

The Relevance of Regenerating Gene 1a Polymorphisms to Radiation Sensitivity and Survival of Nasopharyngeal Carcinoma Receiving Radiotherapy in a Southern Chinese Population

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Objective: Gene polymorphism is closely related to tumor development, therapeutic response and prognosis. The relationship between regenerating gene 1A (Reg1A) polymorphism and nasopharyngeal carcinoma (NPC) is unclear. This retrospective study aimed to analyze the association between Reg1A polymorphisms and metastasis, radiation sensitivity and survivals in patients with NPC.

Methods: A total of 308 patients who had received radiotherapy at the Affiliated Xinhua Hospital, Hainan Medical College, between January 2010 and December 2018 with NPC, were enrolled for assessment of Reg1A polymorphisms through direct DNA sequencing.

Results: In the polymorphism of gene REG1A, patients with rs10165462 20CC genotype had later T stages (OR = 4.051, 95% CI: 1.775–9.244, P = 0.001), whereas carriers with rs12072 2922CC genotype had earlier T stages (OR = 1.891, 95% CI: 1.018–3.514, P = 0.044) after adjustments for age and gender, respectively. Among rs10165462 20 C/T polymorphism, 20TT wild-type was associated with better radiation response (P = 0.0019), and multivariate analysis showed that it was the only genotype of polymorphism that was significantly associated with better radiation response (OR = 0.265, 95% CI: 0.096–0.727, P = 0.01). Patients with the 20TT wild-type had a better five-year overall survival (60.9%) rate and five-year progression-free survival (60.8%) than those with the 20CC genotype (41.8% and 39.4%, P = 0.01 and P = 0.004, respectively). Patients with variant alleles (CC + CT) had significantly poorer OS (45.2%) and PFS (41.8%) compared with wild-type (TT) carriers (60.9% and 60.8%; P = 0.037 and P = 0.015, respectively). As for rs12072, patients with variant alleles (TT + TC) had significantly adverse OS and PFS compared with wild-type (CC) carriers (62.5% vs 44.8% and 62.5% vs 42.9%; P = 0.024 and P = 0.027, respectively). Cox regression showed that rs10165462 20CT was the only prognostic factor for OS (HR = 1.642, 95% CI 1.038–2.598, P = 0.034) and PFS (HR = 1.705, 95% CI 1.080–2.692, P = 0.022).

Conclusion: Reg1A polymorphisms may be a predictor of radiation response, local invasion, OS and PFS in patients with NPC who undergo radiotherapy treatment.

Keywords: regenerating gene 1a, polymorphisms, radiation, sensitivity, nasopharyngeal, survival

Introduction

Nasopharyngeal carcinoma (NPC) is the most common cancer of the head and neck in the south of China.¹ More than 90% of NPC cases are diagnosed histologically as undifferentiated carcinoma. The five-year overall survival (OS) rate for NPC is around 70%. Recurrence and metastasis result from radiation resistance and are the main barriers

to survival.² Although treatment (radiotherapy with or without chemotherapy)^{3,4} is based on a patient's TNM stage rather than their genetic composition, significant inter-individual variability has been observed in radiation sensitivity and prognosis, which suggests that genetic susceptibility plays a role, and that the identification of the biomarkers of NPC may be useful for individual radiotherapy.^{5,6} Since research into novel biomarkers could help predict the curability of individual radiotherapy, it is, therefore, of vital importance.

Growing evidence suggests that genetic polymorphisms, most often single nucleotide polymorphisms (SNPs), influence individual sensitivity to radiotherapy and prognosis in a variety of tumors, although the underlying mechanisms are unclear.^{7,8} P53 polymorphism may influence individual responsiveness to chemoradiotherapy (CRT) for advanced head and neck cancer, ovarian cancer, and cervical cancer.⁹ DNA repair gene (X-ray repair cross-complementing 1, XRCC1; breast cancer susceptibility gene 1, BRCA1; and excision repair cross-complementing group 1, ERCC1) polymorphisms could alter DNA repair capacity and are, therefore, associated with CRT response and survival in lung cancer.¹⁰ The variant alleles of XRCC1 Arg399Gln are significantly associated with poor survival rates and the absence of pathologic complete response (pCR).^{11,12} ERCC1 (rs11615) C118T and C allele, for example, could predict the response to radiotherapy and chemotherapy as a basis for the individualized therapy of advanced esophageal cancer.^{13–16} They could also be used to help identify a subgroup of alleles that suggests patients with NPC who receive either radiotherapy (RT) or cisplatin plus RT have an excellent prognosis.¹⁷

