RESEARCH ARTICLE

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Single Nucleotide Polymorphisms in *APE1*, *hOGG1*, *RAD51* Genes and their Association with Radiotherapy Induced Toxicity among Head and Neck Cancer Patients

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Abstract

Background: Radiotherapy (RT) is a crucial treatment for head and neck cancer however, it causes adverse reactions to the normal tissue and organs adjacent to target tumor. The present study was carried out to investigate possible association of single nucleotide polymorphism in DNA repair genes with toxicity effects of radiotherapy on normal tissue. **Methods:** Three hundred and fifty head and neck cancer patients receiving radiotherapy treatment were enrolled in this study. The adverse after effects of radiotherapy on the normal tissue in the form of skin reactions were recorded. Single nucleotide polymorphisms of *APE1 (rs1130409), hOGG1 (rs1052133)* and *Rad51 (rs1801320, rs1801321)* genes were studied by polymerase chain reaction-Restriction fragment length polymorphism (PCR-RFLP) and direct DNA sequencing methods and their association with development of severe radio-toxicity effects was evaluated logistic regression analysis. **Results:** The 172G/T polymorphism of Rad51 was 2.85 times higher and significantly associated with skin reactions (OR=2.85, 95% CI: 1.50-5.41; p=0.001) and severe oral mucositis (OR=4.96, 95% CI: 2.40-10.25; p<0.0001). These results suggested that the polymorphic nature of Rad51 is responsible for risk of radiotherapy adverse effects in HNC patients. The variant 326Cys and heterozygous 326Ser/Cys genotype of *hOGG1* was significantly associated with high tumor grade (OR=3.16 95% CI: 1.66-5.99; p=0.0004, and OR=3.97 95% CI: 2.15-7.34; p=<0.0001 respectively). The homozygous variant 172TT genotype of Rad51 showed positive association with poor response of both tumor and nodes towards radiotherapy treatment (p=0.007 and p=0.022). **Conclusions:** Interpretation of our results revealed significant association of rs1801321 SNP of Rad51 with development of adverse toxicity reactions in normal tissue of head and neck cancer patients treated with radiotherapy.

Keywords: Head and neck cancer- radiotherapy- toxicity- single nucleotide polymorphism- *APE1- hOGG1- Rad51*

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Introduction

Head and Neck cancer (HNC) is a heterogeneous disease including together hypopharynx, oropharynx, oral cavity, nasopharynx and larynx. Now a days, HNC has becoming major public health problem in low and middle income groups of Indian subcontinent which has become life threatening problem for the country. In India, HNC accounts 30% of all cancers and ranked second in occurrence with new cases 135, 929 (10.30%) and 75, 290 deaths accounting (8.8%) of total cancer deaths in 2020. The epidemiology and etiology of HNC is diverse where tobacco and alcohol intake are considered as main risk factors. Along with, genetic susceptibility affecting genes regulating DNA repair mechanisms are also accounted for HNC carcinogenesis. Radiotherapy (RT) is a commonly used treatment of HNC, administered as adjuvant radiotherapy (aRT) or concurrent chemo-radiotherapy (cRT) [1]. When cancer patients are treated with radiation, radiotherapy is known to cause acute or late toxicity reactions in normal healthy cells. When HNC patient treated with radiotherapy, the normal tissue adjacent to target tumor area is certainly exposed to radiation and causes variety of normal tissue toxicity such as acute radiotoxicity (mucositis, dysphagia and dermatitis) and late radio toxicity reactions such as subcutaneous skin fibrosis, osteoradionecrosis [2,3]. The cellular DNA of an individual is a soft target for radiation and it causes single strand breaks (SSBs) and double strand breaks (DSBs) in DNA which induces apoptotic cell death, thus genetic susceptibility of an individual is associated with radiation toxicity [4]. This brings into interest of research to understand genetic control of radiation effects on normal tissue during radiotherapy. In this regard, several reports

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predicted involvement of genetic and molecular factors in developing radiation induced toxicities in normal tissue. Previous reports on cellular aspects of radiation sensitivity demonstrated genotype dependent cause of acute and late effects on normal tissues in response to radiation therapy [5-8].

