Article published online: 2020-12-28



# Long term results of comparison of concurrent low-dose daily cisplatin versus the standard weekly cisplatin with six fractions per week radiotherapy in locally advanced head neck cancer

**Pramod Kumar Gupta, Punita Lal, Ranjeet Bajpai, Anshu Goel, Rajan Yadav, Mranalini Verma, Shaleen Kumar**


## Abstract

**Aim and Objective:** Weekly administration of cisplatin (cis-diamminedichloroplatinum [CDDP]) appears more feasible and substantially more popular than the 3 weekly schedules due to better compliance. Different concurrent cisplatin schedules have been attempted including a daily schedule. We did a comparison of two consecutive single arm studies, i.e., use of weekly cisplatin versus daily cisplatin when used with concurrently with a moderately accelerated radiotherapy (RT) schedule. **Patients and Methods:** Two prospective feasibility, safety and efficacy studies were carried out consecutively within the department. The weekly CDDP study was done from August 2003 to August 2005 and daily CDDP study was conducted from November 2005 to June 2007. Both studies included locally advanced stage III and IV squamous cell carcinoma of the head and neck region with RT dose of 70 Gy. Concurrent single-agent cisplatin was administered weekly (35 mg/m$^2$) in the first and daily (6 mg/m$^2$) in the second study. **Results:** Weekly cisplatin study had 68 and daily CDDP study had 52 patients. The median follow-up in the two studies was 93 and 63 months, respectively. Compliance in the two studies was comparable. Acute Grade III/IV mucositis and dysphagia were significantly higher in weekly cisplatin study. Late Grade II/III toxicities such as xerostomia, dysphagia, ototoxicity and nephrotoxicity were similar. The 5 years locoregional control was 18% and 25% and 5 years overall survival rate was 32% and 31% in weekly and daily cisplatin studies, respectively. **Conclusions:** Modest acceleration along with either "weekly" or "daily" cisplatin, whichever is possible in one's setup, is do-able, provided due attention is paid to patient selection and supportive care.


**Key words**: Chemotherapy, low dose cisplatin, radiotherapy, weekly cisplatin

## Introduction

Concurrent chemoradiotherapy (CRT) is the standard of care in head and neck cancers (HNCs) after the publication of various meta-analyses.[1-5] Meta-analysis of chemotherapy in HNC reported 8% survival benefit with the addition of concurrent chemotherapy.[3-5] Cisplatin has been the most extensively studied agent (with nonoverlapping toxicity). Various dose schedules have been studied so far, such as 100 mg/m$^2$ at 3 weekly intervals, 35–40 mg/m$^2$ at weekly interval, and 6 mg/m$^2$ daily.[5-12] Although the evidence has been obtained from the 3 weekly cisplatin studies, but across the world, weekly use of cisplatin has become routine clinical practice.[6-8] Optimal timing and dose scheduling still need to be defined. The present report is a comparison of two consecutive prospective safety and efficacy, single arm studies conducted in our department, i.e. use of concurrent cisplatin either as a weekly or a daily schedule. Both chemotherapy schedules were used along with a moderately accelerated radiotherapy (RT) schedule.

## Patients and Methods

Two prospective feasibility, safety and efficacy single arm studies were carried out consecutively within the department following Institutional Review Board clearance. The weekly study was carried out from August 2003 to August 2005 and daily cis-diamminedichloroplatinum (CDDP) study was conducted from November 2005 to June 2007 and this retrospective comparison was not a part of the original study design.

The patient profile was same with the following inclusion criteria-untreated squamous cell carcinoma of the head and neck region, i.e., oral cavity, oropharynx, hypopharynx, or larynx in stage III and IV HNC (T2N2-3M0, T3-T4 any N M0), patients with Karnofsky performance status ≥70, age above 18 years. All the patients had normal liver and kidney function test and glomerular filtration rate (GFR). Patients having a second primary neoplasm, recurrent disease, distant metastasis, carcinoma of the nasopharynx and paranasal sinuses, prior radiation or chemotherapy, and pregnant woman were excluded.

