Pre-radiotherapy Haemoglobin Level is A Prognosticator in Locally Advanced Head and Neck Cancers Treated with Concurrent Chemoradiation

RAJESH KAR NARAYANASWAMY[1], MAHADEV POTHARAJU[2], A N VAIDHYSWARAN[3], KARTHIKEYAN PERUMAL[4]

ABSTRACT

Introduction: Radiation plays a major role in treatment of locoregional control of Head and Neck Squamous cell carcinoma (HNSCC). Anaemia is considered a contributor to intra-tumour hypoxia and tumour resistance to ionizing radiation and most evidences are from developed world, we prospectively investigated the exact role of anaemia in treatment outcome of Stage III/IVA HNSCC in our patient population.

Aim of the Study: Primary end point: To analyse the Pre-Radiotherapy haemoglobin level and early response of treatment in stage III/IVA HNSCC and to determine the relationship of Pre-Radiotherapy haemoglobin level with other prognostic factors.

Materials and Methods: This non-interventional single blinded randomized study enrolled patients attending the OPD consecutively, who met our eligibility criteria. **Inclusion Criteria:** HNSCC patients of Stage III/IVA aged ≥18 years and ≤ 70 years with ECOG status of 1 or 2 and willing for concurrent chemoradiation and at least 6 weeks of follow up. **Exclusion Criteria:** 1) Previous history of treatment for malignancy or radiation in head and neck site. 2) Patients with other fatal and non-fatal pre-morbid or co-morbid conditions that can affect the outcome or the overall survival.

Patients with Pre-radiotherapy haemoglobin status < 10 g/dl were given haematinic support and/or blood transfusion. All patients received concurrent chemotherapy (weekly cisplatin) and radiation in conventionally fractionated dose of 66Gy. Early treatment responses were evaluated with Revised RECIST version 1.1 and Data analysis using SPSS version 17.0.

Results: Ninety one patients enrolled had mean age of 55.63 (range: 32-69), a median of 56 and mode of 60. Seventy one were males (78%) and 20 females (22%) with a performance status of ECOG 1 in 43 (47%) patients and ECOG 2 in 48 (53%); Pre-RT Hb level of <10.7 g/dl in 38 (42%) patients and ≥10.7 in 53 (58%) patients; Pre-RT Hb level was <12 g/dl in 67 (74%) patients and ≥12 in 24 (26%) patients. Tumour sites were - Nasopharynx 7 (8 %), Oral Cavity 18 (20 %), Oropharynx 32 (35 %), Hypopharynx 23 (25 %) and Larynx 11 (12 %). Twenty five (27%) had Grade 2 mucositis and 66 (73%) had Grade 3 mucositis. Fifty eight (64%) patients completed treatment with NO breaks and 33 (36%) with treatment breaks for ≥5 days.

Pre-radiotherapy haemoglobin ≥ 10.7 g/dl (p < 0.001), ECOG performance status (p = 0.0002), Treatment interruptions for > 5 days (p = <0.0001), Mucositis reaction (p = <0.0001) showed statistical significance with outcome of response.

Conclusion: The study found that performance status, pre-RT haemoglobin level, radiotherapy interruptions > 5 days and non-development of grade III mucositis was found to be significantly associated with good loco-regional control. Haemoglobin level ≥10.7 g/dl was associated with better treatment outcome, higher performance status, fewer treatment interruptions and lesser degree of mucositis. Transfusion did not affect the outcome. Definitive conclusions and recommendations need further expansion of our study for better statistical power.

Keywords: Haemoglobin concentration, Hypoxia, Oxygen transport capacity, Tumour oxygenation

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is a loco regional disease [1,2]. Radiation plays a major role in the locoregional control (LRC) of HNSCC [3-7]. Tumour hypoxia and Anaemia are known to adversely affect the efficacy of radiation therapy [8].

Anaemia and cancer are inter-related. Many studies have demonstrated the dramatic adverse impact of anaemia upon loco-regional tumour control and survival and have revealed haemoglobin (Hb) levels as a powerful prognostic factor, a compelling evidence for the value of reversing anaemia and hence tumour hypoxia in head and neck cancer patients [8]. Irrespective of the cause, the existence of anaemia in cancer patients can impair the effectiveness of treatment and negatively impact the outcome [8].

