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Efficacy of Multislice CT Perfusion in Post Therapy Assessment of Nasopharyngeal Carcinoma – A Prospective Study in a Tertiary Care Institute

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Abstract

Objective: (1) To assess usefulness of pre therapy CT perfusion (CTp) in predicting post therapy response in biopsy confirmed case of Nasopharyngeal carcinoma (NPC). (2) To assess the efficacy of CTp in identifying local residue and radiation fibrosis in post therapy cases of NPC.
Methods: Prospective cohort study with 42 voluntary NPC patients in Department of Radiology for a period of 28 months, data acquired on multi-detector 128-slice CT scanner at baseline & after completion of treatment. Treatment outcome dichotomised as complete response, non-response (stable disease / progressive disease) & partial response using RECIST 1.1 criteria. All perfusion parameters compared at baseline and after treatment.
Results: According to 2018 AJCC Classification (8th edition), patients were classified into various stages of NPC. With three deaths & one lost to follow up, cohort size reduced to 38, followed up for CTp at 5 to 6 weeks after therapy. Ten patients showed complete response (CR) taken as control, fourteen patients showed local residue (LR) & fourteen patients showed radiation fibrosis (RF). The pre and post therapy CTp parameters showed significant differences in blood flow BF (blood flow) (p=0.001), PS (permeability surface) (p=0.004) & Tumor size (TS) (p=0.001). Further group wise average reduction of tumor size (TS) analysis found that CR and RF group although statistically insignificant with each other, but significantly differed with LR group**.**
Conclusion: Results demonstrate CTp as reliable predictor of tumor response in NPC post therapy. Further, it empirically established difference of RF from LR taking CR group as control.
Keywords: *Nasopharyngeal carcinoma, NPC, HNSCC, CT perfusion, radiation fibrosis, RECIST 1.1*

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1. Introduction

Nasopharyngeal carcinoma (NPC) is a type of Head and Neck Squamous cell Carcinoma (HNSCC) which arisesfrom the epithelium of nasopharynx most commonly in the pharyngeal recess or 'Fossa of Rosenmuller'. It has a unique and complex aetiology that is not completely understood till date, although there is association with high antibody titres of Ebstein Barr Virus [1]. Although NPC is rare in most populations, it is a leading form of cancer in a few well-defined populations, including Cantonese population of southern China, Southeast Asia, the Arctic

and the Middle East/North Africa [1]. In the Indian subcontinent, it is very common in the North Eastern part of the country, particularly Nagaland, Manipur, and Mizoram [2]. The Mongoloid race in this region has shown an increase in NPC incidence. According to the National Cancer Registry programme (NCRP) 2012-2014, Male: Thirteen North Eastern registry areas had higher AAR, Nagaland PBCR being the highest (15.2/100,000). Delhi registry with an AAR of 0.7/100,000 stood at the fourteenth place, Females: Nine North Eastern registry areas had higher AAR and Nagaland PBCR led the list (6.8/100,000) [2].

Diagnosis is based on clinical (nasopharyngoscopy) and radiological examination with verification histologically by biopsy. Radiological examination include contrast enhanced CT & MRI and is generally performed for the purpose of evaluation extent of tumor and nodal metastasis. Gold standard for diagnosis is nasopharyngoscopy with biopsy [3].

NPC is mainly radiosensitive and combined Chemo-Radiotherapy (CT - RT) is the standard treatment of choice. However, it has been observed that in 7 – 13% of NPC cases residual disease persists after treatment [1].

Evaluation of follow-up imaging of NPC after therapy is one of the most challenging aspects of the radiologic workup as differentiation between granulation tissue/ radiation fibrosis and residual disease is important as radiation induced mucositis somewhat limits repeat biopsy from the nasopharynx [3].