### Treatment protocol

Following build up and dental prophylaxis, patients were planned for a moderately accelerated RT schedule delivering 70 Gy in 35 fractions over 6 weeks (instead of 7 weeks) at 2 Gy per fraction, in both the studies. The RT was delivered in a phased manner using conventional three field technique. Three-dimensional conformation or intensity modulated RT (IMRT) was not practiced in the department at that time. CDDP (35 mg/m$^2$) weekly (maximum 50 mg) along with 3 L of fluids and mannitol was given. In a daily group, CDDP was given at 6 mg/m$^2$ (capped at 10 mg) in 500 ml normal saline (NS) solution for all 6 weeks of treatment.

### Radiotherapy technique

In both the studies, patients were simulated with a thermoplastic head and neck immobilization device. Phase I was planned to include the primary and the draining lymph node regions and a dose of 44 Gy/22 fractions/4.5 weeks was delivered 5 days in a week at 2 Gy/fraction (Monday to Friday). In phase II-off-cord reduction was done, and a dose of 16 Gy/8 fractions/1.5 weeks at 2 Gy/fraction was delivered 5 days in a week (Monday to Friday). Phase III was delivered as a boost on Saturday, as limited volume portal including original GTV with a margin of 2 cm. A dose of 10 Gy/five fractions/over five Saturdays at 2 Gy/fraction was delivered. Scheduled

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/2278-330X.181647

Department of Radiotherapy, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
**Correspondence to:** Prof. Punita Lal, E-mail: punital@yahoo.com



**How to cite this article:** Gupta PK, Lal P, Bajpai R, Goel A, Yadav R, Verma M, *et al*. Long term results of comparison of concurrent low-dose daily cisplatin versus the standard weekly cisplatin with six fractions per week radiotherapy in locally advanced head neck cancer. South Asian J Cancer 2016;5:80-4.

overall treatment time was 40 days. Treatment was delivered using a telecobalt machine (Theratron 780-C, AECL, Canada).

### Chemotherapy delivery

Patients who received weekly CDDP schedule, received prophylactic antiemetic cover (i.e., oral dexamethasone and ondansetron for 3 days). Chemotherapy was administered as "in-patient" since day care facility was not available.

Patients who received a daily dose of CDDP were administered chemotherapy on an outpatient basis, with hydration with one unit of NS over 120 min. A single shot of injection ondansetron was given just before chemotherapy. Cisplatin was delivered as a bolus in 50 ml NS over 10 min. No planned hospitalization or round the clock antiemetic cover was given in this group.

RT was synchronized with CDDP therapy in both the groups and delivered within an hour of administration of CDDP. Chemotherapy was withheld if the total leukocyte count fell below 4000/cumm. Patients were followed up regularly during RT and after completion of treatment.

Compliance, acute and late toxicity including cisplatin-induced nephro and ototoxicity were recorded based on the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) grading system and compared to both protocols.

The two principal toxicity-xerostomia and dysphagia were documented by the treating oncologist. Aspiration was studied using serial video fluorographic studies. Hearing assessment, to study cisplatin-induced hearing loss, was done by serial pure tone audiometry evaluation. Similarly, nephrotoxicity was studied using GFR estimation, as a baseline and during follow-up. Survival outcome measures (LRS and overall survival [OS]) were also computed and compared.

### Statistical analysis

OS was measured from the date of registration. Locoregional control (LRC) was defined as complete disappearance of visible and palpable disease for at least 6 months following initiation of therapy. Locoregional persistence of disease was classified as a failure on day 1. Locoregional relapse beyond 6 months was scored as an event for LRC. Failure at any site including local site was scored as an event for LRC. Death due to any cause was scored as an event for OS. The cases lost to follow-up were considered as events, and the survival outcomes were therefore computed as worst case scenario.

## Results

Comparative results of the two single-arm studies that were carried out are reported. At the time of analysis, in November 2013, the median follow-up of the patients who were alive and was on follow-up, in the two studies was 93 and 63 months, respectively. Comparative demographic profile is elaborated in Table 1. All (120) patients gave a history of tobacco ingestion either in form, paan (betel), pan masala, bidi, or cigarette smoking. Human papillomavirus status was not determined in any of the studies and it was assumed that tobacco was implicated as an etiological factor in all these tumors.[13,14] Most of these patients were staged based on computed tomography (CT) imaging and were considered inoperable by the referring ENT surgeon/head and neck oncologist or the patient had refused surgery.