Prognostic factors are the characteristics of patient which affect survival, treatment outcome and modify the therapeutic strategies. Patient related prognostic factors are weight loss of > 5%, an

Eastern Co-operative Oncology Group (ECOG) performance status; Tumour-related prognostic factors are: site of the tumour, presence of tumour residue, the primary tumour (T) size, depth of invasion, Grade of tumour, presence or absence of vascular invasion, metastatic lymph nodes (N), and their size, number, and position (level), extracapsular tumour spread (ECS) [9]. Poor ECOG performance status is known to be an independent unfavourable prognostic factor [10].

The ECOG Scale of Performance Status (PS) quantifies the functional status of cancer patients, and is an important factor determining prognosis in a number of malignant conditions, describing the status of symptoms and functions with respect to ambulatory status and need for care [11].

Mucositis, inflammatory response of oral mucosa is one of the adverse effects of radiation which is quantified by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [12].

Although anaemia is considered to be a contributor to intra-tumoural hypoxia and tumour resistance to ionizing radiation in cancer patients, most evidences are from developed nations, the exact role of anaemia in treatment outcome of HNSCC patients in developing world (where low haemoglobin levels are usual) needed further prospective investigation.

HNSCC being a good model [8] for analysing this relationship, we undertook this prospective study including Stage III/IVA HNSCC patients.

AIM OF THE STUDY

Primary end point: To analyse the relationship between Pre-Radiotherapy haemoglobin (pre-RT Hb) level and early treatment response (ETR) (six weeks after completion of treatment) in stage III/IVA HNSCC treated with concurrent chemo radiation.

Secondary end point: To determine the relationship of pre-RT Hb level with other potential prognostic factors in stage III/IVA HNSCC.

MATERIALS AND METHODS

This is a non-interventional non-randomized single blinded study. All the investigations, interventions and treatment were being done as part of standard of care and not as part of the study. Our study was limited to collection of de-identified data in federal Health Insurance Portability and Accountability Act of 1996 (HIPPAA) compliant manner from patients attending our outpatient department consecutively, who met the eligibility criteria. Patients were stratified into Anaemic and non-Anaemic group based on the pre-RT Hb status of ≤ 12 g/dl. Stratification of the patients into two groups was done only during the analysis of the data at the end of our study.

Patient Evaluation: As a part of standard of care, the patients were evaluated with complete history, physical examination, clinical and endoscopic evaluation, blood and radiological investigations. Patients with pre-RT Hb status <10g/dl were given haematinic support and/or blood transfusion.

Staging work up and pre-radiotherapy investigations including the laboratory (haematology and biochemistry) as well as the radiological investigations (chest radiography, computed tomography of the site of the primary tumour and the neck) were as per American Joint Committee on Cancer (AJCC) Staging Criteria 7th Edition published in 2010 [13].

Patient population and eligibility criteria

Inclusion Criteria: 1) HNSCC of Stage III/IVA 2) Age of the patient ≥ 18 years and ≤ 70years. 4) ECOG Performance status 1 or 2. 3) Head and Neck Sites: oral cavity (OC), oropharynx (OP), hypopharynx (HP), larynx (LX) and nasopharynx (NP). 5) Patients undergoing concurrent chemoradiation. 6) At least 6 weeks of follow up after completion of treatment.

Exclusion Criteria: Patients with anyone of the following factors were excluded from the protocol.

1) Previous history of malignancy. 2) Previous history of radiation in head and neck site. 3) Patients with uncontrolled co-morbidity like Diabetes and Hypertension. 4) Patients having pre-morbid conditions precluding chemotherapy or radiotherapy. 5) Patients with other fatal and non-fatal co-morbid conditions that can affect the outcome of the treatment or the overall survival (OS) in general.

HNSCC from various sites such as oral cavity (OC), oropharynx (OP), hypopharynx (HP), larynx (LX) and nasopharynx (NP) were included in our study. The selection criteria enrolled patients who came for six weeks of follow-up, precluding any attrition in patient population after enrollment. The methodology included only the accounting for Haemoglobin level prior to radiation therapy. In addition to pre-RT Hb levels, patient variables such as age, gender, Tumour site, T stage, N stage, ECOG Performance status, grade of mucositis were analysed for correlation with ETR.

