**Original Article**

# Estimation of prevalence of pretreatment renal insufficiency and use of mathematical formulae to assess the renal dysfunction in patients of head and neck cancers undergoing concurrent chemoradiotherapy in Northern India

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## ABSTRACT

**Background:** Cisplatin (CDDP)-based concurrent chemoradiotherapy (CRT) is the standard of care in locally advanced head and neck cancers (HNCs). CDDP, a known nephrotoxic drug, has been administered in three different protocols. Baseline renal function needs to be known before CRT. Renal function can be measured directly by measuring the measured glomerular filtration rate (mGFR) using radioisotope and indirectly by either serum creatinine (SCR) levels or estimated GFR (eGFR) using mathematical formulae "abbreviated modification of diet in renal disease (aMDRD)" and "Cockcroft–Gault (CG)." The present study was performed to see the prevalence of pretreatment renal insufficiency (RI) in HNC patients and to find a realistic method using CG and aMDRD formulae for assessing RI instead of doing mGFR and to compare the nephrotoxicity in three CDDP protocols. **Materials and Methods:** The study was carried out between January 2005 and December 2006. Consecutive patients of HNC undergoing RT/CRT were included. Renal function using parameters SCR, mGFR, and eGFR using CG and aMDRD formulae was estimated for pre- and post-treatment and during follow-up. **Results:** Of 295 eligible patients, baseline prevalence of RI was in 17% by mGFR, 6% by SCR, 13% by aMDRD, and 41% patients by CG formula. aMDRD correlated better than CG with the mGFR. Of the 145 patients of CRT, pretreatment RI was seen in 9% by aMDRD and 30% by CG formula as compared to 12% by mGFR and post treatment RI was seen in 12% by aMDRD and 43% by CG formula. All the three CDDP protocols showed similar fall in GFR post treatment, and late renal injury at 6 months was seen in 2%, 4%, and 3%, respectively. **Conclusions:** RI exists in HNC patient. RI assessment by SCR is inadequate and should be done by eGFR estimation using aMDRD or CG formula if not able to do mGFR. Different CDDP protocols have similar nephrotoxicity.

**Key words:** Chemotherapy, glomerular filtration rate, head and neck cancer, radiotherapy, renal insufficiency

## INTRODUCTION

Head and neck cancer (HNC) is the most common malignancy in India. Incidence of HNC in India is 20.5–49.2 per 100,000 population.[1] For locally advanced cancers, cisplatin (CDDP)-based concurrent chemoradiotherapy (CRT) is the current standard of care.[2] However, it is a known nephrotoxic drug. It is secreted by tubules and excreted via urine. Tubular necrosis of both proximal and distal renal tubules can occur.[3] Further, renal function is a dynamic process where compromised functioning

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of kidney is observed with increasing age, comorbidities such as diabetes mellitus and hypertension, and persistent difficulty in swallowing leading to acute weight and muscle mass loss, malnutrition, dehydration, the use of nonsteroidal anti-inflammatory drugs for pain and also in some malignant processes such as multiple myeloma.[4-7]

Renal function can be assessed by knowing glomerular filtration rate (GFR). The current gold standard method for GFR assessment uses measurement of plasma clearance of radioisotope technetium-99m-diethyl-triamine-penta-acetic acid level which in turn is affected by renal function (measured glomerular filtration rate [mGFR]). Indirectly GFR can be estimated (eGFR) by using the mathematically derived Cockcroft–Gault (CG)[8] or abbreviated modification of diet in renal disease (aMDRD) formulae[9] or measuring serum creatinine (SCR) levels.

Incidence of renal insufficiency (RI) among the HNC patients needs documentation. Despite CDDP being the most commonly used drug in CRT, there is no study, to the best of our knowledge, in literature, which documents the prevalence of RI in HNCs in India. We therefore conducted a retrospective study in HNC patients with the objectives of evaluating:

i. Prevalence of RI in HNC patients
ii. To find a realistic, practical method using CG and aMDRD formulae for assessing RI if not able to make mGFR measurement
iii. To compare the risk of nephrotoxicity in CRT between three concurrent chemotherapy protocols using either weekly single agent CDDP or weekly CDDP + 5-flurouracil (5-FU) or daily CDDP.