The genetic polymorphism in radiation responsive genes and their association with normal tissue adverse effects have been studied earlier, however, some of them were unable to prove their clinical significance in normal tissue toxicity [9, 10]. When patients were exposed to radiation during radiotherapy, the single nucleotide polymorphisms (SNPs) of DNA repair genes contribute to occurrence of radiation induced adverse effects [11, 12]. The most common SNPs in radiation responsive DNA repair pathway genes are base excision repair (BER) and homologus recombination repair (HRR) genes, involved in interfering individuals DNA repair capacity are important in determining their association with intrinsic radiosensitivity. The BER and HRR are two important DNA repair mechanisms involved in maintaining genomic stability by removal of oxidative DNA damage. Apurinic/apyrimidinic endonuclease 1 (*APE1*) and 8-oxoguanine DNA glycosylase 1 (OGG1) are essential components of BER pathway. RAD51 is involved in HRR of double strand break repair (DSBs) and maintain genomic stability and integrity [13, 14]. Both *APE1* and *hOGG1* are polymorphic in nature where T>G transversion at 2197 position in exon 5 of *APE1* gene resulted into Aspartate 148 Glutamate polymorphism (rs1130409) and C>G transversion at 1,245 position of exon 7 of *hOGG1* resulting into Serine 326 Cystine (rs1052133) are the commonly studied polymorphisms [15-19]. Both the *BER* pathway genes are reported for their association with radiation induced toxicity during radiotherapy [20]. Similarly *Rad51* is highly polymorphic in nature with two common SNPs, G135C (rs1801320) and G172T (rs1801321) have been reported to be associated with carcinogenesis and radiosensitivity [21-24]. The polymorphisms of *APE1, hOGG1* and *Rad51* are considered for their positive association with radiation sensitivity in patients with variety of cancers [22, 25, 26] however; other studies differ in their outcomes where genetic variants of studied DNA repair genes showed no association with adverse effects of radiotherapy in other cancer [11, 27]. Thus, studies reported association of SNPs of DNA damage, repair responsive genes with individual's sensitivity to radiation proved development of radiation toxicity. In spite of this, others derived inconclusive outcomes where the genetic variants in DNA repair genes are not associated with developing normal tissue reactions. In present study, we selected genotypes and polymorphisms of DNA damage and repair response genes including *rs1130409 (T>G) SNP* of *APE1, rs1052133 (C>G) SNP* of *hOGG1, rs1801320 (G>C), rs1801321 (G>T) SNPs of Rad51* and correlated their role with genetic susceptibility of HNC patients. The current study was also focused to investigate the association of selected *SNPs* of *APE1, hOGG1* and *Rad51* with toxicity effects of radiation given during radiotherapy in HNC patients.

Materials and Methods

Patient enrollment and Clinical data

Three hundred and fifty (350) HNC patients seeking treatment at Department of Oncology of Krishna Hospital and Medical Research Center, Karad were enrolled in this study based on predefined inclusion and exclusion criteria.

Inclusion critera

Patients with 25 to 80 years age, histopathologically confirmed, no metastasis at diagnosis, clinically localised or locally advanced tumors according to standard staging system, and normal skin and oral mucosa before the first radiotherapy fraction were included in this study. Exclusion criteria: No pathological diagnosis, relapsed disease or metastasis, severe co-morbidities, incomplete treatment taken, incomplete follow-up, missing or incomplete data were excluded from the study.

The patients were communicated regarding the purpose of their involvement in the study protocol. Informed written consent was obtained from all patients. The study protocol was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences. The detailed clinical information with all examination findings were recorded in predefined proforma. The detailed clinicopathological and demographic characteristics and follow-up information of the patients was recorded and depicted in Table 1. Radiation toxicity effects in the form of skin reactions and oral mucositis are recorded according to Radiation Therapy Oncology Group (RTOG) criteria. The clinical and radiological responses are documented as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria at planned initial and end of treatment assessment. After giving radiation therapy patients are followed up for six months at regular prespecified intervals to assess the clinical response such as complete response, partial response, stable disease, progressive disease, early death from disease or toxicity or any other cause.

Radiotherapy and Chemo-radiotherapy Regimen

All patients were treated using 3DCRT or Intensity modulated radiation therapy (IMRT). Gross tumor volume (GTV), Clinical Target Volume (CTV) and Planning target volume (PTV) were defined by using computed tomography (CT) positioning. The GTV included all known gross disease as defined by clinical, physical examination and imaging findings. Patients were treated using Linear accelerator (Model: Unique Performance, Make: Varian Medical System, USA) 6-Mega Volt (MV) (X-ray) with the total radiotherapy dose of 60- 66 Gy (2 Gy per fractions for 5 days a week) with 3D-CRT, or IMRT techniques. Patients after surgical resection having positive margins were given a dose of 66 Gy in 33 fractions. Chemotherapy was added if clinically indicated and the drug used was cisplatin at doses of 40 mg/m^2 every week given for 6 doses along with RT.

Follow-up and Toxicity assessment

The HNC patients treated with RT started to follow-up after completion of six weeks radiotherapy until six months at regular intervals for the assessment of response

and toxicity evaluation. The skin over face and neck was selected as the observing area in patients with acute radiation induced acute skin reactions. Acute radiation toxicity in normal tissue such as oral mucosa and skin were documented and evaluated their association with genotype polymorphism of *APE1, hOGG1, Rad51* genes. For comparison of HNC patients with skin reactions such as severe fibrosis (>1 grade) were considered as radiosensitive groups were compared to patients with ≤ 1 grade skin reactions. The patients with oral mucositis grade >2 are radiosensitive groups (cases) compared with ≤2 grade (controls) for determining their association with polymorphism of DNA repair genes.