Thus, the knowledge about new non-invasive techniques of functional imaging like CT perfusion, parameters of which can be taken as surrogate marker for tumour neo-angiogenesis and perfusion, gains importance which may serve the purpose of more reliable detection of residual/recurrent disease, in post therapy patients of NPC. Studying dynamics of perfusion parameters of tumour help in understanding the therapy induced functional changes in tumor tissue [2,3].

Hence, the present study is proposed to analyse the variation /changes in CT perfusion (CTp) parameters after therapy in histologically proven cases of nasopharyngeal carcinoma in comparison to pre therapy baseline CTp and to correlate with responsiveness to therapy & disease status.

2. Materials and Method

The study protocol was approved by the institutional ethics committee as a prospective three-arm study. Written informed consent was obtained from all patients before the commencement of the study. The present study was performed in the Department of Radiodiagnosis for a consecutive period of twenty eight months from 1st July 2016 to 30th November 2018.

The sample size was based on trend in outpatient clinic attendance and cases sent to department of Radiology & Imaging for CT imaging, keeping in mind the period of study.

2.1. Patients

Inclusion criteria:

All suspected cases of nasopharyngeal carcinoma patients irrespective of age and sex referred to Department of Radiology and Imaging underwent baseline CECT & perfusion CT and then biopsy and after biopsy confirmation were included in the study.

Exclusion criteria:

1) Cases which were not confirmed by biopsy
2) Contraindication to CT and contrast
3) History of prior radiotherapy / chemotherapy or both for any condition
4) Terminally ill patients
5) Inability to communicate

2.2 Technique

Patients were trained for quiet breathing and asked not to swallow during the procedure. NCCT of the region of interest was performed to localize the tumor with the following parameters: 100kV, 50 to 220 mA with automated tube current modulation, 0.8s rotation time, 5mm thickness and total exposure time 5s. Scan position were adjusted to cover the entire volume.

CTp performed on 128 slice CT scanner with Z axis coverage of 3 to 4 cm. 40ml of iodinated nonionic contrast with iodine contrast of 350mg/ml was injected at the rate 5ml/s followed by saline flush of 30 ml with an automated pressure injector (IMAXEON) injected through antecubital vein on the site opposite to the tumour to reduce streak artifacts from large veins. Scanning started 5s after start of injection and images acquired for a period of 40 parameters used were 80 kV, 50-200 mAs with automated tube modulation, 0.1s rotation time, thickness 5mm, noise index of 15, processing of perfusion done on 5/5mm slice. This was followed by CECT done from skull base to thoracic outlet with same parameters as NECT. Acquisition was done 40s after 1.25ml/kg of iodinated contrast medium

2.3 Image processing:

Post processing CT perfusion data analysis was done on accompanying workstation (Syngo multimodality workplace, Siemens, Erlangen, Germany). Attenuation thresholds were fixed to exclude bones. The software utilized was Patlak's two-compartment model analysis technique. Perfusion analysis was assessed using three axial images acquired through the tumor with a slice thickness of 7.2 mm. Free-hand drawn region of interest (ROI) encompassing the visualized primary volume on the image of the tumor epicentre were manually placed onto the perfusion maps by using corresponding CECT image as

reference for placing ROI. Arterial input was determined by defining a circular ROI in the internal carotid artery at the level of the tumor. A time-density curve (TDC) was then automatically generated followed by perfusion colour maps representing BF, BV, PS, MTT and TTD. The actual measurements of the CTp values were recorded at baseline and at follow up.

These parameters were defined as follows: -

– BF (ml/100 g/min), volume of blood moving through a given tissue per unit of time.
- BV (ml/100 g), total volume of blood in a given tissue region
- Permeability (ml/100 g/min), rate of leakage of contrast media from capillaries into the interstitium
- MTT (seconds), mean time needed for the iodinated contrast medium to pass from the input artery through the tissue microcirculation and which can be calculated as the ratio of BV by BF (central volume theorem)

2.4 Criteria for morphological Response:

The pre-treatment sizes were compared to those of the post-treatment imaging. The response to therapy in post intervention patients was assessed by the Revised RECIST (Response Evaluation Criteria in Solid Tumors guideline version 1.1) and stratified into various response groups [4,5]. A sum of the diameters of longest diameter for primary tumor and minimal transverse diameter of the nodal lesions for all target lesions on the pre- and post-treatment imaging was calculated and compared [4,5].