## MATERIALS AND METHODS

The study was carried out in the Department of Radiotherapy at a Tertiary Care Hospital in Northern India. The adult patients having biopsy proven primary HNC with stages I, II, III, and IV (American Joint Committee on Cancer tumor, node, metastasis staging, 2007) with all histopathological types were included. All patients received radical radiotherapy with or without concurrent chemotherapy. Routine investigations, such as chest roentgenogram, hematological, liver and kidney functions, were carried out in all patients before treatment. The patients with prior renal disease were excluded.

### Renal function evaluation

Estimation of pretreatment renal function was made by direct mGFR measurement or indirectly by SCR and eGFR estimation using GG and aMDRD formula. SCR was measured by alkaline picrate method by using Jaffe's kinetics with an autoanalyzer. Direct mGFR was measured in the Department of Nuclear Medicine by measuring plasma clearance of technetium-99m-diethyl-triamine-penta-acetic acid. Creatinine clearance (CrCl) or eGFR was measured using the CG formula and the aMDRD formula.[8,9]

Cockcroft–Gault (CG) formula:

$$CrCl\ (ml/min) = k \times ([140 - age] \times weight\ [kg])/SCR\ (\mu mol/L),$$

where $k = 1.23$ (male) or $1.04$ (female).

aMDRD formula:

$$GFR\ (ml/min/1.73\ m^2) = k \times 186 \times (SCR)^{-1.154} \times (age)^{-0.203},$$

where $k = 1$ (men) or $0.742$ (women), GFR indicated glomerular filtration rate, and SCR is measured in mg/dl.

Posttreatment renal function was assessed in the form of SCR and eGFR using both CG and aMDRD formula. GFR measurement by direct method was not repeated at that time due to logistic reasons.

Renal function reported by either direct or indirect method was staged according to clinical practice guideline published by working group of the National Kidney Foundation as under:

- Stage I, GFR ≥90 ml/min;
- Stage II, GFR from 60 to 89 ml/min;
- Stage III, GFR from 30 to 59 ml/min;
- Stage IV, GFR from 15 to 29 ml/min; and
- Stage V, GFR <15 ml/min.

GFR below 90 ml/min has been considered abnormal according to the Kidney Disease Outcome Quality Initiative (K/DOQI) – Kidney Disease Improving Global Outcome official international definition of RI.[10] However, we considered a lower normal cutoff value for mGFR/eGFR <60 ml/min as reported in various studies showing significantly lower GFR in Indian population compared with Western population.[6,11-15] SCR value of >1.5 mg/ml was considered RI.

Cumulative dose of CDDP was considered (regardless of either of three chemotherapy regimens) for comparison. The degree of renal damage due to CDDP was categorized according to RIFLE criteria for acute tubular injury.[16]

- R = Risk (GFR decrease >25% to <50%)
- I = Injury (GFR decrease >50% to <75%)
- F = Failure (GFR decrease >75%)
- L = Loss (complete loss of renal function for more than 4 weeks)
- E = End-stage renal disease (complete loss of renal function for >3 months).

The primary aim of the study was to see prevalence of pretreatment RI and changes in pre- and post-treatment GFR and SCR. The secondary endpoint was to see late renal toxicity among three CDDP-containing chemotherapy protocols.

## Radiotherapy technique

Patients were simulated with a thermoplastic head immobilization device (SAT 10, Shimadzu, Kyoto, Japan) and treated with a telecobalt unit (Theratron 780C, AECL, ON, Canada) or a linear accelerator with 6 MV photons (Clinac 600C, Varian Medical System, Paulo Alto, USA). A three-field technique (parallel pair and an anterior lower neck) was used. In the first phase, 44 Gy/22 fractions/5–6 days in a week was delivered to the primary and draining lymph node regions by a parallel pair prescribed at midplane. The lower neck received 50 Gy/25 fractions/5 weeks, with an anterior field, normalized at 3 cm depth. In the second and third phases, the fields were reduced to exclude the spinal cord and included the primary tumor and nodal sites with a 2–3 cm margin to a dose of 26 Gy/13 fractions/5–6 days a week. The total planned dose was 70 Gy/35 fractions/6–7 weeks.