Other studies have shown a close relationship between genotype and therapeutic response. For example, a polymorphism within the promoter of the transforming growth factor- β (TGF- β) gene has been found to increase radiation sensitivity in lung cancer,¹⁸ and coronin-2A rs1985859 and the putative marker FAM101A rs7955740 have been used to predict radiation sensitivity to preoperative chemo-radiotherapy (pCRT) in rectal cancer patients.¹⁹ In addition, ataxia telangiectasia-mutated gene (ATM) polymorphisms in the heterozygote state have been found to heighten clinical radiation sensitivity and clinical radioprotection in breast cancers.²⁰ The same result was also found in other studies.^{21–23}

In a recent study, polymorphisms in the promoter region of miR-34b/c rs4938723 significantly affected the CRT efficacy for locally advanced ESCC.²⁴ It is clear that

SNPs and SNP sets contribute to radiation sensitivity, so genetic variants hold promise as markers of individual radiation sensitivity.²⁵

The regenerating gene (Reg) was originally isolated in a study that regenerated rats' pancreatic islets and examined the acute phase reactants, lectins, anti-apoptotic factors, and growth factors for pancreatic β -islet cells and epithelial cells in the digestive system.²⁶ Reg1a is a member of the human Reg1 family (Reg I–IV). Initial studies indicated that it is involved in inflammatory diseases²⁷ and gastroenterological carcinogenesis.²⁸ Further studies demonstrated that Reg1a expression is associated with CRT response in patients with ESCC.²⁹ Our previous research showed that overexpression of Reg1a led to variations in the local progression and poor prognosis of NPC;³⁰ moreover, Reg1a (rs12072) polymorphisms have been found to increase the risk of developing NPC.³¹ Therefore, we hypothesized that there might be a link between the functional variants in the Reg1a gene and radiation sensitivity and prognosis in patients with NPC. The present research details a retrospective study that was conducted to verify the association between Reg1a polymorphisms, radiation sensitivity, and survival in southern Chinese patients with NPC. It is hoped that the findings of the study can provide a greater understanding of genetic biomarkers for radiation sensitivity.

Patients and Methods

Patients

A total of 308 patients with previously untreated, non-distant metastatic, newly histologically confirmed NPC who had received radiotherapy at the Affiliated Xinhua Hospital, Hainan Medical College, between January 2010 and December 2018 were enrolled in this retrospective study. The median age was 49.2 years (range 22–74 years) and the median follow-up time was 39.1 months (range 9.8–99.96 months). Staging and grading were employed according to current standard classifications.^{32,33} Table 1 summarizes the patient and clinical baseline data.

Clinical follow-up data were obtained through patients' medical records, for which we obtained written informed consent from each patient or an immediate family member. The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the

Table I Clinical and Pathological Characteristics, Responses to Radiotherapy, and Genotyping Analysis of Enrolled Patients