2.5 Statistical analysis plan (SAP):

Prospective cohort study with pre and post Clinical Intervention (i.e. CT-RT) repeated measure of baseline and follow up CTp parameters in cases of suspected NPC referred to Department of Radiology & Imaging .Follow up CT p done on biopsy confirmed cases of NPC. Follow up post CT-RT data analysis performed using three arm parallel group design with Complete Response (CR)(as control) ,Local Residual disease (LR) in second arm and Radiation Fibrosis(RF) in third arm[10].

A total of 42 volunteers (Female=16, Male=26) were initially recruited and their baseline BF, BV, MTT, PS, TTP, TTD and TS (tumor size) were measured with 38 left at follow up .

The collected data were subjected to a master tabulation in MS excel worksheet according to study protocol. Pre & Post Intervention Data were analysed by Student t test in aggregate and in respective CR, RF and LR groups separately. Multiple and simple linear regression performed to examine the impact of independent variables viz. BF, BV, MTT, PS on TS (outcome). Post intervention Reduction/ Increment of post BF, BV, MTT, PS and TS (tumor size) in various response groups were subjected to one way ANOVA F, Hsu Dunnet and Tuckey's Honest significant difference (HSD) wherever applicable. A P value of < 0.05 considered significant. [11]

Statistical softwares viz. IBM SPSS Statistics 20(SPSS Inc. Chicago) and JMP 10 of SAS 9.3 (SAS Inc. Cary, NC) analysis were used.[11]

3. Results and observation

3.1 Characteristics of the study patients

3.1.1: Age and Gender Characteristics

Total participants included in the study were forty two. There were sixteen females (38.1%) and twenty six males (61.9%). The average age of females (Mean = 35.88 years, SD = 12.30 years, Range =14-59 years) was lower than the average age of males (Mean= 43.69 years, SD = 13.03, Range =16-62 years). (Fig. 1 & 2)

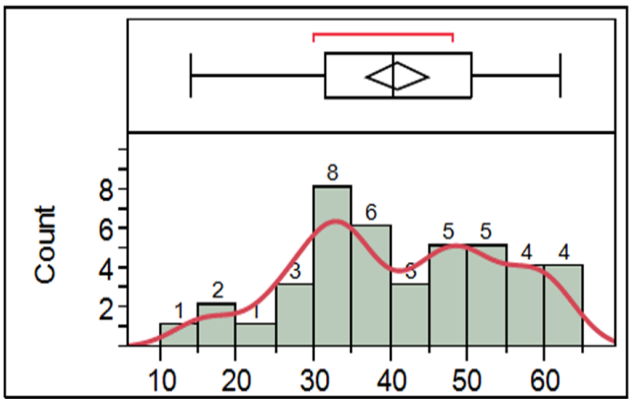

Fig 1: Showing age distribution of the study group .

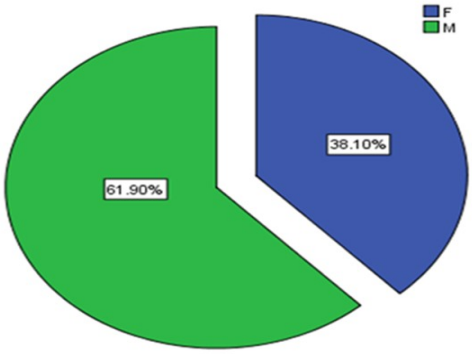

Fig 2: Showing gender distribution

3.1.2 Staging Characteristics:

Characterisation of participant patients is depicted in (Fig 3). It shows that two (4.76%; 95% CI: 1.32-15.79%) patients were in stage II of the disease, thirty five (83.33%; 95% CI: 69.40- 91.68%) patients had stage III disease and five (11.9%; 95% CI: 5.19-25.00%) patients had stage IV A disease according to 2018 American Joint Committee on Cancer Classification, Eighth Edition [6]