## Chemotherapy administration

Patient who had normal (baseline) GFR for their age, gender, and body surface area were taken up for concurrent CRT. There were three protocols that were being used at that time in the department, i.e., either weekly CDDP or weekly CDDP + 5-FU or daily doses of CDDP. In the weekly CDDP protocol, CDDP at 35 mg/m$^2$ (maximum 50 mg) was infused with proper intravenous hydration and antiemetic, usually as an inpatient procedure. In the second protocol, 5-FU was also administered (375 mg/m$^2$, maximum 500 mg) over 12 h infusion after CDDP at 35 mg/m$^2$ (maximum 50 mg) and radiotherapy. In the third protocol, daily CDDP was delivered at 6 mg/m$^2$ (Monday to Friday) with 500 ml of NS solution on an outpatient basis. On the day of chemotherapy in each protocol, RT was usually delivered within 1 h of administration of CDDP. Chemotherapy administration was postponed if the total leukocyte count was <3500 mm$^3$ until recovery was observed. No dose modifications were made.

## Statistical analysis

Demographic and renal function parameters were analyzed using summary measures. To test the significance of difference between pre- and post-treatment renal function parameters, a paired *t*-test was used; to look for association between various estimates of renal function, the Pearson's correlation coefficient was calculated using a two-tailed test.

# RESULTS

A total of 319 chemo-naive consecutive HNC patients, Asian in origin (belonging to Indian subcontinent), were registered in the Department of Radiotherapy from January 2005 to December 2006. Of these, 295 were evaluable because 24 patients did not either report back after the first visit or undergo any investigation. These patients therefore were not considered evaluable for the purpose of this study [Figure 1].

In the 295 patients that were considered evaluable, median age of these patients was 51 years (range 21–91 years). Males predominated and so did oral lesions [Table 1]. Of the 295 cases, 254 received either radical treatment (RT alone [86])

| Table 1: Demographic features of the study (*N*=295) | |
|---|---|
| **Characteristics** | **Distribution (%)** |
| Age (years) | |
| Mean, median (range) | 52,51 (21-91) |
| Gender | |
| Males | 250 (85) |
| Female | 45 (15) |
| Co-morbidities | |
| Diabetes mellitus | 24 (8) |
| Hypertension | 29 (10) |
| Stage | |
| I | 10 (3) |
| II | 37 (13) |
| III | 93 (32) |
| IV | 155 (52) |
| Site | |
| Oral cavity | 131 (44) |
| Oro-pharynx | 61 (21) |
| Larynx | 44 (15) |
| Hypopharynx | 19 (6) |
| Salivary gland | 8 (3) |
| Maxilla | 9 (3) |
| Nasopharynx | 5 (2) |
| Others | 18 (6) |

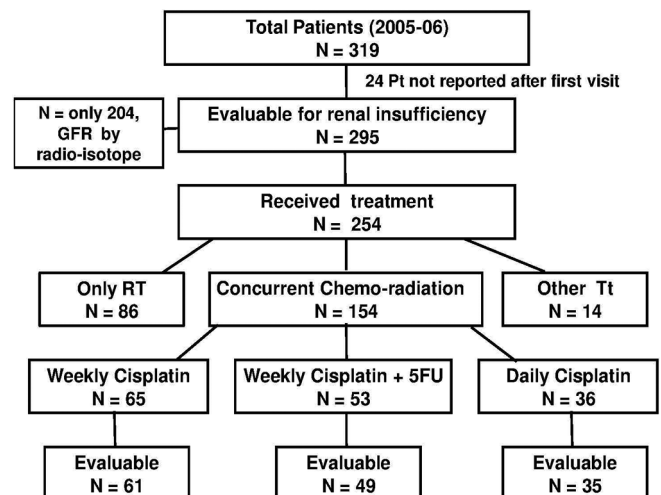Values in parenthesis indicate percentages



**Figure 1:** Schematic diagram

or CRT (154), (*n* = 240) and neo-adjuvant or salvage computed tomography (CT) (*n* = 14). Of 154 patients received CRT using three different CT protocols, 145 were considered evaluable. In the remaining nine patients, at the end of treatment, SCR value was not available; hence, they were excluded for comparison between the three protocols [Figure 1]. The details of treatment are enumerated in Table 2.

