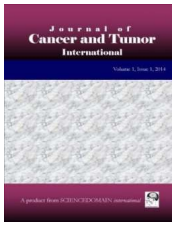

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The Relationship between Single Nucleotide Polymorphisms of Gene XRCC1 and Toxicity Induced Radiation in Patients with Head and Neck Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author RBAS designed the study and wrote the protocol. Authors OAON and GLCV managed the literature searches and wrote the first draft of the manuscript. Author YAM did the genotyping analysis and managed the experimental process. Author JCDP classified effects from RT according RTOG score. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The head and neck cancer is one of the most common types and their treatment brings complications such as dermatitis, mucositis and dysphagia. Studies of genetic variations of patients are those that enable the identification of prognostic factors for treatment, generally based on greater risk of injury to healthy tissue.
Study Design: This study examined the association between single nucleotide polymorphisms (SNPs) of XRCC1 gene in patients with head and neck cancer with adverse reactions presented in

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normal tissues as result of radiotherapy.
Place and Duration of Study: The study was conduct at Pontifícia Universidade Católica de Goiás, and the patients were recruited at Hospital Araújo Jorge, Associação de Combate ao Câncer em Goiás, Radiotherapy Service.
Methodology: We evaluated 54 patients, through a retrospective study, based on data contained in records and teletherapy records of patients with this cancer who underwent radiotherapy for at least 5 years.
Results: The mean age of patients was 58.43±13.79 years and the mean dose was applied 64,02Gy. Regarding the acute and late toxicities, patients analyzed showed a higher frequency of low-grade morbidities when compared to high grade. For acute toxicity, patients presenting polymorphism rs1799782 had an increased risk for developing mucositis, but the other polymorphisms were not statistically significant for the development of these changes (dermatitis, xerostomia and mucositis) acute. Patients who have studied polymorphisms have no increased risk of developing chronic changes of the larynx and esophagus (P>.05). In relation to the suspension of radiotherapy, patients with polymorphism rs25487 had reduced risk to have treatment discontinued, while patients with polymorphism rs25489 have an increased risk.
Conclusion: Studies of genetic variants *XRCC1* gene family should continue, to develop mechanisms to determine the degree of radiosensitivity in risk organs in patients with head and neck tumor. Thus, the personalized treatment with ionizing radiation can be prescribed for patients decreasing complications and improving the effectiveness of treatment and quality of life of patients.

Keywords: Head and neck cancer; XRCC1; adverse effects; radiotherapy; radiosensitivity.

1. INTRODUCTION

The head and neck cancer is one of the most common types of human cancer, with an annual incidence of approximately 600,000 cases worldwide[1], and Brazil, according to the Ministry of Health, 19,000 new cases are diagnosed each year[2]. Its high morbidity is related to the disease and the treatment performed, and the median survival is 50.1% in five years, data with little improvement over the past 20 years [1-3].

Cancer is a genetic disease whose onset and progression involve steps in which the DNA lesions result in new mutations [4]. Recent publications have shown the detection of polymorphisms in various tumor suppressor genes and proto-oncogenes, where minimal changes contribute to the development of tumors [5]. These polymorphisms contribute both to the amplification and activation of proto-oncogenes and for mutations that lead to loss and / or inactivation of tumor suppressor genes alleles. Such structural changes can occur in regions responsible for the regulation or activity of the catalytic domain of the protein, leading to activation of proto-oncogenes [6].

Among the modalities of treatment for head and neck cancer stands out radiotherapy (RT), in which more than 50% of cancer patients have performed this treatment at some stage of the disease [1]. RT acts in the formation of free radicals from the ionization of water molecules. These radicals cause various DNA damage such as, nucleotide loss, and loss or modification of nitrogenous bases, single or double breaks of DNA, which, if not repaired or reconditioned incorrectly can lead to cell apoptosis during mitosis [7].

The disruption in treatment has the ability to reduce local control in considerable proportions. However, the skin radiosensitivity and other target organs is a major cause of treatment interruption. The intensity of these side effects is genetically determined from individual to individual, with notable variations. Two important genes described in the literature in this regard are: XRCC1 (X-ray cross complementing factor 1) and P53 according to their important signaling roles in breaking the double-stranded DNA [8,9].

The acute toxicity of organs at risk is defined as the toxicity from the moment of start of radiation therapy to the ninetieth day after treatment. Since the late toxicity of those structures is considered between 90 days to 5 years after treatment, and the assessment is based on RTOG classification system (Radiation Therapy Oncology Group) [10]. A large number of patient factors, tumor, cellular, molecular and treatment contributes to the diversity of the response to ionizing radiation provided by RT. According to all these factors, it is established that genetic differences of each patient to be responsible for

the variability of the radiosensitivity of normal tissue in radiation treatment [11].

The radiosensitivity of normal tissue in the patient is determined as a characteristic that is the result of a polygenic interactions in cellular pathways diferentes [12], in which the single nucleotide polymorphisms (SNPs) that affect cell growth, may be potential biomarkers to determine the form of normal tissue response after RT [13].