**Table 1: Demographic profile**

| Characteristics | Weekly CDDP + RT (*n*=68) | Daily CDDP + RT (*n*=52) | *P* |
|---|---|---|---|
| Age (years) | | | |
| Median, (range) | 55, (26-77) | 55, (29-75) | 0.3 |
| Gender | | | |
| Male: female | 63 (92):5 (8) | 47 (90):5 (10) | 0.745 |
| Primary site | | | |
| Oral cavity | 13 (19) | 3 (6) | 0.07 |
| Orophx | 27 (40) | 29 (55) | |
| Larynx | 18 (26) | 17 (33) | |
| Hypophx | 11 (12) | 3 (6) | |
| Unknown Primay | 2 (3) | 0 (0) | |
| T stage | | | |
| T2 | 7 (10) | 2 (4) | 0.52 |
| T3 | 36 (53) | 25 (48) | |
| T4 | 25 (37) | 25 (48) | |
| N stage | | | |
| N0 | 23 (34) | 13 (25) | 0.55 |
| N1 | 13 (19) | 12 (23) | |
| N2 | 28 (41) | 23 (44) | |
| N3 | 4 (6) | 4 (8) | |
| TNM stage | | | |
| III | 24 (35) | 15 (29) | 0.55 |
| IV | 44 (65) | 37 (71) | |
| KPS | | | |
| 70 | 5 (7) | 5 (10) | 0.427 |
| 80 | 41 (60) | 34 (65) | |
| 90 | 22 (33) | 13 (25) | |
| Tobacco | 68 (100) | 52 (100) | |
| Diabetes mellitus | 7 (10) | 5 (10) | |

KPS=Karnofsky performance status, TNM=Tumor node metastasis, RT=Radiotherapy, CDDP=Cis-diamminedichloroplatinum, Orophx=oropharynx, Hypophx=hypopharynx

Compliance in the two studies was comparable. In weekly CDDP study, six cases received less than the planned RT dose as compared to seven cases in daily group. Patients were considered to comply with radiation treatment if they completed 70 Gy within 45 days. Chemotherapy compliance (six cycles in weekly or 28–30 cycles in daily cisplatin) were 63% and 73%, respectively.

The primary reason for noncompliance toward chemotherapy (37% vs. 27% in weekly vs. daily CDDP studies, respectively) was due to the development of excessive toxicity. This also included those who left treatment midway (due to any reason) or died during therapy.

Acute toxicity was documented as per the RTOG/EORTC guidelines and is mentioned in Table 2. Grade III/IV mucositis, i.e., confluent mucosal reactions and ulcerations and dysphagia, both were significantly higher in patients receiving weekly CDDP.

During treatment, patients lost weight due to mucositis leading to inadequate oral intake. The enteral/parenteral support was provided either as an outpatient or after hospitalization. On average, the nasogastric/percutaneous endoscopic gastrostomy (PEG) tube insertion was carried out in the 3rd week of RT in both the groups. All patients with Hb <10 g/dl were transfused whole blood as per the departmental policy. Intravenous hydration was given to patients either as day care or as in-patients, as and when clinical signs and symptoms of

dehydration were observed. Antibiotics and growth factors were not used prophylactically.

Hospitalization to take care of treatment-related morbidity was considered as an intervention toward supportive care. This was apart from the regular 1–2 days admission for weekly cisplatin chemotherapy administration. The mean duration of hospitalization for supportive care was 3 days (range: 1–6 days) in both the groups.

Late toxicity was documented as per RTOG/EORTC criteria and is mentioned for both the groups in Table 3. Chemoradiation-related Grade II/III xerostomia, dysphagia, and aspiration and chemotherapy-related ototoxicity and nephrotoxicity were studied and compared. No significant difference in terms of any of the long term sequel was found in either group. Chemotherapy-related hearing loss and renal impairment (which was asymptomatic and transient in nature) were also of similar magnitude.

Regarding mortality, in weekly cisplatin study six patients died during or within 1 month following completion of treatment. One died due to dyselectrolytemia and severe dehydration following RT. Two deaths occurred due to aspiration pneumonitis during treatment, one at 44 Gy plus four cycles of cisplatin and other at 60 Gy plus six cycles of chemotherapy. One patient developed septicemia, due to PEG site infection with peritonitis and died during treatment. The fifth patient had persistence of disease and died after massive tumor bleed at home. The sixth patient died due to myocardial infarction at home. In daily cisplatin study, four patients died during or within 1 month following completion of treatment. Two died due to dyselectrolytemia (persistently low sodium) following RT. Two deaths occurred due to aspiration, one at 42 Gy plus 15 cycles of cisplatin, and other at 44 Gy plus 16 cycles of chemotherapy. The second patient developed septicemia as a consequence of aspiration and died. No second malignancy has been reported thus far in either arm.