Radiation therapy: All eligible patients received concurrent chemotherapy. Radiation consisted of conventionally fractionated dose of 66Gy, 2 Gy per fraction, five fractions per week in 6.5 weeks. Radiation therapy technique was individualized for each patient. However, in general patients were treated in supine position with aquaplast mask for immobilization with shoulder retractor, treatment volume included the primary tumour site, involved lymph nodes and as well as all draining lymph nodes at risk.

Chemotherapy: The patients were treated concurrently with weekly Cisplatin 30 mg/m^2 during radiation.

STATISTICAL ANALYSIS

All the analyses were done using Statistical Package for the Social Sciences (SPSS) version 17.0. All the categorical variables were expressed as either percentages or proportions. The continuous variables were expressed as mean ± standard deviation. Comparison of categorical variables was carried by using Chi-square test of Fisher's exact test whichever is applicable. P-value <0.05 was considered statistical significance. Pre-RT Hb levels were a continuous variable in our study. In our study, mean pre-RT Hb level was 10.7 g/d (σ: 1.2). Response was compared below and above the value of 12 g/dl and also the mean value (Hb 10.7 g/dl).

ETR were categorized into Complete Response (CR), Partial Response (PR), Stable disease (SD) or Progressive disease (PD) as per Revised Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) [14].

Complete Response (CR) is defined as disappearance of all target lesions. Partial Response (PR) is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). Stable Disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study [14].

Computed Tomography (CT) scans of ≤5 mm slice thickness obtained during radiation treatment planning and during follow-up was used to measure the response. For easier analysis responses other than Complete Response (CR) were grouped into non-CR. ETR assessment at six weeks as measured by above criteria was the endpoint in our study. Different pre-RT Hb levels were analysed for correlation with ETR.

RESULTS

Ninety one patients who met the eligibility criteria were enrolled and Patient characteristics (age at diagnosis, gender, and pre-RT Hb level), Tumour characteristics (tumour site, T stage, N stage and pathological grade) and Treatment Characteristics (radiotherapy technique – 3D Conformal Radiotherapy (3DCRT) with Intensity Modulated Radiation Therapy (IMRT), mucositis and treatment withholds were recorded and analysed [Table/Fig-1].

Patient characteristics: Our patient population was characterized by a mean age of 55.63 (range: 32-69). It was skewed towards male population with 71 males (78%) and 20 females (22%). It had a performance status of ECOG 1 in 43 (47%) and ECOG 2 in 48 (53%) patients. It was characterized by a Pre-RT Hb level of <10.7g/dl in 38 (42%) and ≥10.7 g/dl in 53 (58%) patients. Pre-RT Hb level was <12 g/dl in 67 (74%) and ≥12 in 24 (26%) patients.

Tumour characteristics: Our study population was characterized by tumours from various head and neck sites -nasopharynx 7 (8%), oral cavity 18 (20 %), oropharynx 32 (35%), hypopharynx 23 (25%) and larynx 11 (12%). The number of patients with T3 stage were 27 (30%) and T4 a/b stage were 64 (70%); with N1 stage 21 (23%) patients and N2a 9 (10%) patients, N2b 26 (28%) patients, N2c 35 (39%) patients.

Treatment Characteristics: All were treated by high precision radiation technique with 72 (79.12 %) being treated by 3DCRT and 19 (20.88 %) by IMRT. All had concurrent chemotherapy either weekly cisplatin or once in three weeks Cisplatin plus 5-FU regimen. The number of patients experiencing Grade 2 mucositis was 25 (27%) and Grade 3 mucositis was 66 (73%) patients. 58 (64%) patients completed treatment with breaks< 5 days and 33 (36%) with treatment breaks for ≥5 days.

Analysis: Age, Gender, Tumour site, T stage, N stage did not show statistical significance for ETR [Table/Fig-1]. The variables which showed statistical significance are presented below:

Performance Status and ETR: ECOG 1 group had better ETR compared to ECOG 2 group. Performance status showed statistical significance with outcome of response (p < 0.001).

Treatment Interruptions and ETR: Patients with treatment withholds less than five days showed better ETR compared to Treatment interruptions for five and more days showed statistical significance with outcome of response (p < 0.001).