DNA exposed to ionizing radiation has its chromatin altered and this is detected by sensor proteins, which point to the protein kinases of the affected cell that there is a change of the cellular genetic material which needs repair [14]. The XRCC1 gene encompasses domains known as BRCT1 and BRCT2 (C-terminal domain of a breast cancer susceptibility protein), wherein these domains fulfill important and different roles in repair pathway. The BRCT1 domain is the most conserved evolutionarily, being necessary for cell survival after DNA methylation damage, although its exact function is not yet fully understood. It interacts with regulatory proteins of the group of poly (ADP-ribose) polymerase, PARP-1 and PARP-2, which are activated during damage to the genetic material, limiting their activities to regulate gene transcription. The BRCT1 contains a binding site for PARPs enzymes which maintain the integrity of the genome, participating in the repair by base excision. Thus, in response to activation of PARP-1 by breaking single DNA band (SSB - Single Stranded DNA Breaks), XRCC1 is recruited to the rupture sites of chromosomal DNA helices by its BRCT domain [9,15].

But the XRCC1 domain, BRCT2, stabilizes the bond with another protein, DNA ligase III (Lig III). However, damage to the genetic material sensitizes not essential quantities BRCT2, it is proposed that the cells have dependent repair pathways operating XRCC1 specifically to the field BRCT1. Thus, the BRCT2 domain and Lig III protein are dispensable in this direction, in which the BRCT1 domain is essential according to their interactions with PARPs that determine stability genome. With such prospects, it is important to study XRCC1 polymorphisms that modify their BRCT1 domain and can thus change your links involved in this way to control the DNA strand breaks. These genetic changes when expressed in patients undergoing radiotherapy, may represent a factor in radiosensitivity of normal tissues [9,14,15].

Answering the single or double strand break of DNA, the XRCC1 activation requires coordinated events including the detection and signaling of these DNA lesions and the sequential recruitment of repair enzymes. The XRCC1 is a protein that coordinates the assembly repair of damaged local complex. It interacts with the enzyme components kinase polynucleotide (PNK), which processes DNA terminal, and B polymerase (pol b), which assists in breaking repair single strand, in ways that are still being studied. The XRCC1 located DNA replication foci and directly interacts with PCNA (Proliferating Cell Nuclear Antigen), which binds XRCC1 to the progression of DNA replication, being kidnapped by this interaction with PCNA for DNA replication points in order to facilitate the repair of possible SSB with greater efficiency during the S phase of the cell cycle. The literature meant that XRCC1 is phosphorylated by the kinase CK2, and the phosphorylation site in the linker region between domains BRCTs. This phosphorylation is responsible for stimulating the interaction of XRCC1 these complex repair [16,17].

As presented, the BRCTs domains (BRCA1 and BRCA2) of XRCC1 gene have operations in order to mediate a network of protein-protein interactions of damage repair pathways by base excision. Furthermore, studies show XRCC1 strongly stimulates the phosphorylation of p53-Ser15 protein by DNA-PK enzyme [18]. The p53 function has been described in the literature about its role in the control of apoptotic pathway and also its various correlations between polymorphisms of the gene with clinical radiosensitivity in normal tissues have been proven [19].

The p53 protein is related to the delay of the cell cycle for maintaining genome stability [20]. Through its N-terminal portion of p53 modulates the expression of several target genes involved in numerous cellular processes such as the stoppage of the cell cycle, interrupting its division and promoting apoptosis of cells [11]. Accordingly, the detection of the interaction between XRCC1 and P53 may have an important role in the changes of normal tissue affected by radiation according possible polymorphisms that modify these genes [18,19].

Thus, according to the XRCC1 function, which stimulates the activity of DNA-PK enzyme for phosphorylation of p53, a polymorphic copy of the XRCC1 gene may change the pattern of phosphorylation of p53, causing changes in the

pathway. Because these changes in the XRCC1 gene may make changes both in the repair pathway as the apoptotic pathway, individuals who carry polymorphic copies of XRCC1 could, therefore, have increased risk for carcinogenesis and radiosensitivity [15,16,21].

Thus, the aim of this study was to evaluate the association between single nucleotide polymorphisms (SNPs) of XRCC1 gene in patients with head and neck cancer with adverse reactions presented in normal tissues as a result of radiotherapy.

2. EXPERIMENTAL DETAILS

Clinical information of patients undergoing radiotherapy were collected from records of radiotherapy/ teletherapy and records of the Medical Records Department, Hospital Araújo Jorge (HAJ) of the Associação de Combate ao Câncer em Goiás (ACCG) of patients with cancer of the head and neck treated with radiotherapy. It was selected 54 patients with histopathologic diagnosis of cancer of the head and neck nonmetastatic, with no other diagnosis of cancer or prior radiotherapy, which started treatment at Radiotherapy Sector HAJ, the ACCG. Adverse reactions caused by radiotherapy were analyzed and sorted acute morbidity scoring criteria of the RTOG and late morbidity of RTOG/ EORTC. Inclusion criteria were: patients with histological diagnosis of head and neck cancer referred to the Radiotherapy Department of the HAJ to perform adjuvant radiotherapy; patients with no other diagnosis of cancer or prior radiotherapy and patients who agreed to sign the Instrument of Consent Form (ICF) to participate in the study. The exclusion criteria in the study were patients who developed previous cancers elsewhere; patients who evolved to death during treatment; patients referred for radiotherapy services external to HAJ and patients who did not agree to sign the consent form.