For estimating pretreatment prevalence of RI, all 295 patients were considered for RI analysis. Indirect renal function assessment was done by SCR, aMDRD, and CG method in all 295 patients or mGFR measurement in 204/295 (69%) [Table 3]. Pretreatment RI was seen in 19 (6%) patients in terms of SCR criteria. Prevalence of RI was 17% (35/204) with the gold standard mGFR measurement (with cutoff value <60 ml/min) and indirect method (eGFR) using the two mathematical formulae, aMDRD showed 13% (37/295) as against 41% (120/295) by CG formula. It showed that aMDRD correlated better than CG formula in estimating RI in pretreatment stage with respect to mGFR measurement by radioisotope.

Table 4 shows the significant correlation between standard mGFR measurement method and indirect eGFR estimation methods, i.e., aMDRD and CG formulae (*P* = 0.00) [Figures 2 and 3]. aMDRD formula had a stronger association with the mGFR measurement than CG formula (*P* = 0.00).

Prevalence of pretreatment RI using mGFR measurement was seen with respect to gender, age, presence of comorbidities such as DM and HT. In elderly subgroup (age >65 years, *n* = 57), average mGFR was significantly less, i.e., 63 ml/min (as against to 81 ml/min in younger patients [*P* = 0.004]). In diabetic patient subgroup (*n* = 24), baseline mGFR was 67 ml/min (78 ml/min in nondiabetics [*P* = 0.02]). Similar values were seen in hypertensives (*n* = 29) 65 ml/min versus 78 ml/min in nonhypertensives (*P* = 0.10) [Table 5].

Of the 145 patients who received CRT, pretreatment RI (<60 ml/min) was seen in 9% (13/145) by aMDRD formula and 30% (43/145) by CG formula as compared to 12% (16/145) by mGFR method and posttreatment RI was

### Table 2: Radical treatment protocol features of the study (*N*=240)

| Treatment protocol | Radical radiotherapy | 86 |
| | Concurrent chemo Radiotherapy | 154 |
| Chemotherapy protocol (Concurrent CRT) (*N*= 154) | Weekly cisplatin | 65 |
| | Weekly cisplatin + 5-FU | 53 |
| | Daily cisplatin | 36 |
| Cumulative chemotherapy dose | Weekly cisplatin (mg) | |
| | Mean (range) | 243 (50-360) |
| | Weekly cisplatin + 5-FU (mg) | |
| | Mean (range) | 293 (46-500) |
| | Daily cisplatin (mg) | |
| | Mean (range) | 281 (90-330) |

CRT: Chemoradiotherapy

### Table 3: Pretreatment renal function assessment by different methods

| Method | Range | Mean±SD* | Renal function | |
| | | | Parameter | *N* (%) |
|---|---|---|---|---|
| Serum creatinine (mg/ml) (*N*=295) | 0.5-3.84 | 1.02±0.35 | ≥1.5 | 19 (6) |
| | | | <1.5 | 276 (94) |
| (Cockcroft-Gault) (ml/min) (*N*=295) | 9.78-180.25 | 71.36±29.35 | <30 | 11 (4) |
| | | | 30-59 | 109 (37) |
| | | | 60-89 | 109 (37) |
| | | | ≥90 | 66 (22) |
| aMDRD (ml/min/1.73m$^2$) (*N*=295) | 16.34-202.27 | 87.47±30.43 | <30 | 3 (1) |
| | | | 30-59 | 34 (11) |
| | | | 60-89 | 150 (51) |
| | | | ≥90 | 108 (37) |
| Radio-isotope method GFR (ml/min/1.73m$^2$) (*N*=204) | 18-142 | 76±20.5 | <30 | 4 (2) |
| | | | 30-59 | 31 (15) |
| | | | 60-89 | 119 (58) |
| | | | ≥90 | 50 (25) |

