0.30</td>
</tr>
<tr>
<td>Age</td>
<td>54 (24–70)</td>
<td>50 (14–70)</td>
<td>NS</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>6 (8)</td>
<td>29 (37.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70 (92)</td>
<td>48 (63.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>T1–2</td>
<td>32 (42.1)</td>
<td>26 (33.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>T3</td>
<td>30 (51.3)</td>
<td>35 (45.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>T4</td>
<td>15 (19.5)</td>
<td>15 (19.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>N0</td>
<td>21 (27.6)</td>
<td>17 (22.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Node positive</td>
<td>55 (72.4)</td>
<td>60 (77.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Stage II</td>
<td>7 (9.2)</td>
<td>3 (3.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Stage III</td>
<td>24 (36.8)</td>
<td>29 (37.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Stage IV</td>
<td>41 (54)</td>
<td>43 (55.9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

RT, radiotherapy; CRT, chemoradiotherapy; NS, not significant.

Table 2. Treatment outcomes and toxicity

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RT, n (%)</th>
<th>CRT, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>76 (100)</td>
<td>77 (100)</td>
<td></td>
</tr>
<tr>
<td>Treatment completed</td>
<td>71 (93.3)</td>
<td>71 (92.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Interruptions</td>
<td>7 (9.3)</td>
<td>22 (28.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>12 (16)</td>
<td>31 (40)</td>
<td>0.002</td>
</tr>
<tr>
<td>CR</td>
<td>51 (67.1)</td>
<td>62 (80.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Toxicity grade III/IV</td>
<td>14 (20)</td>
<td>30 (40)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole group</td>
<td>27</td>
<td>NR</td>
<td>0.02</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>NR</td>
<td>NR</td>
<td>0.20</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>27</td>
<td>NR</td>
<td>0.01</td>
</tr>
<tr>
<td>3-year OS (%)</td>
<td>42</td>
<td>62</td>
<td>0.3</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>22</td>
<td>24</td>
<td>0.3</td>
</tr>
<tr>
<td>3-year PFS (%)</td>
<td>42</td>
<td>37</td>
<td>0.88</td>
</tr>
<tr>
<td>LR progression</td>
<td>36</td>
<td>26</td>
<td>0.26</td>
</tr>
<tr>
<td>Distant failures</td>
<td>2</td>
<td>8</td>
<td>0.05</td>
</tr>
</tbody>
</table>

RT, radiotherapy; CRT, chemoradiotherapy; CR, complete response; OS, overall survival; NR, not reached; PFS, progression-free survival; LR, locoregional.
survival
Median follow-up of surviving patients was 22 months. OS was significantly higher in the CRT arm \( (P = 0.024) \): 27 months [95% confidence interval (CI) 15.2–36.8] for the RT group versus not reached for the CRT group. Three-year OS for the two groups was 42% (RT) versus 62% (CRT), as shown in Figure 2, giving an absolute survival advantage of 20% for the CRT arm. However, statistically significant difference in PFS between the two groups was not observed. Median PFS for RT arm was 22 months compared with 24 months in CRT arm \( (P = 0.3) \). OS for the two arms is shown in Figure 2. PFS for the two arms is shown in Figure 3.

To know the various prognostic factors for survival, univariate and multivariate analyses using Cox regression method were done (Table 3). Among the various factors, treatment arm (CRT versus RT) with \( P \) value of 0.045, achievement of clinical CR versus no CR with \( P \) value of 0.000, and no disease progression versus progression with \( P \) value of 0.000 were found significant to improve OS. In multivariate analysis also, all these factors were found significant with \( P \) values of 0.049, 0.000, and 0.002 for treatment arm, CR, and no progression, respectively. For PFS also, achievement of CR came out as an independent prognostic factor in multivariate analysis \( (P = 0.000) \).

Figure 2. Overall survival in two groups.

Figure 3. Progression-free survival for two groups.
Multivariate paclitaxel and concurrent RT, 2-year survival rate was 83% in the phase II trial with the aim of organ preservation in locally advanced HNSCC involving various subsites. Patients were given CRT using 35 mg/m² of cisplatin. Compliance for RT and chemotherapy was, respectively, 66% and 73% only. Grade III/IV mucosal toxicity was seen in 79% of patients. Median OS reported was 12 months with the probability of 3-year survival being 27%. They reported a very high mortality rate of 14% during or within 30 days of therapy. Poor nutrition and dehydration were contributory factors for mortality in at least three of them. Compared with this study, our data reported grade III or IV toxicity in 40% of patients and no therapy-related death reiterating that good supportive care can help in checking morbidity and mortality. Also, >90% of patients were able to complete treatment albeit with interruptions in 28% in the CRT arm.