Sample collection and Genomic DNA isolation

Five milliliter (mL) of whole blood from patients was collected in sterile EDTA containing vacutainer after receiving informed consent. Genomic DNA extraction was carried out from the peripheral blood sample using HipurA®Blood genomic DNA miniprep purification kit. (Cat no. MB504-250PR) (HiMedia Laboratories) following the manufacturer's instructions. This genomic DNA was used for genotyping assays.

Genotyping assays:

Genotyping of *APE1, hOGG1, Rad51* genes was performed by PCR-RFLP and direct DNA sequencing methods with appropriate primer sets presented in Table 2. The PCR amplification were carried out separately under different conditions in 20 micro liter (µL) reaction mixtures containing 1X PCR buffer (10 mili molar (mM) Tris-HCl (pH 9.0), 50 mM KCl 1.5 mM MgCl2, 0.01% gelatin), 0.2 mM each dNTP, 10 picomole (pmol) of each primer listed in Table 1, 1U Taq DNA polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA template. The reaction mixtures subjected to PCR amplification with a Master Cycler Gradient PCR (Eppendorf). After performing PCR programme for each of the reaction, the PCR products were analyzed by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer. After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme for genotyping. Ten micro liters of each PCR products were digested overnight at 37°C with specific restriction enzymes in 20 µL reaction mixtures containing buffer supplied with each restriction enzyme (Table 1). After the overnight incubation, digestion products were separated on a 2-3% low EEO agarose (GeNei) gel at 100 V for 30 min stained with ethidium bromide and photographed with Gel Documentation System (BioRad).

Statistical Analysis

The genotypic frequencies for the *BER (APE1, hOGG1)* and *HRR (Rad51)* genes in the patient's were determined. The Odds Ratio (OR) and corresponding 95% confidence interval (CI) were determined through unconditional multiple logistic regression. OR estimated to test whether any association exists between the grade of acute toxicity caused by radiotherapy and selected SNPs. The occurrence of clinical severity of post-radiotherapy adverse effects are defined as skin reactions with >1grade and oral mucositis scored as grade >2. All statistical analyses were carried out using SPSS 11 Software.

Results

Demographic and Clinical characteristics study population

Three hundred and fifty patients were enrolled in the study. There were 261 males and 89 females. The age range was 25 to 80 years, with a median age of 55 years. The distribution of patients based on clinical characteristics, demographic information, histopathological grading and toxicity grades are presented in Table 1. Radiation doses planned were 60 Gy given in 30 fractions in the adjuvant setting and 66 Gy in 33 fractions in the curative setting. Median number of weekly chemotherapy cycles was 5. A total of 253 patients underwent chemo-radiotherapy, while the remaining 97 were given radiotherapy alone. Primary site of disease was oropharynx (42.0%), hypopharynx (23.0%), oral cavity (20.0%), nasopharynx (7.0 %), larynx (4.0%) and remaining 4% were other sites. Out of 350 patients, 162 (46.29%) patients experienced mucositis (grade ≤2) and 53.71 % patients experienced grade >2 mucositis (grade 3 and 4) and 69.43% experienced dermatitis (grade ≤1) where as only 30.57 % patients showed >1 severe dermatitis.

Genotype Distribution of APE1, hOGG1 Rad51 genes and radiotherapy toxicity in HNC patients

The univariate analysis of the genotype polymorphisms of *APE1, hOGG1* and *Rad51* genes and its association with radiation toxicities such as dermatitis as well as mucositis is represented in Table 2. We grouped patient normal tissue toxicity as ≤1 or >1 for skin reactions and ≤2 or >2 for oral mucositis based on earlier grading system of toxicity developed by radiation oncologists. Out of 350 patients, 107 patients showed grade >1 skin reactions and 188 patients reported grade >2 oral mucositis when subjected to radiation exposure. When we studied rs1130409 SNP of *APE1*, rs1052133 SNP of *hOGG1* and rs1801320, 1801321 SNPs of *Rad51*, the results of univariate analysis depicted that none of the SNPs except rs1801321 SNP of *Rad51* were associated with radiotherapy toxicity effects. The Odds ratio (OR) of patients expressing variant genotype 172G/T of *Rad51* was significantly associated with both dermatitis (OR=2.85, 95% CI: 1.50-5.41; p=0.001) which was 2.85 times higher and severe oral mucositis (OR=4.96, 95% CI: 2.40-10.25; p<0.0001). These results suggested that the polymorphic nature of *Rad51* is responsible for risk of radiotherapy adverse effects in HNC patients. When we studied, Asp148Glu polymorphism at exon 5 of *APE1* gene, majority (92.0%) of genotypes were the wild type (Asp) genotype and 95% Asp allele frequency and 6.0 % heterozygous As/Glu genotype and 2.0% variant Glu/Glu genotype and 5% Glu allele. When polymorphism of *hOGG1* codon 326 at exon 7 was investigated, the results showed presence of 42.86% 326Ser genotype and 31.71% 326 Ser/Cys genotype and 25.43% 326Cys genotype in HNC patients. There was no statically significant difference observed between recessive or heterozygous genotypes of *APE1* and *hOGG1*genes when considered