*Mean+standard deviation; Value in parenthesis indicate percentages.
aMDRD: Abbreviated modification of diet in renal disease, GFR: Glomerular filtration rate
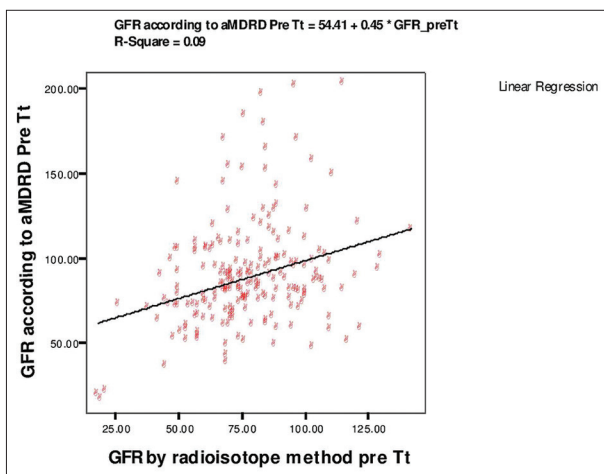


**Figure 2:** Correlation between radioisotope and abbreviated modification of diet in renal disease method to assess the renal function
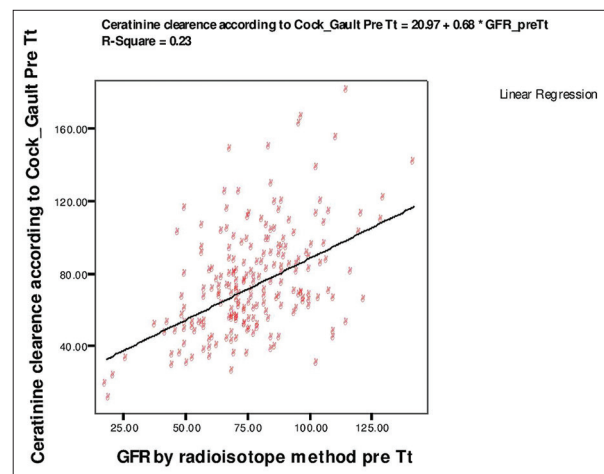


**Figure 3:** Correlation between radioisotope and Cockcroft–Gault method to assess the renal function

seen in 12% (17/145) by aMDRD and 43% (62/145) by CG by the end of treatment. The relative decline in pre- and post-treatment eGFR was 29% by both the aMDRD and CG formula [Table 6].

Further subset analysis was done for comparing the risk of developing RI in patients having three different CDDP protocols. This was done by comparing the percentage fall (before and at the end of treatment) in SCR value or eGFR and categorized into predefined and predictive RIFLES criteria. Risk of damaging the kidney (i.e., mild change) was seen in 15%, 20%, 20% and 20%, 25%, 29% in weekly CDDP, weekly CDDP with 5-FU, and daily CDDP groups by aMDRD and CG formula, respectively. In the "renal injury" (moderate change) group, damage was seen in 7%, 2%, and 6% (*P* = 0.16) (by both aMDRD and CG formula), respectively [Table 7]. However, no clinically overt acute nephrotoxicity was documented in any of the three schedules.

Late "renal injury" at posttreatment 6 months was seen in 2%, 4%, and 3% (*P* = 0.18) by both aMDRD and CG formula, respectively, suggesting that all the three CDDP protocols have similar acute and late nephrotoxicity [Table 8].

During long-term follow-up, renal function was assessed using SCR routinely and by eGFR with or without mGFR measurement when there was a clinical suspicion of renal toxicity and till date, there is no patient receiving CRT who

is alive with or without recurrence has developed moderate to severe late nephrotoxicity.

## DISCUSSION

We observed in this study that baseline RI is prevalent in patients with HNCs undergoing RT or CRT. Our study showed only 6% of patients had pretreatment RI by routinely practiced SCR measurement alone. Measurement of pretreatment RI by mGFR by radioisotope method and eGFR by indirect method using CG and aMDRD formulae (cutoff <60 ml/min) was 17%, 41%, and 13%, respectively. This disparity between SCR and GFR value measurement by direct or indirect method has been well studied in literature.[17] It has been documented that by the time SCR rises above 1.5 mg/dl, the GFR would have fallen by 40%.[4-7] Therefore, SCR, the most commonly used parameter to estimate the renal function, seems to be insufficient and inadequate. Therefore, for the most accurate determination renal function, GFR estimation should be done by directly measuring the clearance of the radioisotopes. However, this method is invasive, expensive, and not available in many hospitals having no Nuclear Medicine Department in India and developing part of the world.