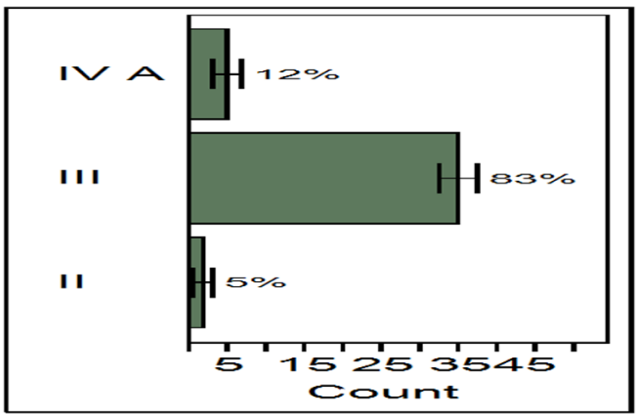

Fig 3: showing staging characteristics

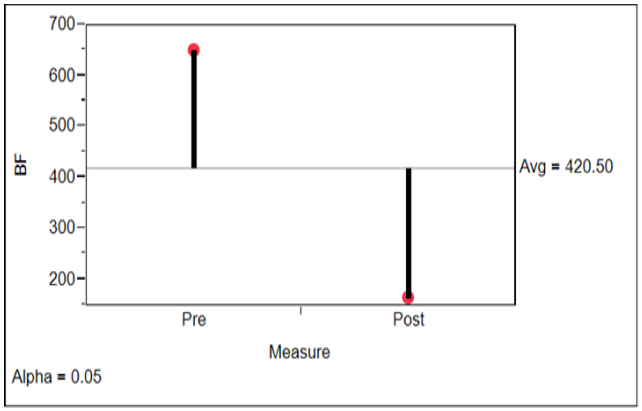

Fig 4: Comparison pre and post therapy blood flow (BF) parameter

3.1.3: Response Characteristics

Among the forty two patients that were included in the study, three (7.14%;) patients expired during the course of treatment, one (2.38%) lost to follow up, ten (23.81%)of them showed complete resolution of the tumorous lesion, belonging to "Complete response(CR)" group, twenty four (65.7%) patients showed more than 30% reduction in tumour volume, belonging to "partial response (PR)" group, three(4.76%) of them with stable disease (SD) and one with "progressive disease(PD)" (2.38%) belonged to "Non-response(NR)" group[4,5]

3.2: Perfusion Characteristics:

3.2.1: Exploratory analysis of CTp parameters in pre and post intervention groups:

We conducted a paired t-test to determine whether, on average, there was a change in pre post BF, BV, PS, MTT, and TS (Fig. 4-6 and Table 1). It was significant in case of BF *(P=0.001),* PS *(P=0.004)* and TS *(P<.001)*. However, it was insignificant in case of BV *(P=0.090),* MTT *(P=0.498)*. At baseline it was found that PS was the only CTp parameter that was significantly higher in complete response (CR) and radiation fibrosis (RF) group in comparison to local residual disease (LR) and non responders (NR) group whereas BF was found to be significantly lower among complete response (CR) and radiation fibrosis (RF) groups. Mean difference in Pre – post intervention CTp parameters viz. BF was 410.10 ± 109.35 ml/100g/min, BV was 18.56 ± 10.67 ml/100 g, PS was 40.91 ± 13.24 ml/100g/min.