Table 1. Details of Baseline Demographic and Clinico-Pathological Characteristics of Head and Neck Cancer Patients Enrolled in the Study

Variables	Number/Percentage (%)
Total Number of patients	350
Age (Mean ± SD) years	55.76 ±13.19 (Range:25-80) Median:55
≤ 50	121 (34.57)
>50	229 (65.43)
Sex	
Male	261(74.57)
Female	89 (25.43)
BMI Kg/m^2	
≤25	314 (89.71)
>25	36 (10.29)
Smoking/Tobacco chewing	
Smokers	312 (89.14)
Non-Smokers	38 (10.86)
Alcohol Consumption	
Drinkers	152 (43.43)
Non-Drinkers	198 (56.57)
Tumor size in cm	
≤ 2	213 (60.86)
> 2	137 (39.14)
Radiation Response	
Tumor Response	
Complete Response	289 (82.57)
Partial Response	61 (17.43)
Node Response	
Complete Response	282 (80.57)
Partial Response	68 (19.43)
Skin reaction (RTOG Grading)	
Grade 0	21 (6.0)
Grade 1	222 (63.43)
Grade 2	100 (28.57)
Grade 3	7 (2.0)
Mucositis (RTOG Grading)	
Grade 1	15 (4.29)
Grade 2	147 (42.0)
Grade 3	183 (52.29)
Grade 4	5 (1.42)
Genotype APE1 (Asp148Glu)	
Asp/Asp	322 (92.0)
Asp/Glu	21 (6.0)
Glu/Glu	7 (2.0)
Asp Allele	665 (95.00)
Glu Allele	35 (5.0)
Genotype hOGG1(Ser326Cys)	
Ser/Ser	150 (42.86)
Ser/Cys	111 (31.71)
Cys/Cys	89 (25.43)
Ser Allele	411 (58.71)
Cys Allele	289 (41.29)
Genotype RAD51 (G135C)	
G/G	202 (57.71)
G/C	127 (36.29)
C/C	21 (6.0)
G Allele	531 (75.86)
C Allele	169 (24.14)
Genotype RAD51(G172T)	
G/G	177 (50.57)
G/T	119 (34.0)
T/T	54 (15.43)
G allele	473 (67.57)
T allele	227 (32.43)

with the degree of radiotherapy toxicity (Table 3) where both recessive and heterozygous genotype of *rs1801321 SNP* were positively associated with dermatitis skin reactions and mucosal reactions in HNC patients when administered with radiotherapy.

Association of APE1, hOGG1, Rad51 gene polymorphisms with tumor and node response towards radiotherapy in HNC patients

The results of logistic regression analysis was carried out to find out the association of *APE1, hOGG1* and *Rad51* genes with tumor grade and tumor response to radiotherapy were shown in Table 4 and Table 5. The univariate analyses showed that *rs1130409 SNP* of *APE1* gene was not associated with tumor stage or grade. The recessive (G/G) as well as heterozygous (C/G) genotypes of *hOGG1* (rs1052133) showed significant association with high tumor stage OR=3.16 95% CI: 1.66-5.99; p=0.0004, and OR=3.97 95% CI: 2.15-7.34; p=<0.0001 respectively. Similarly, recessive C/C genotype of *Rad51 (rs1801320)* was associated with tumor grade >3 (OR=3.07 95% CI: 1.08-8.71; p=<0.034), but *Rad51* (rs1801321) did not show any association with histopathological grade >3 (Table 4). The relationships between genotypes of *APE1*, *hOGG1* and *Rad51* polymorphisms and the response to radiotherapy demonstrated no association of polymorphisms of *APE1*, and *hOGG1* genes but both SNPs (*rs1813220, rs1801321*) of *Rad51* showed tumor as well as node response towards radiotherapy are presented in Table 5. No genotypes of *APE1* and *hOGG1* were significantly associated with response to radiotherapy after 3 months of evaluation (Chi square test). Positive association of *Rad51* (rs18013220) SNP with heterozygous G/C genotype was noted with poor response of tumor towards radiotherapy (p=0.025). The homozygous recessive C/C genotype of rs18013221 SNP of *Rad51* demonstrated positive association with poor response of both tumor and nodes towards radiotherapy (p=0.007 and p=0.022).