Various mathematical equations are available which can eGFR. Most commonly used and accepted is aMDRD and CG formula. We observed in this study that both CG and aMDRD correlated with mGFR measurement. Between the two mathematical formulae, it appears from literature and the present study that aMDRD correlates more with mGFR measurement.[4-7] However, realistically speaking, aMDRD needs a scientific calculator so may be a less practical tool. K/DOQ guidelines also recommend the use of either aMDRD or CG equations to predict GFR.[10] These formulae can be used in day-to-day clinical practice on OPD basis instead of only using SCR. In case the CG and the aMDRD estimates differ (as is seen in the present study), it may be useful

### Table 4: Correlation between radio-isotope, Cockcroft-Gault and aMDRD method to assess renal function

| Method | Number | Pearson correlation | Sig. (2-tailed) |
|---|---|---|---|
| Radio-isotope | 204 | 1 | |
| Cockcroft-Gault | 204 | 0.476 | 0.000** |
| aMDRD | 204 | 0.299 | 0.000** |

**Correlation is significant at the 0.01 level (2-tailed). aMDRD: Abbreviated modification of diet in renal disease

### Table 5: Subgroup analysis of SCR and GFR according to gender, age, diabetes mellitus and hypertension

| Subgroup | SCR (mg/dl) | | | | GFR by radio-isotope method (ml/min/1.73m²) | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | Range | Mean±SD† | *P* value | *N* | Range | Mean±SD† | *P* value |
| Sex | | | | | | | | |
| Male | 250 | 0.5-3.8 | 1.0±0.3 | 0.07 | 176 | 18-142 | 77.6±20.4 | 0.9 |
| Female | 45 | 0.6-2.5 | 0.8±0.3 | | 28 | 21-129 | 76.4±20.8 | |
| Age | | | | | | | | |
| <65 years | 238 | 0.5-3.5 | 1.0±0.3 | 0.8 | 168 | 18-142 | 80.6±19.7 | 0.004 |
| ≥65 years | 57 | 0.6-3.8 | 1.0±0.4 | | 36 | 19-101 | 62.9±17.5 | |
| *DM | | | | | | | | |
| Yes | 24 | 0.5-3.5 | 1.2±0.6 | 0.3 | 14 | 18-142 | 67.2±35.1 | 0.02 |
| No | 246 | 0.5-3.8 | 0.9±0.3 | | 175 | 19-130 | 77.9±18.9 | |
| Unknown | 25 | 0.6-1.9 | 1.0±0.2 | | 15 | 50-117 | 82.2±18.2 | |
| **HT | | | | | | | | |
| Yes | 29 | 0.5-3.8 | 1.1±0.5 | 0.4 | 16 | 19-130 | 64.8±21.3 | 0.10 |
| No | 238 | 0.5-3.5 | 1.0±0.3 | | 172 | 18-142 | 78.0±20.1 | |
| Unknown | 28 | 0.6-1.9 | 1.0±0.2 | | 16 | 50-117 | 84.3±19.3 | |

†Mean+standard deviation; *DM: Diabetes Mellitus; **HT: Hypertension. SCR: Serum creatinine, GFR: Glomerular filtration rate