Thus, all patients included in the study signed the informed consent before obtaining the biological sample. Peripheral blood was collected and all the material was stored in appropriately labeled tubes and stored at -80℃ for later DNA extraction, DNA integrity and quantification to analyze the selected polymorphisms. Genomic DNA was quantified using the NanoDrop bioanalisador DNA (ThermoScientific, California, USA). The DNA integrity was analyzed on 0.8% agarose gel and photodocumentation Molecular Imager Gel Doc XR System (Bio-Rad Laboratories, USA).

Polymorphisms of the XRCC1 gene were analyzed by microarray technique, and the following SNPs analyzed: rs1799782, rs25487, rs25489, rs25490, rs25496, rs2307177, rs201967712, rs2307182, rs2307191, rs144559135, rs2228487, rs146168662, rs2307184, rs141783396, AX83022862, as present in the panel Axiom®Exome319 (Affymetrix, Inc California, USA).

To analyze the data, all the information provided on the forms of teletherapy and the medical records of patients diagnosed with head and neck cancer were analyzed using logistic regression with the software SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA), for Windows®. The data generated by the microarrays were translated using the *Genotyping Console Software version 4.2* (Axiom®Exome, Affymetrix, Inc California, USA). Univariate analysis between allele frequencies of SNPs and the degree of acute and chronic effects were measured by odds ratio (OR) and 95% confidence interval. A p-value of 0.05 was considered statistically significant for the study.

3. RESULTS AND DISCUSSION

It was evaluated 54 records, reviewed on different days to be avoided selection biases. The classification RTOG was performed by an experienced radiation oncologist. The average age of patients was found 58.4±13.79 years, 43 (79.6%) males and 11 (20.4%) female patients (Table 1). The average dose applied was 64.02±6.67 Gy (Table 4.1). The clinical staging of patients was conducted between the range I to IV (Table 1). Of the patients analyzed, 15 (27.8%) denied family history of cancer, 12 (22.2%) reported family history of cancer elsewhere (other than the head and neck) and 1 (1.9%) patient reported family history of head and neck cancer. The other 26 (48.1%) patients had no such information in their files (Table 1).

As to life habits, 46 (85.2%) patients had a history of smoking and 5 (9.3%) refused, 28 (51.9%) had a history of alcoholism and 22 (40.7%) patients denied. Evaluated for prior diagnosis of diabetes mellitus, 38 (70.4%) patients had this diagnosis and 7 (13.0%) patients, denied. Some patients were excluded from these counts have not had such information in their files (Table 1).

Table 1. Distribution of patients according to epidemiological, clinical and morphological variables

Variable	n	%
Age (mean ± SD)	58.43±13.79	
Gender		
Male	43	79.6
Female	11	20.4
Family history of cancer		
Absent	15	27.8
Present (head and neck)	1	1.9
Other tumor sites	12	22.2
No information*	26	48.1
Diabetes Mellittus		
Yes	38	70.4
No	7	13.0
No information*	9	16.6
Smoking		
Yes	46	85.2
No	5	9.3
No information*	3	5.5
Alcoholic habit		
Yes	28	51.9
No	22	40.7
No information*	4	7.4
Histology		
SCC	53	98.1
Others	1	1.9
Primary Site		
Oral cavity	8	14.8
Oropharynx	9	16.7
Hypopharynx	3	5.6
Primary hidden	1	1.9
Supraglottis	3	5.6
Glottis	24	44.4
Infraglottis	3	5.6
Transglottic	3	5.6
Differentiation		
I	9	16.7
II	30	55.6
III	12	22.2
NOS	3	5.6
Staging		
I	22	40.7
II	5	9.3
III	13	24.1
IVa	13	24.1
IVb	1	1.9
Affected lymph nodes		
Present	12	22.2
Absent	42	77.8

Legend: n: number of patients; %: Percentage of the total; SD: standard deviation; SCC: squamous cell carcinoma; NOS: not otherwise specified.

** Count patients were excluded due to lack of information in some records*

The mean treatment duration (in days) was 56.3±8.1 days, and 23.0% of patients the treatment interrupted due to complications as the adverse effects presented (Tables 4 and 4.1). For each side effect evaluated, the division was made between the degree presented by the patients, and then stratified into two groups with different degrees ≥2 and <2 determined respectively as high and low grade RTOG groups for adverse effects in radiotherapy (Tables 2 and 3).

Regarding the acute toxicity (from the beginning of RT up to 90 days after treatment), patients analyzed showed higher frequency morbidities low grade when compared to high grade. Modifications were analyzed in the skin (dermatitis), mucosa (mucositis) and dysphagia (pharyngeal / laryngeal and esophageal), and the values described in Table 2, based on the RTOG classification system.

As for late toxicity (between 90 days and 5 years after treatment), this study also showed a higher frequency of low-grade morbidities compared to similar high-grade morbidities, 44 patients had low-grade changes in the pharynx / esophagus and 30 patients laryngeal, contrasting with 8 patients showed changes / pharyngeal and esophageal 11 patients larynx, both high grade, following the RTOG system (Table 3).