Association of APE1, hOGG1, Rad51 gene polymorphisms with risk of toxicity effects of radiotherapy in HNC patients

We observed no significant association between

Table 3. Univariate Analysis of Candidate SNPs of *APE1, hOGG1, RAD51* Genes and Radiation Induced Skin Reactions and Mucositis in Head and Neck Cancer Patients

Gene Name (SNP)	Genotype	Skin Reaction ≤1 n=243	Skin reaction >1 n=107	Odds Ratio (OR) 95% CI	p value	Oral mucositis ≤2 n=162	Oral mucositis >2 n=188	Odds Ratio (OR) 95% CI	p value
APE1 (rs1130409)	TT	225	97	1 (Reference)		150	184	1(Reference)	
	TG	15	6	0.91 (0.34-2.43)	0.864	11	9	0.66 (0.26-1.65)	0.381
	GG	3	4	3.09 (0.67-14.08)	0.144	1	5	4.07 (0.47-35.26)	0.201
hOGG1 (rs1052133)	CC	104	46	1 (Reference)		67	83	1(Reference)	
	CG	77	34	0.99 (0.58-1.69)	0.995	56	55	0.79 (0.48-1.29)	0.355
	GG	62	27	0.98 (0.55-1.74)	0.957	39	50	1.03 (0.61-1.75)	0.898
RAD51 (rs1801320)	GG	137	65	1 (Reference)		91	111	1(Reference)	
	GC	92	35	0.80 (0.49-1.30)	0.375	60	67	0.91 (0.58-1.42)	0.697
	CC	14	7	1.05 (0.40-2.73)	0.914	11	10	0.74 (0.30-1.83)	0.522
RAD51 (rs1801321)	GG	136	41	1 (Reference)		99	78	1 (Reference)	
	GT	78	41	1.74 (1.04-2.91)	0.034*	52	67	1.63 (1.02-2.61)	0.039*
	TT	29	25	2.85 (1.50-5.41)	0.001*	11	43	4.96 (2.40-10.25)	<0.0001*

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance $p< 0.05$; *, Indicates significant Odds Ratio ($p<0.05$), p value determined based on χ^2

Table 2. The List of Candidate Genes Selected in the Present Study with Details of PCR and RFLP Procedures Including Primers and Restriction Enzymes and Expected Products of Selected Genes.

Gene Genotype	rs number	Amino acid/ nucleotide change	Primer Sequence Forward/Reverse	PCR product size	Enzyme / Digestion conditions	Dominant (Wild type)	Heterozygous	Recessive (Mutant)
APE1 codon-148 exon-5 (T2197G)	rs1130409	Asp148Glu (T>G)	FP:5'-CTG TTT CAT TTC TAT AGG CTA-3' RP:5'- AGG AAC TTG CGA AAG GCT TC-3'	164 bp	BfaI 37°C for 16h	144 bp, 20 bp	164 bp, 144 bp, 20 bp	164 bp
hOGG1 codon-326 exon-7 (C1245G)	rs1052133	Ser326Cys (C>G)	FP:5'- CTG TTC AGT GCC GAC CTG CGC CGA -3' RP: 5' ATC TTG TTG TGC AAA CTG AC -3'	247bp	MboII 37°C for 16h	224 bp, 23 bp	247 bp 224 bp 23 bp	247 bp
RAD51 5'UTR (G135C)	rs1801320	(G>C)	FP:5'- TGG GAA CTG CAA CTC ATC TGG -3' RP:5'- GCG CTC CTC TCT CCA GCA G -3	157 bp	MvaI 37°C for 16h	86 bp, 71 bp,	157 bp, 86 bp, 71 bp,	157 bp
RAD51 5'UTR (G172T)	rs1801321	(G>T)	FP: 5'- TGG GAA CTG CAA CTC ATC TGG -3' RP:5'- GCT CCG ACT TCA CCC CGC CGG -3'	131 bp	NgoMIV 37°C for 16h	110 bp, 31 bp	131 bp, 110 bp, 21 bp	131 bp

Table 5. Association between Genotypes of *APE1, hOGG1, RAD51* Genes with Tumor and Node Response in Head and Neck Cancer Patients towards Radiotherapy.