Parameters	Case	rs10165462(C/T)		rs117580393(G/T)		rs768985544(A/G)		rs12072(T/C)	
		Genotype Distribution ^a	P value	Genotype Distribution ^a	P value	Genotype Distribution ^a	P value	Genotype Distribution ^a	P value
Age (years)									
≤49	138	32/63/43	0.2864	0/4/166	0.2610	0/1/169	NA	26/72/72	0.2163
>49	170	40/92/38		0/1/137		0/0/138		12/72/54	
Gender									
Male	279	64/146/69	0.0679	0/5/274	NA	0/1/278	NA	33/136/110	0.0939
Female	29	8/9/12		0/0/29		0/0/29		5/8/16	
Pathology									
WHO II	44	8/23/13	0.378	0/1/43	NA	0/1/43	NA	8/19/17	0.2595
WHO III	264	64/132/68		0/4/260		0/0/264		30/125/109	
T stage									
T1-2	187	54/88/45	0.0177	0/4/183	NA	0/0/187	NA	20/77/90	0.0059
T3-4	121	18/67/36		0/1/120		0/1/120		18/67/36	
N stage									
N0	212	47/113/52	0.2964	0/4/208	NA	0/1/211	NA	25/108/79	0.0851
N+	96	25/42/29		0/1/95		0/0/96		13/36/47	
Radiation response			0.0019		NA		NA		NA
Sensitivity	281	63/150/68		0/5/276		0/1/280		38/129/114	
Resistance	27	9/5/13		0/0/27		0/0/27		0/15/12	

Notes: ^aMutant homozygote/heterozygote/wild homozygote; Hardy-Weinberg equilibrium (all $P > 0.05$).

Abbreviation: NA, not applicable.

Affiliated Xinhua hospital of Hainan Medical College and informed consent was taken from all the patients.

Treatment

All patients received radical radiotherapy through three-dimensional conformal intensity modulated radiation therapy (3DCRT). The median radiation dose was 72 Gy (range 70–78 Gy) at the primary site and 64.20 Gy (range 60–72 Gy) for lymph node metastasis, dosed at a daily fraction of 1.8 to 2 Gy five times per week. All patients were followed up for more than three months and underwent computerized tomography (CT) scans and nasopharyngeal/neck and nasopharyngeal endoscopies in order to evaluate treatment response during follow-up. Response was assessed three months after completion of radiotherapy.

Response Evaluation

Tumor response was defined, based on the new Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) from the World Health Organization (WHO), as complete response (CR), partial response (PR), stable disease (SD),

or progressive disease (PD). The objective response rate was defined by CR.

DNA Extraction and Genotyping

Based on the DNA sequences (GenBank ID: 5967) of the human Reg1a gene, six pairs of specific polymerase chain reaction (PCR) primers, covering the six exons, were designed using Primer Premier v5.0 software to amplify the exons (see Table 2). DNA extraction and genotyping was performed as previously described.³¹ In brief, genomic DNA was extracted from pre-treatment paraffin-embedded NPC tissue for genotyping by direct sequencing.

Amplification and Sequencing

The first PCR reaction was carried out with 2.5 µL of 10 × Good's buffer (Applied Biosystems, USA), 200 µM of dNTP, 1.5 µM of primer, 1.25 U of AmpliTaq Gold™ Polymerase (Applied Biosystems, USA), and about 20 ng of DNA (25 µL total volume). Thermal cycling was performed in a Veriti system (Applied Biosystems, USA) and consisted of an initial 5-minute denaturation step at 95°C, 35 cycles of 30

Table 2 Primer Sequences of PCR for the *Reg1a* Gene

Primer	Sequence (5'-3')	Product Length
REG1A-S1-F1	AAAGGCTCGTACTGGTGCC	637bp
REG1A-S1-R1	GAGACACCCACACCTTCAAATGTTTCTCTTGAGAGT	
REG1A-S1-F2	ATTTGAAGGTGTGGGTGTCTCAGAGGACCTTCCT	
REG1A-S1-R2	TGCTTGGGGATAGAGTGAAGTC	
REG1A-S2-F1	ACCCTGAGAGCCTCCTTTAATTG	661bp
REG1A-S2-R1	GATGCTGTCACTGACCACCAGGTTCTTTGTGCTG	
REG1A-S2-F2	TGGTGGTCAGTGACAGCATCATCACGGACATTACT	
REG1A-S2-R2	GAACCTCCTTCTTACTTCTCAAACC	
REG1A-S3-F1	TGAGTGACCACTGCCTCTGT	654bp
REG1A-S3-R1	TGGCTTTAGGACTCAGGACAAAAACCAACAT	
REG1A-S3-F2	TGTCCTGAGTCCTAAAGCCAGGAGGGTCAT	
REG1A-S3-R2	CCAGGCATCAGCTGTGGAA	