In this study, 23 patients (42.6%) had treatment interrupted after reporting low radiation resistance, with adverse effects related to treatment. Among patients treated, 30 (55.6%) underwent prior surgery, and partial or total laryngectomy, lesion resection and neck dissection frequently modalities. The response to radiotherapy was effective in 51 (94.4%) patients analyzing the response after 2 months of treatment, they were found without disease progression (Tables 4 and Table 4.1).

In our work we associate genotypes based on the studied polymorphisms and adverse effects presented by each patient due to radiotherapy. Treatment discontinuation was also taken into account for probable statistical correlations with polymorphisms and adverse effects. In all 54 patients, the genotypes of 43 individuals were obtained, and the 15 SNPs analyzed only the rs141783396 got no data on genotyping. Adverse events were analyzed that are constant in radiotherapy, such as dermatitis, mucositis, xerostomia and esophagus and larynx changes in 42 patients, since one of the patients with genotype obtained did not provide sufficient data for statistical analysis. These effects were compared with genotypes using logistic regression.

Through microarray technique, polymorphisms XRCC1 gene were analyzed and evaluated SNPs were rs1799782, rs25487, rs25489, rs25490, rs25496, rs2307177, rs201967712, rs2307182, rs2307191, rs144559135, rs2228487, rs146168662, rs2307184 and AX83022862 (Table 5). These SNPs were present in 43 patients, with only differences in the proportions of their alleles, which varied according to each SNP (Table 5). SNPs rs1799782, rs25487, rs25489, rs25490, rs25496, rs2307182, and rs146168662 rs201967712 that have different frequencies of their alleles obeyed the Hardy-Weinberg principle. As for the SNPs rs2307177, rs2307191, rs144559135, rs2228487, rs2307184 and AX83022862 it could not determine whether they obeyed or not the Hardy Weinberg Principle because all patients had only one type of allele, which prevented the establishment or not of Principle (Table 5).

Table 2. Distribution of acute morbidity in low and high high school RTOG

Degree of toxicity	Skin		Mucous		Pharynx / Esophagus		Larinx	
Acute	n	(%)	n	(%)	n	(%)	n	(%)
LG (<2)	35	(66)	23	(82.1)	44	(84.6)	38	(84.4)
HG (≥2)	18	(34)	5	(17.9)	8	(15.4)	7	(15.6)

Abbreviations: RTOG = Radiation Therapy Oncology Group. High grade = HG (≥2). Low grau = LG (<2).

Table 3. Distribution of chronic morbidity in low and high high school RTOG

Chronic toxicity grade	Pharynx / Esophagus		Larinx	
	n	(%)	n	(%)
LG (<2)	44	(84,6)	30	(73,2)
HG (≥2)	8	(15,4)	11	(26,8)

Abbreviations: RTOG = Radiation Therapy Oncology Group. High grade = HG (≥2). Low grau = LG (<2).

Table 4. Frequency of therapeutic modalities

Variables	n	(%)
RT interruption		
Yes	23	42.6
No	31	57.4
Prior Surgery		
Yes	30	55.6
No	24	44.4
Total dose RT (Gy)		
≤5.000 cGy	1	1.9
>5.000 cGy	53	98.1
Evolution		
NED	38	70.4
Progression	1	1.9
Follow-up loss	4	7.4
Death related to CA	2	3.7
Recurrence	8	14.8
Metastasis	1	1.9
Radiotherapy		
Answer 2 months after treatment		
NED	51	94.4
Residual Disease	2	3.7
Disease progression	1	1.9

Legenda: RT= radiotherapy; NED= No evidence of disease, CA= cancer

Table 4.1. Frequency of therapeutic modalities

Variables	Mean	SD
Follow-up (months)	51,5	± 23,9
Applications RT	32,2	± 3,3
Total dose cGy	6402,2	± 667,9
RT Duration (days)	56,3	± 8,1
RT interruption (days)	9,0	± 4,4

Table 6 shows the results of the relationship between polymorphisms of XRCC1 and acute side effects on healthy tissue. Patients who had polymorphism rs1799782 shown to have increased risk for development of acute mucositis (*P* = .034; OR = 30.0; 95% CI = 1.30 to 693.13), and patients with other polymorphisms did not show correlation with adverse effects of RT. The polymorphisms analyzed showed no correlation with the development of xerostomia and acute dermatitis (*P*> .05).

Table 7 describes the association data between the side effects of acute larynx, pharynx / esophagus and polymorphisms of XRCC1. Patients with the analyzed polymorphisms did not show an increased risk for the development of these events (*P*> .05).

Table 8 shows the association between chronic side effects, XRCC1 polymorphisms and response 2 months after RT. Patients with polymorphisms analyzed do not present an increased risk of developing chronic changes of the larynx and esophagus (P> .05).

When analyzing the presence of side effects after 2 months of radiation therapy, it became apparent that the vast majority of patients (n = 40) showed low-grade changes, in contrast to a much smaller number of patients (n = 3) presented high grade changes. But none of the analyzed polymorphisms correlated with chronic side effects (*P*> .05) (Table 8).

Table 9 shows the association between the suspension of radiotherapy and studied polymorphisms. Patients with reduced risk polymorphism rs25487 had to have treatment interrupted where the allele "T" was crucial for the maintenance of radiotherapy (OR = 0.22, *P* = .025). Patients with XRCC1 rs25489 polymorphism had an increased risk of having the suspended radiotherapy; allele "T" determining the undesired response to treatment for patients with this SNP (OR: 13.63; P = .022). Individuals who have other polymorphisms analyzed showed no correlation with respect to discontinuation of radiation.