**Table 6: Renal function pre and post treatment in patients treated by radical concurrent chemoradiotherapy schedule**

| | Radical concurrent chemoradiotherapy schedule | Mean±SD* | Renal function | | P value |
|---|---|---|---|---|---|
| | | | Parameter | N (%) | |
| Serum creatinine (mg/ml) (*N*=145) | | | | | |
| Pre treatment | 0.50-2.20 | 0.97±0.26 | ≥1.5 | 7 (5) | 0.01 |
| | | | <1.5 | 138 (95) | |
| Post treatment | 0.50-2.90 | 1.03±0.18 | ≥1.5 | 10 (7) | |
| | | | <1.5 | 135 (93) | |
| Cockcroft-Gault (ml/min) (*N*=145) | | | | | |
| Pre treatment | 24.54-180.25 | 76.57±27.94 | <30 | 2 (1) | 0.000 |
| | | | 30-59 | 41 (29) | |
| | | | 60-89 | 65 (45) | |
| | | | ≥90 | 37 (25) | |
| Post treatment | 25.03-179.97 | 64.66±23.08 | <30 | 6 (4) | |
| | | | 30-59 | 56 (39) | |
| | | | 60-89 | 63 (43) | |
| | | | ≥90 | 20 (14) | |
| aMDRD (ml/min/1.73m$^2$) (*N*=145) | | | | | |
| Pre treatment | 34.77-202.27 | 90.68±28.44 | <30 | 0 (0) | 0.001 |
| | | | 30-59 | 13 (9) | |
| | | | 60-89 | 69 (48) | |
| | | | ≥90 | 63 (43) | |
| Post treatment | 25.48-208.93 | 82.82±21.94 | <30 | 1 (1) | |
| | | | 30-59 | 16 (11) | |
| | | | 60-89 | 84 (58) | |
| | | | ≥90 | 44 (30) | |
| Radio-isotope method GFR (ml/min/1.73m$^2$) (*N*=136) | | | | | |
| Pre treatment | 42-142 | 80.93±19.18 | <30 | 0 (0) | - |
| | | | 30-59 | 16 (12) | |
| | | | 60-89 | 80 (58) | |
| | | | ≥90 | 40 (30) | |
| Post treatment | – | – | – | | |

* Mean+standard deviation; Value in parenthesis indicate percentages. CRT: Chemoradiotherapy, aMDRD: Abbreviated modification of diet in renal disease, GFR: Glomerular filtration rate

**Table 7: Acute renal injury (by eGFR measurement) post treatment in patients treated by different chemotherapy schedule**

| Patients treated by different chemotherapy schedule | RIFLE | Weekly cisplatin (*N*=61) | Weekly cisplatin and 5 FU (*N*=49) | Daily cisplatin (*N*=35) |
|---|---|---|---|---|
| (Cockcroft-Gault) (ml/min) | R = GFR ↓ by >25% | 12 (20) | 12 (25) | 10 (29) |
| | I = GFR ↓ by >50% | 4 (7) | 1 (2) | 2 (6) |
| | F = GFR ↓ by >75% | 0 (0) | 0 (0) | 0 (0) |
| aMDRD (ml/min/1.73m$^2$) | R = GFR ↓ by >25% | 9 (15) | 10 (20) | 7 (20) |
| | I = GFR ↓ by >50% | 4 (7) | 1 (2) | 2 (6) |
| | F = GFR ↓ by >75% | 0 (0) | 0 (0) | 0 (0) |

Value in parenthesis indicate percentages; ↓: Decrease, GFR: Glomerular filtration rate

to consider a measure of the actual mGFR (if possible). However, in elderly population, Launay-Vacher *et al.* have recommended use of aMDRD formula over CG.[4,18]

It is also evident that the frequency of RI is underestimated in routine clinical practice because most often physicians do SCR measurements to know the RI. Since SCR is not interpreted together with the gender, age, and weight of the patient, it may not be an appropriate tool. These parameters (age, weight, and gender) represent the muscle mass of the patient and the creatinine production rate.[18] As described by others, age, diabetes, and hypertension did impact significantly on baseline renal function in this study (numbers in the two subgroups were disproportionate and less).[10] Accurate quantification of RI is important for diagnosing and monitoring progression of renal dysfunction and for calculating adequate doses of nephrotoxic drugs that are excreted by the kidneys. Cutoff value of normal GFR by international K/DOQI guidelines is >90 ml/min, below this is considered abnormal GFR. Chronic kidney disease is considered GFR below 60 ml/min. However, studies from India and Pakistan do emphasize that muscle mass, ethnicity, and dietary habits have impact on the normal values of renal functioning and possibly <60 ml/min may be considered the cutoff for abnormal renal function in our set of patients in this part of the world.[6,11-15] The impact of diet could not be assessed as the case records did not reveal the diet details.