Gene Name (SNP)	Genotype	Tumor Response		Risk Ratio	p value	Node Response		Risk Ratio	p value
		CR, n=289	PR/NR, n=61	95% CI		CR , n=282	PR/NR, n=68	95% CI	
APE1 (rs1130409)	TT	269	53	1 (Reference)		259	63	1(Reference)	
	TG	15	6	2.03 (0.75-5.47)	0.161	18	3	0.68 (0.19-2.39)	0.554
	GG	4	3	3.80 (0.82-17.50)	0.085	5	2	1.64 (0.31-8.67)	0.557
hOGG1 (rs1052133)	CC	124	26	1 (Reference)		120	30	1(Reference)	
	CG	90	21	1.11 (0.58-2.10)	0.741	85	26	1.22 (0.67-2.21)	0.505
	GG	75	14	0.89 (0.43-1.81)	0.748	77	12	0.62 (0.30-1.29)	0.203
RAD51 rs1801320	GG	173	29	1 (Reference)		170	32	1(Reference)	
	GC	90	29	1.92 (1.08-3.41)	0.025*	96	31	1.71 (0.98-2.98)	0.056
	CC	18	3	0.99 (0.27-3.59)	0.993	16	5	1.66 (0.56-4.85)	0.354
RAD51 rs1801321	GG	153	24	1 (Reference)		147	30	1 (Reference)	
	GT	98	21	1.36 (0.72-2.58)	0.338	98	21	1.05 (0.56-1.93)	0.876
	TT	38	16	2.68 (1.29-5.54)	0.007*	37	17	2.25 (1.12-4.51)	0.022*

SNP, Single nucleotide polymorphism; CR, Complete Response; PR, Partial Response; NR, No Response; RR, Risk ratio; CI, Confidence interval; Significance $p< 0.05$; *, Indicates significant Odds Ratio ($p<0.05$), p value determined based on χ^2

Table 4. Association between Genotypes of *APE1, hOGG1, RAD51* Genes with Tumor Stage and Tumor Grade in Head and Neck Cancer Patients

Gene Name (SNP)	Genotype	Tumor stage		OR	p value	Histological Grade		OR	p value
		T1, T2 n=168	T3, T4 n=182	95% CI		I, II n=123	III, IV n=227	95% CI	
APE1 (rs1130409)	TT	154	168	1 (Reference)		112	210	1(Reference)	
	TG	12	9	0.68 (0.28-1.67)	0.41	6	15	1.33 (0.50-3.53)	0.562
	GG	2	5	2.29 (0.43-11.98)	0.325	5	2	0.21 (0.04-1.11)	0.067
hOGG1 (rs1052133)	CC	71	21	1 (Reference)		53	97	1(Reference)	
	CG	51	60	3.97 (2.15-7.34)	<0.0001*	38	73	1.04 (0.62-1.75)	0.853
	GG	46	43	3.16 (1.66-5.99)	0.0004*	32	57	0.97 (0.56-1.68)	0.922
RAD51 rs1801320	GG	99	103	1 (Reference)		71	131	1(Reference)	
	GS	60	67	1.07 (0.68-1.67)	0.755	44	83	1.02 (0.64-1.62)	0.925
	CC	5	16	3.07 (1.08-8.71)	0.034*	8	13	0.88 (0.34-2.22)	0.788
RAD51 rs1801321	GG	86	91	1 (Reference)		63	114	1 (Reference)	
	GT	56	63	1.06 (0.66-1.69)	0.796	40	79	1.09 (0.66-1.78)	0.725
	TT	26	28	1.01 (0.55-1.87)	0.954	20	34	0.93 (0.49-1.76)	0.846

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance $p< 0.05$; *, Indicates significant Odds Ratio ($p<0.05$), p value determined based on $\chi 2$

Table 6. Association of *APE1, hOGG1, RAD51* Gene Polymorphisms with Risk of Skin Reaction after Radiotherapy in Head and Neck Cancer Patients

Gene /SNP	Genotypes	All Patients	Radiosensitive patients	OR 95% CI	p value
APE1	TT	322	299	1 (Reference)	
(rs1130409)	TG	21	11	0.56 (0.26-1.18)	0.132
	GG	7	5	0.76 (0.24-2.44)	0.657
hOGG1	CC	150	134	1 (Reference)	
(rs1052133)	CG	111	96	0.96 (0.67-1.38)	0.859
	GG	89	85	1.06 (0.73-1.55)	0.728
RAD51	GG	202	172	1 (Reference)	
rs1801320	GG	127	122	1.12 (0.81-1.55)	0.461
	GS	21	21	1.17 (0.62-2.22)	0.621
RAD51	CC	177	147	1 (Reference)	
rs1801321	GG	119	116	1.17 (0.83-1.64)	0.35
	GT	54	52	1.15 (0.74-1.79)	0.509