**Table 2: Acute morbidity (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring criteria)**

| Variable | Reactions grade | Weekly cisplatin + RT *n* (%) | Daily cisplatin + RT *n* (%) | *P* |
|---|---|---|---|---|
| Mucositis | Grade I/II | 6 (9) | 18 (35) | 0.00 |
| | Grade III/IV | 62 (91) | 34 (65) | |
| Dysphagia | Grade II | 4 (6) | 17 (33) | 0.00 |
| | Grade III/IV | 64 (94) | 35 (67) | |
| Leucopenia | Grade I/II | 21 (31) | 11 (21) | 0.23 |
| | Grade III | 4 (6) | 6 (12) | |
| Anemia | Grade I | 17 (25) | 8 (15) | 0.17 |
| | Grade II | 8 (12) | 3 (6) | |
| Weight loss in kg (median) | | 5 (9.5) | 5 (9) | 0.44 |

RT=Radiotherapy

**Table 3: Late toxicity (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scoring criteria)**

| Variable | Weekly cisplatin + RT *n* (%) (*n*=68) | Daily cisplatin + RT *n* (%) (*n*=52) | *P* |
|---|---|---|---|
| Xerostomia (Grade II/III) | 30 (44) | 21 (40) | NS |
| Dysphagia and aspiration (Grade II/III) | 19 (27) | 9 (17) | NS |
| Ototoxicity | 4 (6) | 3 (6) | NS |
| Nephrotoxicity (>50% fall in GFR) | 1 (2) | 2 (4) | NS |
| Second malignancy | - | - | |

RT=Radiotherapy, GFR=Glomerular filtration rate, NS=Not significant

In weekly CDDP group, 40% (27/68) patients were lost to follow-up at the time of analysis. The 5 years LRC was 18% (median - 18 months) and 5 years OS rate was 32% (median - 24 months). In daily CDDP, 31% (16/52) patients were lost to follow-up at the time of analysis. Five years LRC was 25% (median - 11 months) and 5 years OS was 31% (median - 11 months) [Figure 1]. Locoregional persistence of disease was seen in five patients in the weekly study and three patients in the daily study and all these were subjected to salvage surgery. Locoregional recurrences were seen in 11 and nine patients, respectively, between 4 and 61 months in weekly and daily CDDP studies, respectively. Salvage treatment in the form of second-line chemotherapy or surgery or re-irradiation was offered. Eight patients developed distant metastasis to lung ($n$ = 4) following liver ($n$ = 2), bone ($n$ = 1), and brain ($n$ = 1) in the weekly CDDP study and six patients developed distant metastasis to lung (3) followed by bone (2) and liver (1) in the daily CDDP study.

## Discussion

Daily cisplatin when administered with modestly accelerated RT schedule has similar 5 years outcomes as with weekly schedule when delivered with the same RT protocol. Acute toxicity was expectedly higher with weekly CDDP administration, but no difference in late toxicity was observed. The two studies were carried out consecutively in different time period and therefore the median follow-ups were different (i.e. 93 months vs. 63 months for weekly vs. daily groups, respectively).

Above-mentioned protocols were practiced at a time when the department did not have a linear accelerator or a day care ward. All patients that were treated by concurrent weekly chemotherapy needed to be hospitalized for a day for the purpose of administration of drug. Both chemotherapy and RT infrastructure (i.e. an indoor ward and a telecobalt unit) were burdened (as is the case in any busy RT Department in India) and we needed to find ways of decreasing the load in the ward and on the machine.

A modestly accelerated protocol six fractions a week RT was adopted from the International Atomic Energy Agency (IAEA) trial conducted in Asian and African countries.[15] This trial had a similar patient profile as ours, i.e., advanced presentation. They reported a similar benefit of 10% improvement in local control as in the DAHANCA study.[16] In IAEA conducted trial, a significant proportion of patient were treated by a telecobalt machine. This was a pragmatic and useful approach when adopted in our set up since it helped in easing the load on the machine by reducing the overall treatment time by 1 week. In fact, our RT practice during the study period reflects the RT scenario in the majority of centers in India currently and many parts of the world even today, i.e., use of non-IMRT-based RT planning techniques, i.e., using large field size and treatment by telecobalt unit.