Characteristics	n	CR	NO CR	p-value
Age in Years				
≤55	41	27	14	0.8
>55	50	27	23	
Gender				
Male	71	40	31	0.31
Female	20	14	06	
Tstage				
T3	27	21	6	0.138
T4a/b	64	33	31	
N stage				
N1	21	09	12	0.215
N2a	09	07	02	
N2b	26	16	07	
N2c	35	19	16	
Pre-RT Hb in g/dl				
<10.7	38	07	31	< 0.0001
≥10.7	53	47	06	
Pre-RT Hb in g/dl				
<12	67	34	33	< 0.0001
≥12	24	20	4	
Mucositis				
Grade 2	25	22	03	0.001
Grade 3	66	32	34	
Treatment Breaks for ≥5 days				
YES	33	09	24	<0.0001
NO	58	45	13	
ECOG Status				
1	43	35	08	0.0002
2	48	19	29	
Tumour Site				
NP	7	06	01	0.503
OC	18	10	08	
OP	32	22	10	
HP	23	13	10	
LX	11	03	08	

**[Table/Fig-1]:** Characteristics of study population and treatment response

 Patients with grade 2 mucositis had a better ETR compared to grade 3 mucositis. Mucositis reactions showed statistical significance with outcome of response (p < 0.001).

Correlation of Pre-treatment Hb level and treatment response: We did our analysis based on WHO criteria for Anaemia [15], which defined the same as Hb level of less than 12 g/dl. Patients with Pre –RT Hb ≥ 12 g/dl better ETR compared to patients with Pre –RT Hb <12 g/dl. Pre-RT Hb ≥ 12 g/dl showed statistical significance with outcome of response (p < 0.001) [Table/Fig-2].

The Hb level of Indian population tends to be lower than international standards. The mean Hb level of our population was found to be 10.7 g/dl.

To present the more realistic scenario in India, we did our analysis based on this value too. Our results were as below:
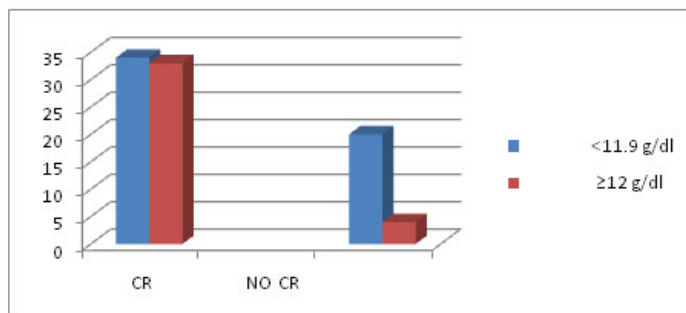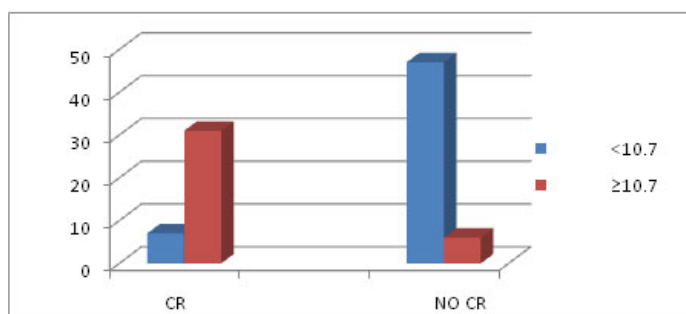

[Table/Fig-2]: Pre-RT Hb more than & less than 12 g/dl and early response

Patients with Pre–RT Hb ≥ 10.7 g/dl better ETR compared to patients with Pre –RT Hb <10.7 g/dl. Pre-RT haemoglobin ≥ 10.7 g/dl showed statistical significance with ETR (p< 0.001) [Table/Fig-3]. We also analysed various Pre-RT Hb levels serially. There was no statistical significance when the cohorts were divided based on Pre-RT Hb level ≤ 10 g/dl.

We also analysed the correlation of the above prognostic factors showing significance to pre-RT Hb levels.

Relationship of ECOG performance status was analysed with pre-RT Hb.   ECOG 1 group had better haemoglobin status compared

**[Table/Fig-3]:** Pre-RT Haemoglobin more than & less than 10.7 g/dl and early response

to ECOG 2 group. ECOG performance status showed statistical significance with pre-RT Hb (p = 0.0002) [Table/Fig-4].