4. DISCUSSION

The aim of our study was to contribute to the elucidation of possible associations between genotype (single nucleotide polymorphisms, SNPs, the XRCC1 gene) of patients with head and neck cancer with acute and late actinic reactions of normal tissue presented due radiotherapy. For this we conducted a retrospective study having as database the adverse effects and clinical factors contained in medical records and patient records teletherapy with this cancer who underwent radiotherapy for oncological reference hospital and microarray assay for genotyping polymorphisms.

Epidemiological evidence shows that the incidence of head and neck cancer increases with age. For example, in Europe 98% of patients are over 40 years of age [22]. The mean age in our study was 58.4 years and only three patients (5.5%) were younger than 40 years, supporting the literature.

Table 5. Frequency of polymorphisms studied

SNPs *XRCC1*	n (%)	SNPs *XRCC1*	n (%)
rs1799782		***rs2307182***	
Homozygous minor (AA)	0 (0,0)	Homozygous minor (TT)	0 (0,0)
Heterozygous (AG)	8 (18,6)	Heterozygous (TC)	1 (2,3)
Homozygous major (GG)	35 (81,4)	Homozygous major (CC)	42 (97,7)
rs25487		***rs2307191***	
Homozygous minor (TT)	4 (9,3)	Homozygous minor (AA)	0 (0,0)
Heterozygous (TC)	18 (41,9)	Heterozygous (GA)	0 (0,0)
Homozygous major (CC)	21 (48,8)	Homozygous major (GG)	43 (100,0)
rs25489		***rs144559135***	
Homozygous minor (TT)	1 (2,3)	Homozygous minor (AA)	0 (0,0)
Heterozygous (TC)	6 (14,0)	Heterozygous (GA)	0 (0,0)
Homozygous major (CC)	36 (83,7)	Homozygous major (GG)	43 (100,0)
rs25490		***rs2228487***	
Homozygous minor (CC)	0 (0,0)	Homozygous minor (TT)	0 (0,0)
Heterozygous (TC)	3 (7,0)	Heterozygous (CT)	0 (0,0)
Homozygous major (TT)	40 (93,0)	Homozygous major (CC)	43 (100,0)
rs25496		***rs146168662***	
Homozygous minor (GG)	0 (0,0)	Homozygous minor (AA)	0 (0,0)
Heterozygous (AG)	3 (7,0)	Heterozygous (AG)	1 (2,3)
Homozygous major (AA)	40 (93,0)	Homozygous major (GG)	42 (97,7)
rs2307177		***rs2307184***	
Homozygous minor (GG)	0 (0,0)	Homozygous minor (TT)	0 (0,0)
Heterozygous (TG)	0 (0,0)	Heterozygous (GT)	0 (0,0)
Homozygous major (TT)	43 (100,0)	Homozygous major (GG)	43 (100,0)
rs 201967712		***AX-83022862***	
Homozygous minor (TC)	1(2,3)	Homozygous minor (AA)	0 (0,0)
Heterozygous (AG)	1 (2,3)	Heterozygous (CA)	0 (0,0)

The average total dose used for treatment of the patients was 6402.2 (±667.9) cGy, divided into 32.2 (±3.3) sessions lasting an average total treatment of 56.3 (±8.1) days. Oncologists have been cautious in prescribing radiation therapy for patients with skin and mucous disease, and its complications are causes of treatment discontinuation. Some clinical factors such as the type of treatment, radiation dose, pretreatment symptoms, age and comorbidities are associated with the development of adverse effects [23]. Therefore, the development of mechanisms to determine the degree of radiosensitivity of risk organs in patients with head and neck tumor is necessary for the prescribed radiation dose is individualized in order to prevent undesirable side effects, with improved tumor control.

The individual variability in radiosensitivity is large in cancer patients. Single base polymorphisms in genes involved in DNA repair and protection against reactive oxygen species (ROS) may be responsible for these cases of radiosensitivity.

The change of XRCC1 function through its gene polymorphisms cause changes in its signaling function by modifying their role in maintaining the integrity of the genome repair pathway for base excision. With these modifications, healthy cells prone to become the most common adverse events in patients with squamous cell carcinoma of the head and neck, in response to ionizing radiation provided by radiation therapy, if expressing as mucositis, dermatitis, dysphagia, odynophagia these patients [23]. In this sense, these SNPs of XRCC1 may indicate changes predisposing factors for patients undergoing radiotherapy and thus may require the suspension of treatment.