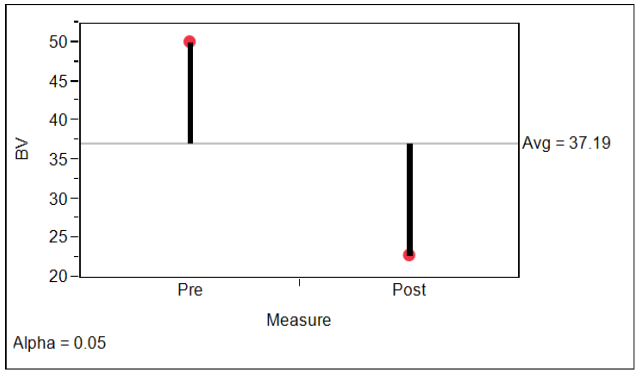

Fig 5: Comparison pre and post therapy blood volume (BV) parameter

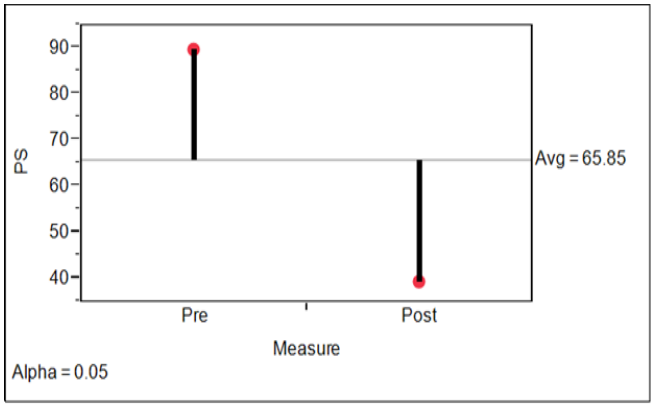

Fig 6: Comparison pre and post therapy permeability surface area product (PS) parameter

Table 1: Comparison of Pre- Post Intervention Mean ±SE of CTp parameters in Different Response Group

Parameter	Group						*P*-value
	CR		LR		RF		
	Mean± SE	n	Mean± SE	n	Mean± SE	n	
ΔBF	463.94± 119.26	10	413.01±276.47	14	368.73±92.83	14	0.946^{NS}
ΔBV	32.93 ±14.03	10	11.2±23.43	14	15.66±14.7	14	0.723^{NS}
ΔMTT	-1.61±1.77	9	-0.25±0.74	14	0±1.36	14	0.674^{NS}
ΔPS	77.05±26.2	10	18.92±27.65	14	37.08±11.8	14	0.227^{NS}
Δ TS †	$4.70±0.29^{A}$	10	$3.02±0.35^{B}$	14	$4.05±0.18^{A}$	14	<0.001**

NS not Significant (P>0.05); **P(<0.001); Δ = Pre – post Intervention (RT) differences of respective CTp parameters

3.2.2 Prediction of Outcome from CTp parameter differentials: An attempt was made to find patterns in CTp parameters and predict TS reduction outcome as dependent variable after stratifying patients into various patterns of perfusion .To cover every aspect of statistical investigation cycle, a multiple linear regression was applied to the pre and post intervention CTp differentials (Table 2).

Table 2: Pearson Correlations(r) Half Matrix summarizes CTp Differentials

CTp Differentials		BV(100 g/min)	MTT (Sec)	PS (ml/100g/min)	TS (Outcome)
BF(ml/100g/min)	r	0.838**	-0.084	0.845**	0.078
	P	<0.001	0.622	<0.001	0.641
	n	38	37	38	38
BV(ml/100g)	r		-0.218	0.809**	0.207
	P		0.195	<.001	0.212
	n		37	38	38
MTT (Sec)	r			-0.201	-0.206
	P			0.233	0.221
	n			37	37
PS(ml/100g/min)	r				0.314
	P				0.055
	n				38

** Significant at P (<0.01); NS Not significant (P>0.05); BF(ml/100g/min), BV(ml/100g), PS (ml/100g/min), MTT(sec).

On the basis of Correlation half matrix, Multiple linear equation showing effect of BF (blood Flow) and BV (Blood Volume) on PS (permeability surface) was found to be: **ΔPS = 5.28 + 0.68** ΔBF + 0.042*Δ BV; Rsq = 73.29%**