Notes: S1-F1/R1 is used for the first exon amplification and S1-F2/R2 is used for the second exon. After that, both the products are taken as a template and F1/R2 is used as a primer for overlap amplification and the first and second exon sequences are obtained by product sequencing. S2-F1/R1 is used for the third exon amplification and S2-F2/R2 is used for the fourth exon. After that, both the products are taken as a template, and F1/R2 is used as a primer to conduct overlap amplification and the third and fourth exon sequences are obtained by product sequencing. S3-F1/R1 is used for the fifth exon amplification and S3-F2/R2 is used for the sixth exon. After that, both the products are taken as a template, and F1/R2 is used as a primer to conduct overlap amplification and the fifth and sixth exon sequences are obtained by product sequencing.

Abbreviations: F, forward; R, reverse; S, slice.

seconds at 95°C, 30 seconds at 58°C, and a 40-second extension step followed by 5 minutes at 72°C. The second PCR was the same as the first except that about 2 µL product of the first amplification was used instead of 20 ng of DNA. The final PCR products were cleaned up and sequenced.

Statistical Analysis

Genotype and minor allele frequency for *Reg1a* were counted, and the genotyped data were analyzed using the PLINK statistical package (<http://pngu.mgh.harvard.edu/~purcell/plink>), version 1.07.³⁴ The genotypes in the control and case groups were tested for deviation from the Hardy-Weinberg equilibrium (HWE) using Fisher's exact test, and the odds ratio (OR) for each genotype was calculated. Analysis of single markers was performed using the PLINK toolset. The associations between SNP genotype and different clinic-pathological characteristics and radiation response were analyzed using a chi-square test or Fisher's exact test. Univariate and multivariate logistic regressions were conducted to evaluate the association of T stage and radiation response rate with variant genotypes (unconditional or after adjustment for clinic-pathological characteristics) and presented as odds ratio (OR) and 95%

confidence interval (CI). Linkage disequilibrium (LD) analyses, haplotype analyses and LD block construction were carried out using Haploview version 3.32 (Daly Lab, Broad Institute, MA, USA).³⁵

The primary endpoint was progression-free survival (PFS), and the secondary endpoint was OS. The duration of time to loco-regional relapse was measured from the date of the start of radiotherapy until the failure of documented treatment. PFS was assessed from the start of treatment to the first defined event of failure, ie, loco-regional relapse and/or distant metastasis in patients who completely responded to radiation therapy, as well as definite progression of disease in patients who partially responded. The duration of OS was calculated from the start of radiotherapy until death due to any cause or until the date of the last follow-up visit for patients who are still alive.

A Kaplan–Meier curve and Log rank test were used to compare OS and PFS in *Reg1a* SNPs. Cox proportional hazards modeling was conducted to evaluate prognostic factors for OS and PFS. Two-sided P values < 0.05 were considered statistically significant. The statistical analysis was performed using SPSS 19.0 (IBM, Armonk, NY, USA).

Results

Recurrence, Metastasis and Progression During the Follow-Up Period

During the follow-up period, recurrence and metastasis occurred in 17 (16.88%) cases (local relapse 4 cases, regional relapse 3 cases, local-regional relapse 4 cases, and distant metastasis 6 cases), and 27 cases that were assessed with resistance to radiotherapy were regarded as a progression of the disease. Analysis was not performed due to the small size of this category.

Detection of Reg1a Polymorphisms

Rs10165462 (20C/T; exon 1), rs117580393 (369G/T; exon 2), rs768985544 (1201A/G; exon 3), and rs12072 (2922T/C; exon 6) were detected in the Reg1a gene. Their distribution among the 308 patients is shown in [Table 1](#). The test showed that the Reg1a allele and genotype frequencies in each paired group conformed to the Hardy–Weinberg equilibrium; all were $P > 0.05$ (see [Supplementary Tables 1–5](#)). Linkage disequilibrium (LD) was not observed.