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on χ^2

genetic variants of *APE1* and *hOGG1* and the development of increased acute skin toxicity after radiotherapy. The logistic regression analysis in current study showed that *APE1*, *hOGG1* and *Rad51* polymorphisms presented no association to skin reaction in patients of HNC after giving radiotherapy (Table 6). The Odds ratios with 95% confidence intervals of the patients with skin reactions like acute dermatitis with recessive allele of *APE1* (rs1130409) OR=0.76 95% CI: 0.24-2.44; p=0.657, *hOGG1* (rs1052133) OR=1.06 95% CI: 0.73-1.55; p=0.728, *Rad51* (rs1801320) OR=1.17 95% CI: 0.62-2.22; p=0.621; and (rs1801321) OR=1.15 95% CI: 0.74-1.79; p=0.509. The ORs with 95% CI of heterozygous variant alleles of *APE1* OR=0.56 95% CI: 0.26-1.18; p=0.132, *hOGG1* OR=0.96 95% CI: 0.67-1.38; p=0.8959, *Rad51* (rs1801320) OR=1.12 95% CI: 0.81-1.55; p=0.461, and (rs1801321) OR=1.17 95% CI: 0.83-1.64; p=0.350 which showed no association with toxicity skin reactions after exposure to radiation in HNC patients. Univariate analysis of an association of *APE1, hOGG1* and *Rad51* polymorphisms demonstrated no association of polymorphisms of *APE1, hOGG1* or *Rad51* genes with oral mucositis in HNC patients after giving radiotherapy (Table 7). The Odds ratio of patients experiencing oral mucositis (>2) with recessive GG genotype of *APE1* (*rs1130409*) was OR=0.32 95% CI: 0.06-1.58; p=0.164); and heterozygous T/G genotype (OR=0.70 95% CI: 0.34-1.43; p=0.338). Similarly OR of *hOGG1* (rs1052133) recessive (G/G) and heterozygous (C/G) genotypes were OR=1.13 95% CI: 0.77-1.66; p=0.526 and OR=1.14 95% CI: 0.79-1.64; p=0.457 respectively. The ORs with 95% CIs of *Rad51* gene SNPs are (*s181320*) recessive C/C genotype: (OR=1.20 95% CI: 0.62-2.29; p=0.3576) heterozygous G/C genotype: (OR=1.19 95% CI: 0.86-1.65; p=0.0.286) (*rs181321*) recessive T/T genotype: (OR=1.32 95% CI: 0.84-2.05; p=0.218) and heterozygous G/T genotype: (OR=1.27 95% CI: 0.90-1.80; p=0.159) which showed non-significant association with oral mucositis toxicity after radiotherapy given in HNC patients.

Table 7. Association of *APE1, hOGG1, RAD51* Gene Polymorphisms with Risk of Mucositis after Radiotherapy in Head and Neck Cancer Patients

Gene /SNP	Genotypes	All Patients	Radiosensitive patients	OR 95% CI	p value
APE1	TT	322	282	1 (Reference)	
(rs1130409)	TG	21	13	0.706 (0.34-1.43)	0.338
	GG	7	2	0.32 (0.06-1.58)	0.164
hOGG1	CC	150	119	1 (Reference)	
(rs1052133)	CG	111	101	1.14 (0.79-1.64)	0.457
	GG	89	80	1.13 (0.77-1.66)	0.526
RAD51	GG	202	160	1 (Reference)	
rs1801320	GC	127	120	1.19 (0.86-1.65)	0.286
	CC	21	20	1.20 (0.62-2.29)	0.576
RAD51	GG	177	129	1 (Reference)	
rs1801321	GT	119	119	1.27 (0.90-1.80)	0.159
	TT	54	52	1.32 (0.84-2.05)	0.218

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on χ^2

Discussion

Radiotherapy is a curative treatment for many cancers and also for palliation of tumor specific symptoms. However, exposure of patients with malignant tumors to radiation may cause adverse after effects to the normal tissues and organs. In HNC patients when normal cells adjacent to cancer target tumors are exposed to radiation it causes severe acute toxicities such as mucositis, dermatitis, dysphagia, odynophagia and late toxicities like xerostomia, osteoradionecrosis and subcutaneous skin fibrosis, burning mouth syndrome. Genetic variations have proved the genetic susceptibility of an individual towards radiation induced adverse reactions and such understanding can help to understand treatment response and toxicity profile of radiotherapy. The SNPs of DNA repair genes are one of the important components of genetic variability which may alter the repair ability of damaged DNA of normal cells caused by radiation therapy resulted into severe toxicity to the normal cells. Several other epidemiological studies on SNPs of different DNA repair pathway genes described their role in determining susceptibility towards after effects of radiotherapy in cancer patients [18, 28-31]. Furthermore there remained a scope to explore further role of SNPs of base excision repair and homologous recombination repair genes in depicting normal tissue toxicity in response to radiotherapy in HNC patients. Therefore, in this study, we evaluated possible associations of SNPs of the DNA repair genes, *APE1*, *hOGG1* and *Rad51*, with the risk of developing acute after-effects in normal tissue in response to radiotherapy. We did not find association of genotypic variations of base excision repair genes such as *APE1* and *hOGG1*with the risk of developing skin reactions and oral mucositis in HNC patients. However, when we studied two SNPs (*rs1801320, rs1801321*) of *Rad51*with univariate analysis, we observed significant association of *rs1801320* polymorphism with developing risk of radiation induced skin dermatitis and oral mucositis in HNC patients treated with radiotherapy. No extensive research have been carried out to signify the polymorphisms in *APE1*, *hOGG1* and *Rad51* genes and their association with radio-toxicity with head and neck cancer or other malignancies.