Table 6. Association between the acute side effects of skin, mucosa, xerostomia and XRCC1 polymorphisms

	***Radiation Therapy Oncology Group* – RTOG**																			
SNPs XRCC1	**Acute Skin RTOG**							**Xerostomia**							**Acute Mucous RTOG**						
	LG		**HG**		**P**	**OR**	**IC95%**	**LG**		**HG**		***P***	**OR**	**IC95%**	**LG**		**HG**		***P***	**OR**	**IC95%**
	n	**(%)**	**n**	**(%)**				**N**	**(%)**	**n**	**(%)**				**n**	**(%)**	**n**	**(%)**			
rs1799782																					
Major (GG)	21	87.5	13	72.2				10	90.9	5	71.4				15	93.8	1	33.3			
Heterozig (AG)+ Minor (AA)	3	12.3	5	27.8	0.222	0.69	0.54-13.19	1	9.1	2	28.6	0.301	4.00	0.29-55.47	1	6.3	2	66.7	0.034*	30.00	1.30-693.13
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs25487																					
Major (CC)	9	37.5	11	61.1				6	54.5	3	42.9				8	50.0	1	33.3			
Heterozig (TC)+ Minor (TT)	15	62.5	7	38.9	0.133	0.38	0.11-1.34	5	45.5	4	57.1	0.630	1.60	0.24-10.81	8	50.0	2	66.7	0.600	2.00	0.15-26.73
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs25489																					
Major (CC)	22	91.7	13	72.2				8	72.7	6	85.7				13	81.3	2	66.7			
Heterozig (TC)+ Minor (TT)	2	8.3	5	27.8	0.112	4.23	0.71-25.02	3	27.3	1	14.3	0.520	0.44	0.04-5.41	3	18.8	1	33.3	0.574	2.17	0.14-32.53
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs25490																					
Major (TT)	22	91.7	18	100.0				9	81.8	7	100.0				14	87.5	3	100.0			
Heterozig (CT)+ Minor (CC)	2	8.3	-	0,0	1.000	-	-	2	18.2	-	0,0	1.00	-	-	2	12.5	-	0.0	1.000	-	-
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs25496																					
Major (AA)	24	100.0	16	88.9				11	100.0	7	100.0				15	93.8	3	100.0			
Heterozig (AG)+ Minor (GG)	-	0.0	2	11.1	1.000	-	-	-	-	-	0,0	1.00	-	-	1	6.3	-	0.0	1.000	-	-
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs2307182																					
Major (CC)	24	100.0	17	94.4				11	100.0	7	100.0				16	100.0	3	100.0			
Heterozig (TC)+ Minor (TT)	-	0.0	1	5.6	1.000	-	-	-	0.0	-	0.0	-	-	-	-	0.0	-	0.0	-	-	-
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs201967712								11	61.1	-	0.0										

	***Radiation Therapy Oncology Group* – RTOG**																			
SNPs XRCC1	**Acute Skin RTOG**							**Xerostomia**							**Acute Mucous RTOG**					
	LG		**HG**		**P**	**OR**	**IC95%**	**LG**		**HG**		***P***	**OR**	**IC95%**	**LG**		**HG**		***P***	**OR**	**IC95%**
	n	**(%)**	**n**	**(%)**				**N**	**(%)**	**n**	**(%)**				**n**	**(%)**	**n**	**(%)**			
Major (GG)	23	95.4	18	100.0				11	100	7	100.0				16	100.0	3	100.0			
Heterozig (AG)+ Minor (AA)	1	4.2	-	0.0	1.000	-	-	-	0.0	-	0.0	-	-	-	-	0.0	-	0.0	-	-	-
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			
rs146168662																					
Major (GG)	23	95.4	18	100.0				11	100	7	100.0				16	100.0	3	100.0			
Heterozig (AG)+ Minor (AA)	1	4.2	-	0,0	1.000	-	-	-	0.0	-	0.0	-	-	-	-	0.0	-	0.0	-	-	-
Total	24	100.0	18	100.0				11	100.0	7	100.0				16	100.0	3	100.0			

*Abbreviations: RTOG = Radiation Therapy Oncology Group. HG = High grade RTOG≥2. LG = Low grade RTOG<2. OR = Odds Ratio. IC = Confidence Interval. * P = .05*

Table 7. Association between acute side effects of the larynx, pharynx / esophagus and polymorphisms of XRCC1

SNPs *XRCC1*	***Radiation Therapy Oncology Group*– RTOG**													
	Acute Larynx RTOG							**Acute pharynx / esophagus RTOG**						
	LG		**HG**		***P***	**OR**	**IC95%**	**LG**		**HG**		***P***	**OR**	**IC95%**
	n	**(%)**	**N**	**(%)**				**n**	**(%)**	**n**	**(%)**			
rs1799782														
Major (GG)	22	78.6	6	85.7				27	79.4	7	87.5			
Heterozig (AG)+ Minor (AA)	6	21.4	1	14.3	0.679	0.61	0.06-6.10	7	20.6	1	12.5	0.604	0.55	0.06-5.25
Total	28	100.0	7	100.0				34	100.0	8	100.0			
rs25487														
Major (CC)	15	83.3	13	76.5				14	41.2	6	75.0			
Heterozig (TC)+ Minor (TT)	3	16.7	4	23.5	0.613	1.54	0.29-8.18	20	58.8	2	25.0	0.101	0.23	0.04-1.33
Total	18	100.0	17	100.0				34	100.0	8	100.0			
rs25489														
Major (CC)	22	78.6	6	85.7				30	88.2	5	62.5			
Heterozig (TC)+ Minor (TT)	6	21.4	1	14.3	0.675	0.61	0.06-6.10	4	11.8	3	37.5	0.096	4.50	0.77-26.45
Total	28	100.0	7	100.0				34	100.0	8	100.0			
rs25490														