Concurrent administration of cisplatin at 3 weekly intervals along with RT is the standard of care but is associated with severe mucosal and hematological toxicities. A lower and

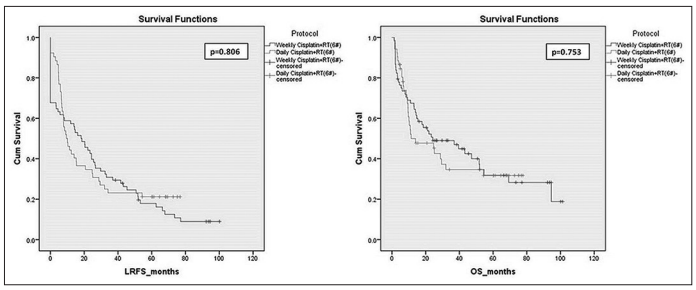


**Figure 1: Locoregional relapse-free survival and overall survival in months**

radiosensitizing doses of cisplatin (35–40 mg/m$^2$) administered once every week has been widely used and shown similar efficacy and less toxicity and this was the basis for choosing weekly cisplatin protocol world over.[6-8]

Theoretically, daily administration of low-dose cisplatin may derive maximum benefit from fractionated administration of both treatment modalities concurrently. With each fraction of RT, cisplatin acts as a radiosensitizer.[17] We initiated a single arm study of using low-dose CDDP daily, based on the experience reported by Jeremic *et al*. and Bartelink *et al*.[9-11,18-21] Low-dose daily cisplatin offers ease of administration in the outpatient clinic (obviating the need for hydration, diuresis, prophylactic antiemesis, and hospitalization) along with better tolerability than other regimes and superior outcomes in epithelial cancers.[18-20,22]

The question of which RT schedule benefits more with low-dose daily cisplatin has been addressed by Jeremic *et al*. comparing conventional RT with HFRT (hyperfractionated RT) with or without daily CT.[11,19,20] They indicated similar patient profile as ours and reported that hyperfractionated RT along with daily cisplatin had superior OS.[20] Our study design for the second single arm study was based on their work.

Acute toxicity in the present report is higher than what has been reported by contemporary Indian studies wherein weekly chemotherapy was delivered along with conventional RT.[8] Double intensification may have been the reason for increased mucosal toxicity to (over 90% in weekly group and 65% in the daily group). The possible explanations for greater mucositis in the weekly group could have been (1) more oral cavity tumors (19% vs. 6%) leading to more of oral mucosa encompassed in the RT field (2) with time our awareness and understanding the need for nutritional support grew; therefore, enteral support rate increased which could have reflected in lesser mucosal reaction in the study that was carried out using daily cisplatin (3) finally, it may well be that daily cisplatin is less toxic than weekly. Our late radiation-related swallowing changes and/or aspiration rate was similar in both the studies and was comparable with other RT series.[23,24] Late ototoxicity and nephrotoxicity were also similar in both weekly and daily CDDP protocol and was similar to studies using weekly or 3 weekly cisplatin.[15,16,20,25]

Glicksman *et al*. combined low dose cisplatin with late intensification hyper-fractionated RT in stage III, IV cases.[26] They reported an excellent compliance with no Grade III or IV toxicity. This was due to the rigorous supportive care provided to all patients right from the start of the treatment. RTOG–9914 conducted a phase II trial of concomitant boost RT with concurrent CT in HNC patients. They had an equally impressive compliance. Once again, all patients had a gastrostomy tube insertion. This study clearly emphasized the need for proper selection of patients for such intense protocols along with the need for supportive care.[27]

A study by Staar *et al*. did not show significant improvement with combining altered fractionated RT (accelerated) and chemotherapy.[28] Similar inference can be drawn from both these single arm studies in the present report when they are compared to phase II studies using intensification strategy only.[25,28-32]

As regarding nutritional support, comparison with the studies of Glicksman *et al*. and Staar *et al*. showed us that our enteral support rate (77%) comparable in the daily group but it was less in weekly CDDP group (34%). Late insertion of nasogastric/PEG tube around the 3$^{rd}$ week of RT may have resulted in high hospitalizations and early mortality as compared to other studies.[8,11,19,20,25,27] The initial delay in initiation of enteral nutrition was due to the resistance offered by the patients for any intubation. The reason behind resistance was probably lack of awareness, myths and financial constraints.