Studies on *APE1* gene polymorphisms and their association with cancer suggested increased toxicity effects in response to radiotherapy. The *Asp148Glu* genotype polymorphism in *APE1* codon 148 associated with an increased risk of radiation induced toxicities in lung cancer [32-34]. Another studies found significant protective association of *APE1148Glu* polymorphism with acute side effects after radiotherapy in breast cancer patients [25]. The *rs1052133 SNP* of *hOGG1* was negatively associated with primary toxicity effects at the end of radiotherapy in patients with nasopharyngeal carcinoma [35]. However, other studies stated contradictory outcomes with no association of *rs1130409* and *rs1052133 SNPs* of *APE1* and *hOGG1*genes with radiation induced toxicities in breast, esophageal and laryngeal cancers [27, 35-37]. Our findings on association of *SNPs* of *APE1* and *hOGG1* genes with radiation induced after effects also corroborated with other studies showing non-significant association with radio-toxicity [11]. The *Rad51* gene with *rs1801320* and *1801321 SNPs* was studied earlier for their predictive role in acute adverse events caused by radiotherapy in different cancers including lung cancer [32], rectal cancer [38], and breast cancer [39]. However, limited studies demonstrated association of rs1801320 SNP of *Rad51*in HNC patients to develop oral mucositis and dysphagia in response to radiotherapy [22], while other studies reported no association of *rs1801320* and *rs1801321 SNPs* of *Rad51* with radio-toxicity in HNC patients [11]. Conversely, we observed significant association of *rs1801321 SNP* of *Rad51* with development of oral mucositis and skin reactions in normal tissue of HNC patients treated with radiotherapy. When we analyzed clino-pathological parameters such as tumor stage and histopathological tumor grade, and its association with polymorphisms of *APE1, hOGG1* and *Rad51* gene by multivariate analysis, we noticed that higher tumor stage were significantly associated with variant 326Cys genotype of *hOGG1* (p=0.0004) and 135C genotype of *Rad51* gene (p=0.034). We also noted significant association heterozygous 135 G/C genotype (p=0.025) of *rs1801320 SNP* with poor tumor response and 172T genotype (p=0.022) of *rs1801321 SNP* of *Rad51* with poor tumor and node response to radiotherapy in HNC patients.

In conclusion, our findings are significant for DNA repair gene *Rad51* (*rs1801320* and *rs1801321*) *SNPs* and their relation with severe risk of adverse toxicity reactions in normal tissue of HNC patients from India treated with radiotherapy. These results suggest that genetic polymorphisms in homologous recombination repair pathway genes contribute to the toxicity reactions in normal tissue in response to radiotherapy. To the best of our knowledge, this is the prime attempt to investigate association between SNPs of RAD51 with radiation induced toxicities in HNC patients of rural Indian population.

Author Contribution Statement

Concept: AKG, SJB, KDD, RAG, Design: KDD, SJB, AKG, Experimental Studies: SRK, ALM, KDD Clinical studies: AKG, RAG, Data analysis: KDD, AKG, Statistical analysis: KDD, Manuscript preparation: KDD, SJB, AKG, RAG. All authors read and approved the final manuscript.

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The study protocol was approved by protocol committee of Krishna Vishwa Vidyapeeth (Deemed to be University).

Ethics Committee Approval

The study protocol was approved by Institutional Ethics Committee of Krishna Vishwa Vidyapeeth 'Deemed to be University', Karad.

Abbreviations

HNC: Head and Neck Cancer
APE1: Apurinic/apyrimidinic endonuclease 1
hOGG1: 8-oxoguanine DNA glycosylase 1
HRR: Homologus recombination repair
PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
SNP: Single Nucleotide Polymorphism
DNA: Deoxyribose Nucleic Acid
aRT: Adjuvant Radiation Therapy
CRT: Concurrent Chemoradiation
BER: Base excision repair
SSBs: Single strand breaks
DSBs: Double strand breaks
IMRT: Intensity modulated radiation therapy
RTOG: Radiation Therapy Oncology Group
RECIST: Response Evaluation Criteria in Solid Tumors
GTV: Gross tumor volume
CTV: Clinical Target Volume
PTV: Planning target volume
CT: computed tomography
VRS: Verbal Rating Scales

Declaration of Conflict of interest

The authors declare that they have no competing financial or any other conflict of interests that could have appeared to influence the work reported in this paper.

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