In the landmark Intergroup 0099 trial, 147 stage III–IV nasopharyngeal cancer patients were randomly assigned to RT alone or RT with concurrent cisplatin, followed by adjuvant cisplatin and 5-FU. RT was delivered by two-dimensional planning technique. In this trial, 63% patients could complete planned chemoradiation and only 55% could complete adjuvant chemotherapy. Five-year OS was 67% versus 37% (P = 0.001) and PFS was 58% versus 29% (P < 0.001), both favoring the CRT arm [6, 16]. Wee et al. [17] reported results from a trial which was similar in design to Intergroup 0099. In this study, 2-year distant metastases were 13% versus 30% (0.0029) in the CRT versus the RT-alone arm. One of the initial trials using weekly DDP in nasopharyngeal cancer was reported by Chan et al. [18] from Hong Kong. In this trial, 5-year OS was 70.3% versus 58.6% (P = 0.049) for the CRT and the RT arm, respectively.

Three-year OS and toxicity reported here are comparable with or better than other published literature [9, 10]. Grade III and IV toxic effects in the CRT arms were >70% in the studies by Calais et al. [9] and Briezel et al. [10] and ~50% in the study by Chan et al. [18]. In the present report, we did not use adjuvant chemotherapy for nasopharyngeal cancer. We are not sure if the adjuvant chemotherapy could have improved the outcome further. The difference in PFS between the two groups in this trial was not statistically significant. Median PFS was 22 months for the RT-alone group compared with 24 months for the CRT group (P = 0.3). One possible explanation and flaw in the study may be that since there were more patients with nasopharyngeal primary in the CRT group who as expected developed distant metastases and the benefit of CRT was offset by increased number of distant failures. There were eight patients in the CRT arm who developed distant metastases compared with three in the RT group; six of the distant failures in the CRT arm had nasopharynx as the primary site.

Table 3. Univariate and multivariate analyses of prognostic factors for OS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment arm</td>
<td>1.74</td>
<td>0.98–3.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (&lt;50 or ≥50 years)</td>
<td>1.49</td>
<td>0.85–2.62</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>1.01</td>
<td>0.43–2.39</td>
<td>0.96</td>
</tr>
<tr>
<td>Primary site (nasopharynx/oropharynx)</td>
<td>0.58</td>
<td>0.27–1.24</td>
<td>0.16</td>
</tr>
<tr>
<td>Stage (cIV or V)</td>
<td>0.81</td>
<td>0.46–1.42</td>
<td>0.47</td>
</tr>
<tr>
<td>Completed or incomplete</td>
<td>1.39</td>
<td>0.63–4.02</td>
<td>0.32</td>
</tr>
<tr>
<td>CR or no CR</td>
<td>5.33</td>
<td>3.04–9.35</td>
<td>0.000</td>
</tr>
<tr>
<td>Admission or no admission</td>
<td>1.51</td>
<td>0.85–2.67</td>
<td>0.15</td>
</tr>
<tr>
<td>Interruption</td>
<td>1.41</td>
<td>0.73–2.70</td>
<td>0.29</td>
</tr>
<tr>
<td>Progression or no progression</td>
<td>3.27</td>
<td>1.74–6.01</td>
<td>0.000</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment arm</td>
<td>1.69</td>
<td>0.88–2.81</td>
<td>0.04</td>
</tr>
<tr>
<td>CR or no CR</td>
<td>4.58</td>
<td>2.57–8.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Progression or no progression</td>
<td>2.66</td>
<td>1.42–4.99</td>
<td>0.002</td>
</tr>
</tbody>
</table>

OS, overall survival; HR, hazard ratio; CI, confidence interval; CR, complete response.