SNPs *XRCC1*	*Radiation Therapy Oncology Group*– RTOG													
	Acute Larynx RTOG							Acute pharynx / esophagus RTOG						
	LG		HG		*P*	OR	IC95%	LG		HG		*P*	OR	IC95%
	n	(%)	N	(%)				n	(%)	n	(%)			
Major (TT)	28	100.0	7	100.0				32	94.1	8	100.0			
Heterozig (CT)+ Minor (CC)	-	0.0	-	0.0	-	-	-	2	5.9	-	0.0	1.00	-	-
Total	28	100.0	7	100.0				34	100.0	8	100.0			
rs25496														
Major (AA)	26	92.9	7	100.0				32	94.1	8	100.0			
Heterozig (AG)+ Minor (GG)	2	7.1	-	0.0	1.00	-	-	2	5.9	-	0.0	1.00	-	-
Total	28	100.0	7	100.0				34	100.0	8	100.0			
rs2307182														
Major (CC)	28	100.0	6	85.7				34	100,.	7	87.5			
Heterozig (TC)+ Minor (TT)	-	0.0	1	14.3	1.00	-	-	-	0.0	1	12.5	1.00	-	-
Total	28	100.0	7	100.0				34	100.0	8	100.0			
rs201967712														
Major (GG)	28	100.0	7	100.0				33	97.1	8	100.0			
Heterozig (AG)+ Minor (AA)	-	0.0	-	0.0	-	-	-	1	2.9	-	0.0		-	-
Total	28	100.0	7	100.0				34	100.0	8	100.0			
rs146168662														
Major (GG)	28	100	6	85.7				34	100.0	7	87.5			
Heterozig (AG)+ Minor (AA)	-	0	1	14.3	-	-	-	-	0.0	1	12.5	1.00	-	-
Total	28	100.0	7	100.0				34	100.0	8	100.0			

*Abbreviations: RTOG = Radiation Therapy Oncology Group. HG = High grade RTOG≥2. LG = Low grade RTOG<2. OR = Odds Ratio. IC = Confidence Interval. * P = .05*

Table 8. Association between chronic side effects, XRCC1 polymorphisms and response after RT

	***Radiation Therapy Oncology Group* – RTOG**																
***XRCC1* SNPs**	**Chronic Larynx RTOG**							**Chronic esophagus RTOG**							**Follow-up 2 months after RT**				
	LG		**HG**		***P***	**OR**	**95% IC**	**LG**		**HG**		***P***	**OR**	**95% IC**	**LG**		**HG**		***P***
	N	**(%)**	**n**	**(%)**				**n**	**(%)**	**n**	**(%)**				**n**	**(%)**	**n**	**(%)**	
rs1799782																			
Major (GG)	19	82.6	7	87.5				29	82.9	6	85.7				32	80.0	3	100.0	
Heterozig (AG)+ Minor (AA)	4	17.4	1	12.5	0.747	0.68	0.06-7.16	6	17.1	1	14.3	0.853	0.81	0.08-7.97	8	20.0	-	0.0	0.530
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs25487																			
Major (CC)	11	47.8	6	75.0				18	51.4	2	28,				19	47.5	2	66.7	
Heterozig (TC)+ Minor (TT)	12	52.2	2	25.0	0.196	0.30	0.05-1.84	17	48.6	5	71.4	0.281	2.65	0.45-15.52	21	52.5	1	33.3	0.482
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs25489																			
Major (CC)	20	87.0	6	75.0				30	85.7	5	71.4				34	85.0	2	66.7	
Heterozig (TC)+ Minor (TT)	3	13.0	2	25.0	0.436	2.22	0.30-16.56	5	14.3	2	28.6	0.365	2.40	0.36-15.94	6	15.0	1	33.3	0.421
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs25490																			
Major (TT)	22	95.7	7	87.5				33	94.3	6	85.7				37	92.5	3	100.0	
Heterozig (CT)+ Minor (CC)	1	4.3	1	12.5	0.439	3.14	0.17-57.08	2	5.7	1	14.3	0.437	2.75	0.21-35.33	3	7.5	-	0.0	0.801
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs25496																			
Major (AA)	23	100.0	6	75.0				32	91.4	7	100.0				37	92.5	3	100.0	
Heterozig (AG)+ Minor (GG)	-	0.0	2	25.0	**-**	**-**	-	3	8.6	-	0.0	1.00	-	-	3	7.5	-	0.0	0.801
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs2307182																			
Major (CC)	23	100.0	7	87.5				34	97.1	7	100.0				39	97.5	3	100.0	