Patients with Pre –RT Hb ≥10.7 g/dl had fewer treatment interruptions compared to patients with Pre –RT Hb <10.7 g/dl. Treatment interruptions ≥ five days and pre RT Hb showed statistical significance (p = <0.0001) [Table/Fig-5].
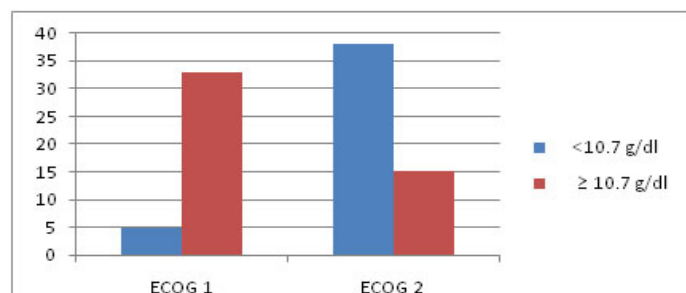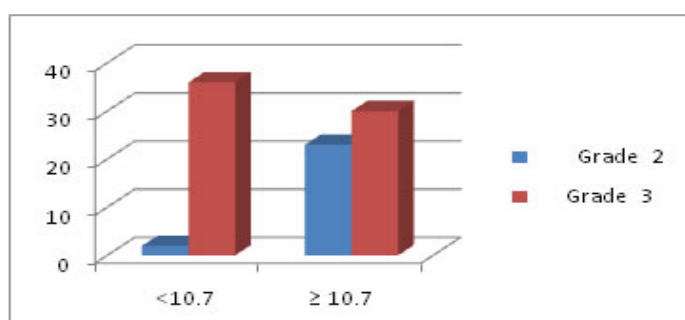

[Table/Fig-4]: Performance status and Pre –RT Hb less than and more than 10.7g/dl

[Table/Fig-6] Patients with Pre –RT Hb ≥10.7 g/dl had lesser grade of mucositis compared to patients with Pre –RT Hb <10.7 g/dl. Mucositis reaction and pre-RT Hb showed statistical significance (p = <0.0001) [Table/Fig-7].
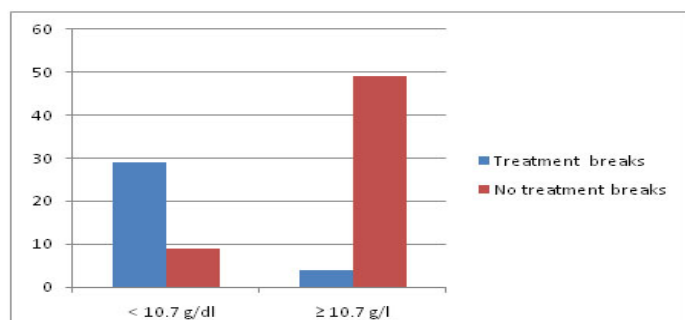
[Table/Fig-5]: Treatment withholds and Pre –RT Hb in g/dl

[Table/Fig-6]: Mucositis reaction and Pre –RT Hb less than and more than10.7g/dl

Pre-RT Hb g/dl	<10.7	≥10.7	p-value
Mucositis			
Grade 2	02	23	<0.0001
Grade 3	36	30	
Treatment interruptions for ≥ 5 days			
YES	29	04	<0.0001
NO	09	49	
ECOG Status			
1	05	38	0.002
2	33	15	

[Table/Fig-7]: Pre-RT Hb with other factors

DISCUSSION

Only a few reports could be identified in the literature that prospectively evaluated prognostic factors of chemoradiation in HNSCC patients [16-22]. This is the first data on Indian population studying the prognostic significance of pre-RT Hb levels.

Danish Head and Neck Cancer (DAHANCA) Group Trial: DAHANCA 5 randomized HNSCC patients treated with the hypoxic radiosensitizer nimorazole or placebo, and in addition, patients with "low" pre-irradiation Hb values (females<13 g/dL; males<14.5 g/dL) were sub-randomized to plus or minus transfusion and found that, patients with high Hb levels had a significantly better probability of LRC, disease-specific survival (DSS) and overall survival (OS) compared to 'low Hb no transfusion' patients [23]. The univariate analysis (UVA) demonstrated prognostic significance of high Hb levels in HNSCC treated with radiotherapy; But in both UVA and multivariate analysis (MVA), transfusion prior to and during treatment did not improve the outcome in patients with low Hb values [24].

Further analysis by combining DAHANCA 5 and 7 to provide the statistical power for the analysis showed that patients with low Hb level had a significant reduced probability of LRC, DSS and OS. In the low Hb group, transfusion did not improve the outcome in LRC, DSS or OS. In MVA, there was no significant influence of transfusion or Hb level on endpoints [24].