discussion

HNSCC is one of the common cancers in India and one of four head and neck cancer patients in the world is from this country. With this trial, we have tried to address the issue of feasibility and utility of concomitant chemoradiation in oropharyngeal and nasopharyngeal cancer patients. Also, we tried to prospectively analyze the use of 40 mg/m² of weekly cisplatin as a single-drug schedule. There are only few trials evaluating CRT versus RT for oropharyngeal cancer only. Two of these trials have used platinum compounds with 5-fluorouracil (5-FU). Calais et al. [9] reported that concomitant chemoradiotherapy arm is superior to RT-alone arm in advanced oropharyngeal cancer with regard to OS, DFS, and locoregional control (3-year OS 51% versus 31%). However, in this trial, DDP and continuous infusion of 5-FU were used. In another study, even though recurrence-free survival was superior in the concomitant arm, OS was not different [10]. In the French trial (GORTEC 94-01), 226 stage III or IV oropharyngeal cancer patients were randomly assigned to RT alone or RT with 5-FU and carboplatin. Five-year OS (22.4 versus 15.8; P = 0.05) and DFS (26.6 versus 14.6%; P = 0.001) favored chemoradiotherapy arm [14]. Cmelak et al. in a phase II trial with the aim of organ preservation in locally advanced laryngeal and oropharyngeal cancer reported that with paclitaxel and concurrent RT, 2-year survival rate was 83% in the subset of oropharyngeal primary; >90% of patients could complete full-dose RT and at least 5 weeks of paclitaxel. Two-year organ preservation rate was 81%. In this trial, induction chemotherapy was also used [15].

Weekly cisplatin is being explored as an alternative to high-dose 3-weekly cisplatin in concurrent setting. One phase II study has been reported from India. Kumar et al. [13] reported phase II data consisting of 95 patients with advanced HNSCC involving various subsites. Patients were given CRT using 35 mg/m² of cisplatin. Compliance for RT and chemotherapy was, respectively, 66% and 73% only. Grade III/IV mucosal toxicity was seen in 79% of patients. Median OS reported was 12 months with the probability of 3-year survival being 27%. They reported a very high mortality rate of 14% during or within 30 days of therapy. Poor nutrition and dehydration were contributory factors for mortality in at least three of them. Compared with this study, our data reported grade III or IV toxicity in 40% of patients and no therapy-related death reiterating that good supportive care can help in checking morbidity and mortality. Also, >90% of patients were able to complete treatment albeit with interruptions in 28% in the CRT arm.

In the landmark Intergroup 0099 trial, 147 stage III–IV nasopharyngeal cancer patients were randomly assigned to RT alone or RT with concurrent cisplatin, followed by adjuvant cisplatin and 5-FU. RT was delivered by two-dimensional planning technique. In this trial, 63% patients could complete planned chemoradiation and only 55% could complete adjuvant chemotherapy. Five-year OS was 67% versus 37% (P = 0.001) and PFS was 58% versus 29% (P < 0.001), both favoring the CRT arm [6, 16]. Wee et al. [17] reported results from a trial which was similar in design to Intergroup 0099. In this study, 2-year distant metastases were 13% versus 30% (0.0029) in the CRT versus the RT-alone arm. One of the initial trials using weekly DDP in nasopharyngeal cancer was reported by Chan et al. [18] from Hong Kong. In this trial, 5-year OS was 70.3% versus 58.6% (P = 0.049) for the CRT and the RT arm, respectively.

Three-year OS and toxicity reported here are comparable with or better than other published literature [9, 10]. Grade III and IV toxic effects in the CRT arms were >70% in the studies by Calais et al. [9] and Briezel et al. [10] and ~50% in the study by Chan et al. [18]. In the present report, we did not use adjuvant chemotherapy for nasopharyngeal cancer. We are not sure if the adjuvant chemotherapy could have improved the outcome further. The difference in PFS between the two groups in this trial was not statistically significant. Median PFS was 22 months for the RT-alone group compared with 24 months for the CRT group (P = 0.3). One possible explanation and flaw in the study may be that since there were more patients with nasopharyngeal primary in the CRT group who as expected developed distant metastases and the benefit of CRT was offset by increased number of distant failures. There were eight patients in the CRT arm who developed distant metastases compared with three in the RT group; six of the distant failures in the CRT arm had nasopharynx as the primary site.

conclusions

This Indian trial confirms that chemoradiotherapy using single-agent weekly DDP is safe and superior to RT in advanced oropharyngeal and nasopharyngeal cancers even in developing countries and can replace 3-weekly high-dose DDP. However, there is requirement of good supportive care and interdepartmental coordination at the treating center. Treatment interruptions and toxic effects are expected and may be of concern, when adequate adherence to chemoradiation schedule is intended. The high compliance rate achieved in this study makes this approach well suited for nonsurgical-site tumors of the head and neck region.
funding
All India Institute of Medical Sciences.

references