**Table 8: Late renal injury (by eGFR measurement) post treatment 6 months in patients treated by different chemotherapy schedule**

| Months in patients treated by different chemotherapy schedule | RIFLE criteria | Weekly cisplatin (N=61) | Weekly cisplatin and 5 FU (N=49) | Daily cisplatin (N=35) |
|---|---|---|---|---|
| (Cockcroft-Gault) (ml/min) | R = GFR ↓ by >25% | 6 (10) | 5 (10) | 4 (12) |
| | I = GFR ↓ by >50% | 1 (2) | 2 (4) | 1 (3) |
| | F = GFR ↓ by >75% | 0 (0) | 0 (0) | 0 (0) |
| aMDRD (ml/min/1.73m²) | R = GFR ↓ by >25% | 5 (8) | 4 (10) | 5 (14) |
| | I = GFR ↓ by >50% | 1 (2) | 2 (4) | 1 (3) |
| | F = GFR ↓ by >75% | 0 (0) | 0 (0) | 0 (0) |

Value in parenthesis indicate percentages; ↓: Decrease, eGFR: Estimated Glomerular filtration rate, aMDRD: Abbreviated modification of diet in renal disease

CDDP is a known nephrotoxic drug. Different chemotherapy regimens have been used for administering CDDP worldwide. To reduce the nephrotoxicity, patients are hydrated well, especially when high dose schedules are being administered, i.e., 100 mg/m² at 3 weekly interval or 35 mg/m² at weekly interval.[2,19] No hydration has been advised by studies which have used daily CDDP at 6 mg/m² which has also been reported to be as safe and efficacious.[20-22]

Despite all precautions, CDDP has been found to leave permanent renal damage in some patients.[23,24] The effects of CDDP on renal function have been extensively studied in animal models. In rats, like in humans, nephrotoxicity affects different segments of the nephron such as the tubular apparatus and the glomerulus. Functional and morphological impairment of the proximal and distal tubules are well demonstrated and can result in a reversible polyuric renal failure.[25-29] In a study, Nosaka *et al.* have shown reversible damage up to necrosis in the proximal tubule, especially in the S3 segment on morphological examination 3–4 days after CDDP administration.[27] Glomerular toxicity can be both acute and chronic and can manifest in the form of reduction in the GFR due to reduced glomerular blood flow.[29] The mechanisms of this toxicity are not yet fully understood. In the tubular cells, the generation of free oxygen radicals has been proposed as a mechanism of toxicity.[30-32] Other mechanisms described in literature includes inhibition of proteins, RNA, and DNA synthesis as a consequence of the intrinsic property of CDDP to bind to DNA and form adduct to interfere with protein synthesis.[33]

On subset analysis, there was no significant change in the long-term eGFR/mGFR values in daily CDDP group as compared to the weekly group (34% vs. 26% by CG formula and 26% vs. 22% by aMDRD formula [$P = 0.18$]). It is known that with CDDP, GFR would fall by 20% to 30% in patients despite prophylactic intensive hydration and forced diuresis.[34] The dose administration schedule did not appear to influence the acute and late toxicity in the present study. Although there is no literature regarding this issue, Jeremic *et al.* did not find any excessive toxicity when daily CDDP was added to either conventional or hyperfractionated RT.[21,22]

During the time period of this study, three chemotherapy regimens were practiced in the department. The impact of CDDP on renal function on subsequent visits during long-term follow-up was assessed using SCR routinely and by eGFR/mGFR measurement when there was a clinical suspicion of renal dysfunction. However, no clinically overt moderate to severe late nephrotoxicity was documented in any of the three CDDP schedules at the time of analysis until July 2015 (minimum 8 years of follow-up).

## CONCLUSIONS

In HNCs, pretreatment baseline prevalence of RI was seen in 6% by SCR method and 17% by direct GFR measurement using gold standard radioisotope method. eGFR estimation by both CG and aMDRD formulae correlated with the mGFR (aMDRD > CG). Baseline renal function was lesser in elderly, diabetic, and hypertensive subgroups as compared to their counterparts. Therefore, all patients of locally advanced HNCs who undergo CRT need to be evaluated for renal function assessment by one or both of these formulae if mGFR estimation is not done due to logistic reasons, instead of using SCR only. Different CDDP administration protocols have similar acute and late nephrotoxicity without any clinical manifestation on long-term follow-up.

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There are no conflicts of interest.

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