With growing experience and awareness regarding nutritional needs, the mortality rate of 14% as reported in our earlier study, was down to 8% in the present report.[25,31] It is still higher than other reports.[8,9,11,12,27] In fact, early mortality and high lost to follow-up rate are two reasons for the inferior survival outcomes considering worst case scenario in this study as compared to peer studies.[8,11,19,20,27] Treatment-related mortality, especially due to aspiration, is a well-recognized killer and needs proper patient selection and intense supportive care and compliance on the part of patient and his caretakers in order to prevent it.[23,24] Most series, especially from Indian subcontinent, are silent about the issue of high lost to follow-up rate which is a reflection of the lack of education, awareness and financial limitations existing in our patients.[33] This is applicable to a healthcare system where the patient pays for his/her treatment and follow-up visits, patient attrition, change of address and telephone numbers of patients and lack of long-term motivation on the part of the family.

We identify the reasons for poor outcomes in the present study as the following: (1) Patient selection, i.e., higher stage tumor (90% were T3/T4 and over 50% were N2/N3 disease) were included in both the studies (2) toxicity-related deaths were higher (which could be due to double intensification, use of large portals, and possibly due to poor baseline nutritional and hydration reserves, orodental hygiene and high rate of comorbidities (3) all patients lost to follow-up were considered dead for the purpose of analysis. High rate of lost to follow-up is expected since studies are being reported after the time period they were designed to be followed up for.

To summarize, combined toxicities of cisplatin and accelerated RT were higher and needed attention as compared to RT alone studies.[4,7-9,11,12] Specific toxicities of cisplatin, i.e. hematological and adverse impact on renal functioning were no greater than reported with other CRT schedules.[4,8,11,15,18-21,25] Growing emphasis on nutritional/enteral support witnessed a slight decline in mucositis and dysphagia in daily CDDP study.[25] A randomized trial of noninferiority design comparing daily

schedule with weekly or 3 weekly schedule is likely to provide the answer.