It showed significant impact of reduction of BF on PS ($p < 0.01$) and BV on PS ($p< 0.05$) i.e. decrease in PS was directly proportional to the decrease in BF and BV. An attempt was further made to improve the predictability of the initial multiple linear regression equation which found significant impact of BF *(P= .025)* and PS *(P= 0.004)* in prediction of TS (outcome). The predictive ability of the regression model was estimated to be 22.1 % as seen below: **ΔTS (outcome) = 3.798 - 0.001ΔBF + 0.013 ΔPS; R sq = 22.1%, ANOVA F (2, 35) = 4.97, p = .013)**

Thus, prognostically, it was found that patients with high PS and low BF at baseline were more likely to respond to Chemo-Radiotherapy (CT-RT) with statistical significance.

3.2.3Efficacy of CT perfusion in identifying local residue and radiation fibrosis in patients with nasopharyngeal carcinoma after Chemo–Radio therapy (CT- RT):

Post hoc test for pair wise significance carried out revealed that the pair wise reduction in TS i.e. ΔTS (Mean ± SE) analysis found that average reduction in CR group (4.70± 0.29) was statistically at par with RF (4.05±0.18) Group (*P*=0.267). However, RF group was significantly different with LR (3.02±0.35) Group (*P*=0.026). Also CR group differed significantly with LR group (*P*<.001). (Fig. 8). Analysis of Means by Hsu – Dunnet Test (Fig. 7) also graphically showed the difference between RF and LR groups taking CR as control group.

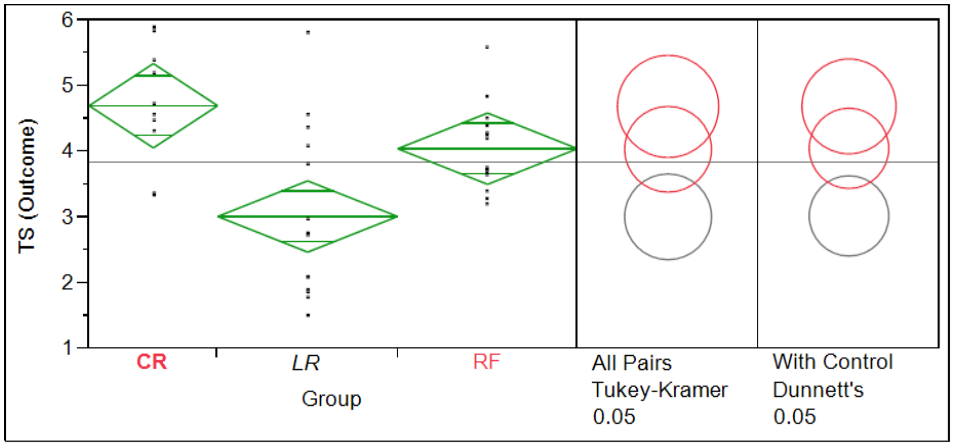

Fig 7: Hsu – Dunnet Test showing comparison between post therapies various response groups