	***Radiation Therapy Oncology Group* – RTOG**																	
***XRCC1* SNPs**	**Chronic Larynx RTOG**							**Chronic esophagus RTOG**							**Follow-up 2 months after RT**				
	LG		**HG**		***P***	**OR**	**95% IC**	**LG**		**HG**		***P***	**OR**	**95% IC**	**LG**		**HG**		***P***
	N	**(%)**	**n**	**(%)**				**n**	**(%)**	**n**	**(%)**				**n**	**(%)**	**n**	**(%)**	
Heterozig (TC)+ Minor (TT)	-	0.0	1	12.5	1.00	**-**	-	1	2.9	-	0.0	1.00	-	-	1	2.5	-	0.0	0.930
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs201967712																			
Major (AA)	23	100.0	8	100.0				35	100.0	6	85.7				39	97.5	3	100.0	
Heterozig (AG)+ Minor (GG)	-	0.0	-	0.0	-	-	-	-	0.0	1	14.3	1.00	-	-	1	2.5	-	0.0	0.930
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	
rs146168662																			
Major (GG)	23	100.0	7	87.5				35	100.0	6	85.7				39	97.5	3	100.0	
Heterozig (AG)+ Minor (AA)	-	0.0	1	12.5	1.00	-	-	-	0.0	1	14.3	1,00	-	-	1	2.5	-	0.0	0.930
Total	23	100.0	8	100.0				35	100.0	7	100.0				40	100.0	3	100.0	

*Abbreviations: RTOG = Radiation Therapy Oncology Group. HG = High grade RTOG≥2. LG = Low grade RTOG<2. OR = Odds Ratio. IC = Confidence Interval. * P = .05*

Table 9. Association between the suspension of radiotherapy and studied polymorphisms

	Interruption of RT						
	No		Yes		*P*	OR	95% IC
	n	%	n	%			
Genotype *XRCC1* rs1799782							
Major (GG)	21	80.8	14	82.4			
Heterozig (AG)+ Minor (AA)	5	19.2	3	17.6	0.896	0.90	0.18-4.38
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs25487							
Major (CC)	9	34.6	12	70.6			
Heterozig (TC)+ Minor (TT)	17	65.4	5	29.4	0.025*	0.22	0.06-0.83
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs25489							
Major (CC)	25	96.2	11	64.7			
Heterozig (TC)+ Minor (TT)	1	3.8	6	35.3	0.022*	13.63	1.46-127.15
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs25490							
Major (TT)	24	92.3	16	94.1			
Heterozig (CT)+ Minor (CC)	2	7.7	1	5.9	0.820	0.75	0.06-8.98
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs25496							
Major (AA)	24	92.3	16	94.1			
Heterozig (AG)+ Minor (GG)	2	7.7	1	5.9	0.820	0.75	0.06-8.97
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs2307182							
Major (CC)	26	100.0	16	94.1			
Heterozig (TC)+ Minor (TT)	-	0.0	1	5.9	1.000	-	-
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs201967712							
Major (GG)	25	96.2	17	100.0			
Heterozig (AG)+ Minor (AA)	1	3.8	-	0.0	1.000	-	-
Total	26	100.0	17	100.0			
Genotype *XRCC1* rs146168662							
Major (GG)	26	100.0	16	94.1			
Heterozig (AG)+ Minor (AA)	-	0.0	1	5.9	1.000	-	-
Total	26	100.0	17	100.0			

In our study, the SNP rs1799782 associated with increased risk of developing acute mucositis (P = 0.03, OR = 30.00 and 95% CI = 1.30-693.13). The development of acute reactions (oral mucositis, erythema and dysphagia) was associated with genetic polymorphisms, such as the exchange that occurs in the XRCC1 gene c.1196A> L, which is related to the detection of radiosensitivity of normal tissue. Patients with allele XRCC1-399Gln may have a higher probability of developing high-grade dysphagia and other changes that demonstrate the occurrence of acute toxicity [24]. In our study, the analyzed polymorphisms were not associated with increased risk of developing chronic complications of larynx and esophagus, they had no significant statistical data. These findings showed the need for further study of the gene in question and could be associated with clinical radiosensitivity.

In addition to patients with head and neck cancer, XRCC1 polymorphisms were also studied in other types of cancers. The association of single nucleotide polymorphisms in XRCC1 with late side effects induced by radiation in patients with prostate cancer treated with radiation therapy may also be significant. In another study, three polymorphisms probably would bring larger changes of the XRCC1 gene were analyzed (Arg194Trp; Arg280His; Arg399Gln) as well as the adverse effects presented by each patient group according to the genotypes shown [25]. Contrary to expectations

for the study said, the XRCC1 rs25489 polymorphism (Arg280His) demonstrated statistically significant relationship as a protective factor in the degree of late toxicity after radiotherapy in patients with prostate cancer. In our study, it was also evident when comparing rs25487 (Gln399Arg) and the suspension of radiotherapy, where the chance of having suspended radiotherapy shows that this polymorphism may be a protective factor to adjacent normal tissue.

According to published studies, the XRCC1 polymorphisms should be analyzed even more broadly to be responsible for maintaining the function of the gene in the apoptosis pathway, providing support for a possible radiosensitivity or radioresistance of the patients, and prior knowledge of the analyzed genetic profile contribute to a personalized treatment in radiotherapy [26-29].

5. CONCLUSION

The present study showed that the patients who had polymorphism rs1799782 had increased risk for development of acute mucositis, while the other evaluated polymorphisms showed no significant relevance to the development of other acute events analyzed. Moreover, none of the polymorphisms showed statistically significant correlation to the increased risk of developing chronic changes of the larynx and esophagus.

As for the analysis of the suspension of radiation because of radiosensitivity, this study demonstrated that the polymorphism rs25487 is associated with a reduced risk to have treatment discontinued, unlike polymorphism rs25489, which showed increased risk of having the suspended radiotherapy.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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