## Conclusions

As per this comparative report of two prospective single-arm studies carried out consecutively, daily cisplatin group appears to be comparable to weekly schedule in terms of survival outcomes, compliance and toxicity. Therefore, if an intensified treatment protocol has to be used, i.e. modest acceleration along with either "weekly" or "daily" cisplatin, both can be used, provided patients are selected properly and due attention is paid to timely and adequate supportive care.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. Br J Cancer 1995;71:83-91.
2. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol 1996;14:838-47.
3. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet 2000;355:949-55.
4. Pignon JP, le Maître A, Bourhis J; MACH-NC Collaborative Group. Meta-analyses of chemotherapy in head and neck cancer (MACH-NC): An update. Int J Radiat Oncol Biol Phys 2007;69 2 Suppl: S112-4.
5. Pignon JP, Baujat B, Bourhis J. Individual patient data meta-analyses in head and neck carcinoma: What have we learnt? Cancer Radiother 2005;9:31-6.
6. Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT, *et al.* The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. Radiat Oncol 2012;7:215.
7. Newlin HE, Amdur RJ, Riggs CE, Morris CG, Kirwan JM, Mendenhall WM. Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer. Cancer 2010;116:4533-40.
8. Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: A single-institution experience. Head Neck Oncol 2009;1:17.
9. Haselow RE, Warshaw MG, Oken MM, Adams GL, Aughey GL, Cooper JS, *et al*. Radiation alone versus radiation with weekly low dose cis-platinum in unresectable cancer of the head and neck. In: Fee WE Jr., Goepfert H, Johns ME, Strong EW, Ward PH, editors. Head and Neck Cancer. Totonto, ON: BC Dekker; 1990. p. 279-81.
10. Tobias JS, Smith BJ, Blackman G, Finn G. Concurrent daily cisplatin and radiotherapy in locally advanced squamous carcinoma of the head-and-neck and bronchus. Radiother Oncol 1987;9:263-8.
11. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Hyperfractionated radiation therapy alone or with or without concurrent low dose daily either cisplatin or carboplatin on locally advanced unrescectable squamous cell carcinoma of the head and neck: A prospective randomized trial. Radiother Oncol 1997;43:29-37.
12. Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L; Cancer Care Ontario Practice Guideline Initiative Head and Neck Cancer Disease Site Group. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systematic review of the published literature with subgroup analysis. Head Neck 2001;23:579-89.
13. John RM. Tobacco consumption patterns and its health implications in India. Health Policy 2005;71:213-22.
14. Elango KJ, Suresh A, Erode EM, Subhadradevi L, Ravindran HK, Iyer SK, *et al.* Role of human papilloma virus in oral tongue squamous cell carcinoma. Asian Pac J Cancer Prev 2011;12:889-96.
15. Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, *et al.* Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): A randomised, multicentre trial. Lancet Oncol 2010;11:553-60.
16. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, *et al.* Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362:933-40.
17. Kurihara N, Kubota T, Hoshiya Y, Otani Y, Ando N, Kumai K, *et al.* Pharmacokinetics of cis-diamminedichloroplatinum (II) given as low-dose and high-dose infusions. J Surg Oncol 1996;62:135-8.
18. Bartelink H, Van den Bogaert W, Horiot JC, Jager J, van Glabbeke M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: A randomised phase II EORTC trial. Eur J Cancer 2002;38:667-73.
19. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, *et al.* Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: A prospective randomized trial. J Clin Oncol 2000;18:1458-64.
20. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3540-8.
21. Hoebers FJ, Heemsbergen W, Balm AJ, van Zanten M, Schornagel JH, Rasch CR. Concurrent chemoradiation with daily low dose cisplatin for advanced stage head and neck carcinoma. Radiother Oncol 2007;85:42-7.
22. Takata I, Ueoka H, Kiura K, Tabata M, Takigawa N, Katayama H, *et al.* Daily low-dose cisplatin and concurrent thoracic irradiation for poor-risk patients with unresectable non-small-cell lung cancer. Acta Med Okayama 2002;56:261-6.
23. Nguyen NP, Frank C, Moltz CC, Vos P, Smith HJ, Bhamidipati PV, *et al.* Aspiration rate following chemoradiation for head and neck cancer: An underreported occurrence. Radiother Oncol 2006;80:302-6.
24. Mortensen HR, Jensen K, Grau C. Aspiration pneumonia in patients treated with radiotherapy for head and neck cancer. Acta Oncol 2013;52:270-6.
25. Gupta PK, Goel A, Raj MK, Kumar S, Bajpai R, Lal P. Long-term results of low dose daily cisplatin chemotherapy used concurrently with modestly accelerated radiotherapy in locally advanced squamous cell carcinomas of the head neck cancer region. Clin Cancer Investig J 2014;3:315-21.
26. Glicksman AS, Slotman G, Doolittle C 3rd, Clark J, Koness J, Coachman N, *et al.* Concurrent cis-platinum and radiation with or without surgery for advanced head and neck cancer. Int J Radiat Oncol Biol Phys 1994;30:1043-50.
27. Garden AS, Harris J, Trotti A, Jones CU, Carrascosa L, Cheng JD, *et al.* Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: A phase II trial of the radiation therapy oncology group (RTOG 99-14). Int J Radiat Oncol Biol Phys 2008;71:1351-5.
28. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, *et al.* Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy – results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;50:1161-71.
29. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, *et al.* A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7-16.
30. Ang KK, Harris J, Garden AS, Trotti A, Jones CU, Carrascosa L, *et al.* Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: Radiation therapy oncology group phase II trial 99-14. J Clin Oncol 2005;23:3008-15.
31. Kumar S, Pandey M, Lal P, Rastogi N, Maria Das KJ, Dimri K. Concomitant boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: A phase II trial. Radiother Oncol 2005;75:186-92.
32. Jackson SM, Weir LM, Hay JH, Tsang VH, Durham JS. A randomised trial of accelerated versus conventional radiotherapy in head and neck cancer. Radiother Oncol 1997;43:39-46.
33. Bajpai R, Srivastava A, Lal P, Kumar S. Defining the standard of care: Waiting times, data recording, adverse effects reporting, radiotherapy compliance and follow-up of head and neck cancer patients, at a tertiary cancer center in India. Int J Radiat Oncol Biol Phys 2008;72:S412-3.