Denis et al., reported on a cohort of Stage III or IV oropharynx cancer patients treated with radiotherapy alone or chemoradiation [16] that a pretreatment Hb level of <12.5 g/dL is a significant negative prognostic factor. A significant impact of the pretreatment Hb level on treatment outcome has also been reported for primary tumours of other sites such as esophageal cancer, lung cancer, and cervix cancer [20-22].

The range of Hb levels considered optimal for tumour oxygenation was reported to be 12–14 g/dL [22].The predictive value of the Hb may be explained by radioresistance associated with hypoxia. Tumour oxygenation can be affected by several factors such as adequacy of the blood supply, microcirculation, and oxygen-carrying capacity of the blood, might be represented by the Hb level [25]. This explanation is supported by our data, in particular by the fact that the higher Hb level was significantly associated with LRC.

Treatment Interruption: Another major finding of this study was the negative impact of radiotherapy interruptions more than five days resulting in poor LRC. These findings are in accordance with the available literature. The negative effect of interruptions during radiotherapy has also been described for various head and neck cancer sites. In a retrospective study on 1,102 patients, 1-day interruption was found to increase the risk of local failure by almost 5% [26]. Another study demonstrated a 3.5% decrease in control of the carcinoma larynx if the interruption lasted 5 days [27]. Few authors reported that the rate of loco-regional failure increases by 3.3% for each day of interruption in a retrospective series of 796 patients with nasopharyngeal carcinoma who received either continuous-course or split course radiotherapy [28]. Another retrospective review of 868 patients with head and neck cancer at various sites suggested that the time of the interruption during the series of radiotherapy has no impact on LRC [29].

Associated Findings: Third finding of this study was the patients with grade II mucositis had better treatment outcome compared to patients with grade III mucositis (p< 0.001). Patients with pre-RT Hb level of ≥10.7 g/dl had statistically significant lower incidence grade III mucositis compared to patients with patients with pre–RT Hb level of < 10.7 g/dl (p<0.001) – signifying patients with higher pre- RT Hb level tend to suffer lesser grade of mucositis.

Fourth finding of this study was the patients with performance status ECOG 1 had better treatment outcome compared to patients with ECOG 2 (p< 0.001). Patients with pre –RT Hb level of ≥10.7 g/dl had statistically significant better performance status of ECOG 1 compared to patients with patients with pre –RT Hb level of < 10.7 g/dl (p<0.001) – signifying patients with higher pre-RT Hb level tend to have better performance status.

The value of transfusion or poietic proteins in improving treatment outcome is controversial and needs further well designed studies. The idea of tumour biology being different and aggressive in anaemic patients is debatable and an area of potential research. It is important to assess pre-RT Hb to prognosticate and identify subgroup of patient population with poor outcome. It is necessary to avoid treatment interruptions to achieve the best possible treatment outcomes, which may require maximum supportive care during and after treatment and is in line with those, published prospective and retrospective data.

CONCLUSION

In our study the level of Hb having a significant effect on treatment outcome was at 10.7 g/dl. In addition to pretreatment Hb levels > 10.7 g/dL, we found that improved LRC in Stage III/IVA HNSCC is significantly associated with better performance status, lesser grade of mucositis and no interruptions or interruptions less than five days during radiotherapy.

However, definitive conclusions and recommendations need further expansion of our study for better statistical power and significance.

REFERENCES

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277–300.

[2] Cancer Facts & Figures - 2010___- acspc-024113.pdf [Internet]. Available from: http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf [cited 2013 Aug 1].

[3] Manual of clinical oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. pp. 169-88.

[4] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol*. 2004;22(1):69–76.

[5] Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. 1999;91(24):2081–86.

[6] Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2003;21(1):92–98.

[7] Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med*. 1993;328(3):184–94.

[8] Kumar P. Impact of Anaemia in patients with head and neck cancer. *The oncologist*. 2000;5 Suppl 2:13–18.

[9] Nakamura T, Sumi M. Nodal imaging in the neck: recent advances in US, CT and MR imaging of metastatic nodes. *Eur Radiol*. 2007;17(5):1235–41.

[10] Corrêa GTB, Bandeira GA, Cavalcanti BG, Santos FBG, Rodrigues Neto JFR, Guimarães ALS, et al. Analysis of ECOG performance status in head and neck squamous cell carcinoma patients: association with sociodemographical and clinical factors, and overall survival. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2012;20(11):2679–85.