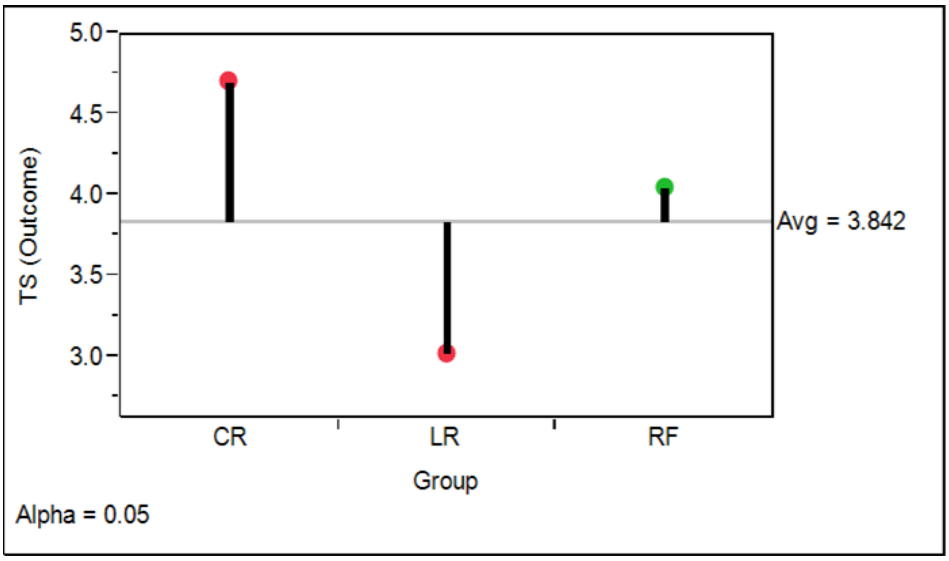

Fig 8: Graphical comparison between post therapy various response groups

4. Discussion

The exploratory analysis of interaction between various CTp functional parameters in the pooled patient population (38 patients) revealed that a relationship existed between baseline CTp values and follow-up. In the responders, the dynamics of BF, BV, and PS values over the course of treatment demonstrated either a pattern of significant reduction (PS), of significant increase (BF), of significant initial reduction followed by a plateau (BV), or non significant fluctuations (MTT). These phenomena might be attributed to the cytotoxic effects of x-rays on the vascular endothelium and malignant cells.

Based on the correlation matrix analysis, a further attempt was made to explore various predictive models to predict the impact of pre - treatment CTp parameters on post intervention TS (outcome) in responders. A suitable predictive model was thus proposed. We concluded that among the various CTp parameters, low BF *(P =0.025)* and high PS *(P=0.004)* had the strongest statistically significant impact on the reduction of TS (outcome) with predictive ability of 22.1 %, a finding different from the previous study by Rana *et al*[7]. This can be explained by the fact that initial pre – treatment tumour had a hypoxic environment resulting in reduced blood flow (BF) and upregulation of angiogenesis factors like VEGF resulting in immature leaking vessels causing rise in permeability (PS). With the initiation of cytotoxic effects of CT- RT, there is correction in the hypoxia due to reduction in tumor bulk with resultant increase in BF and decrease in PS and subsequently reduction TS[10].

In our patients, although the tumor size (TS) was reduced after CT - RT, interestingly, the morphologic changes (TS) in various response groups were accompanied by variations in the functional parameters, however, without any statistical significance. Presumably, this may due to the different trends in perfusion changes that were observed between individual patients, multicolinearity of the data, inhomogeneity of the study population with respect to TNM staging and other latent confounding variables. A finding which was similar to Surlan Popovic *et al*.[8]

5. Conclusion

Direct nasopharyngoscopy and biopsy, although, gold standard in monitoring therapeutic response in nasopharyngeal carcinoma, are invasive procedures which has significant limitation in post therapy patients owing to CT - RT induced mucositis.

Our study demonstrated that CTp integration into routine CECT protocol is clinically feasible for monitoring the effects of concomitant CT-RT in Nasopharyngeal carcinoma. The results support the hypothesis that CTp can detect the changes in dynamics of functional parameters and the proposed predictive model may help to predict early tumor response to applied therapy. Thus, may contribute significantly to selection of appropriate therapeutic regimen for locoregional control. Further, it also demonstrated the difference between post therapy complete response, radiation fibrosis and local residue groups, thus, contributing to decision regarding end point of therapy in patients of Nasopharyngeal Carcinoma.

Estimation of locoregional tumour control after 1 or 2 years is a more reliable criterion for therapeutic effectiveness and justifies the predictive value of the CTp. This was a limitation encountered in the study owing to the study design. Thus, next step is to follow up these patients and further evaluate the predictive role of CTp in future studies.

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Potential Conflict of Interest:

The authors have no potential conflicts of interest to disclose.

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