[11] Sørensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer*. 1993;67(4):773–75.

[12] Protocol Development [Internet]. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [cited 2015 Mar 31].

[13] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–74.

[14] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer Oxf Engl* 1990. 2009;45(2):228–47.

[15] Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity .pdf [Internet]. [cited 2014 Aug 29]. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf

[16] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol*. 2004;22(1):69–76.

[17] Cerezo L, Millán I, Torre A, Aragón G, Otero J. Prognostic factors for survival and tumour control in cervical lymph node metastases from head and neck cancer. A multivariate study of 492 cases. *Cancer*. 1992;69(5):1224–34.

[18] Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. *Cancer*. 1993;71(2):452–56.

[19] Leibel SA, Scott CB, Mohiuddin M, Marcial VA, Coia LR, Davis LW, et al. The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: results of an analysis from the RTOG head and neck database. *Int J Radiat Oncol Biol Phys*. 1991;21(3):549–56.

[20] Rades D, Schild SE, Bahrehmand R, Zschenker O, Alberti WA, Rudat VR. Prognostic factors in the nonsurgical treatment of esophageal carcinoma with radiotherapy or radiochemotherapy: the importance of pretreatment haemoglobin levels. *Cancer*. 2005;103(8):1740–46.

[21] Langendijk H, de Jong J, Wanders R, Lambin P, Slotman B. The importance of pre-treatment haemoglobin level in inoperable non-small cell lung carcinoma treated with radical radiotherapy. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2003;67(3):321–25.

[22] Vaupel P, Thews O, Mayer A, Höckel S, Höckel M. Oxygenation status of gynecologic tumours: what is the optimal haemoglobin level? *Strahlenther Onkol Organ Dtsch Röntgenges Al*. 2002;178(12):727–31.

[23] Hoff CM, Lassen P, Eriksen JG, Hansen HS, Specht L, Overgaard M, et al. Does transfusion improve the outcome for HNSCC patients treated with radiotherapy? - results from the randomized DAHANCA 5 and 7 trials. *Acta Oncol Stockh Swed*. 2011;50(7):1006–14.

[24] Hoff CM, Hansen HS, Overgaard M, Grau C, Johansen J, Bentzen J, et al. The importance of haemoglobin level and effect of transfusion in HNSCC patients treated with radiotherapy--results from the randomized DAHANCA 5 study. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2011;98(1):28–33.

[25] Becker A, Stadler P, Lavey RS, Hänsgen G, Kuhnt T, Lautenschläger C, et al. Severe Anaemia is associated with poor tumour oxygenation in head and neck squamous cell carcinomas. *Int J Radiat Oncol Biol Phys*. 2000;46(2):459–66.

[26] Barton MB, Keane TJ, Gadalla T, Maki E. The effect of treatment time and treatment interruption on tumour control following radical radiotherapy of laryngeal cancer. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 1992;23(3):137–43.

[27] Robertson C, Robertson AG, Hendry JH, Roberts SA, Slevin NJ, Duncan WB, et al. Similar decreases in local tumour control are calculated for treatment protraction and for interruptions in the radiotherapy of carcinoma of the larynx in four centers. *Int J Radiat Oncol Biol Phys*. 1998;40(2):319–29.

[28] Kwong DL, Sham JS, Chua DT, Choy DT, Au GK, Wu PM. The effect of interruptions and prolonged treatment time in radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 1997;39(3):703–10.

[29] Suwinski R, Sowa A, Rutkowski T, Wydmanski J, Tarnawski R, Maciejewski B. Time factor in postoperative radiotherapy: a multivariate locoregional control analysis in 868 patients. *Int J Radiat Oncol Biol Phys*. 2003;56(2):399–412.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Radiation Oncology, Apollo Speciality Hospital, Chennai, India.
2. Senior Consultant, Department of Radiation Oncology, Apollo Speciality Hospital, Chennai, India.
3. Senior Consultant, Department of Radiation Oncology, Apollo Speciality Hospital, Chennai, India.
4. Senior Resident, Department of Radiation Oncology, Apollo Speciality Hospital, Chennai, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Karthikeyan Perumal,
Senior Resident, Department of Radiation Oncology, Apollo Speciality Hospital, Chennai-600035, India.
E-mail : sindash@yahoo.com