Association Between Reg1a Polymorphisms and Clinical Characteristics

Reg1a variant genotypes were detected in the patients. rs10165462 20C/T existed in 54 (CC), 88 (CT), and 45 (TT) cases and rs12072 2922T/C existed in 20 (TT), 77 (TC), and 90 (CC) cases in local early-stage patients (T1–T2); rs10165462 20C/T existed in 18 (CC), 67 (CT), and 36 (TT) cases, while rs12072 2922T/C existed in 18 (TT), 67 (TC), and 36 (CC) cases corresponding in local advanced-stage patients (T3–T4). There was a significant difference between local early-stage patients and advanced-stage patients at both loci ($P = 0.018$ and $P = 0.0059$, respectively). These results show that rs10165462 20C/T and rs12072 2922T/C variant genotypes are associated with local invasion in NPC.

Stratified analysis found that occurrence of the rs10165462 20CC genotype was significantly different compared with CT and TT ($P < 0.01$ respectively), and that patients with the 20CC genotype had a later T stage than those with CT and TT (OR = 3.652, 95% CI: 1.623–8.217, $P = 0.002$) and (OR = 4.051, 95% CI: 1.775–9.244, $P = 0.001$) after adjusting for age and gender. Conversely, carriers with the rs12072 2922CC genotype tended to have earlier T stages than TC and TT ($P < 0.05$ respectively), (OR = 2.020, 95% CI: 1.106–

3.692, $P = 0.022$) and (OR = 1.891, 95% CI: 1.018–3.514, $P = 0.044$) after adjusting for age and gender. These results indicate that the rs10165462 20CC genotype and the rs12072 2922CC genotype are contributors to and independent predictors of local invasion in NPC.

No association was found between the rs10165462 20C/T and rs12072 2922T/C variant genotypes and other clinical characteristics (all $P > 0.05$). Moreover, no statistically significant association was observed when comparing other Reg1a SNPs, including rs117580393 369G/T and rs768985544 1201A/G, with different clinical characteristics (all $P > 0.05$) (see [Supplementary Tables 1–5](#)).

Association of Reg1a Polymorphisms with Radiation Sensitivity

In this study, 281 cases were assessed as radiation sensitive, and 27 cases (including 17 PR cases, 6 SD cases, and 4 PD cases) were assessed as resistant three months after complete treatment. The total sensitivity rate was 91.23% (281/308) and the resistance rate was 8.77% (27/308) (see [Table 1](#)).

Variant genotypes of rs10165462 20C/T existed as follows: in radiation-sensitive patients there were 63 CC cases (22.42%), 150 CT cases (53.38%), and 68 TT cases (24.20%); in radiation-resistant patients there were 9 CC cases (33.33%), 5 CT cases (18.52%), and 13 TT cases (48.15%). Analysis of these results showed that Reg1a rs10165462 20C/T polymorphisms were significantly associated with radiation response ($X^2 = 13.410$, $P = 0.0019$). Stratified analysis results showed that occurrence of the rs10165462 20CT genotype was significantly different when compared with occurrence of the CC, TT, and CC + TT genotypes (all $P < 0.01$). Patients with the Reg1a rs10165462 20C/T CT genotype experienced significantly more frequent radiation response (OR = 0.275, 95% CI: 0.102–0.739, $P = 0.01$). Multivariate logistic regression analysis showed that the Reg1a rs10165462 20C/T genotype was also significantly associated with radiation response (OR = 0.265, 95% CI: 0.096–0.727, $P = 0.01$) after adjusting for other clinical-pathological factors, such as age, gender, T stage, N stage, pathology, and other Reg1a polymorphisms.

No statistically significant association was observed when comparing the other Reg1a variant genotypes with radiation response (all $P > 0.05$). Therefore, the Reg1a rs10165462 20C/T genotype was the only predictor for radiation response in NPC (see [Supplementary Tables 6 and 7](#)).

Association of Reg1a Polymorphisms with OS and PFS

The five-year OS and PFS rates of the patients was 49.5% and 47.1%, respectively (see [Supplementary Figure 1](#)). The five-year OS rate of patients with the rs10165462 20C/T variant genotype was 41.8% for the CC genotype, 53.6% for the CT genotype and 60.9% for the TT genotype (log-rank = 8.110, $P = 0.017$). Patients with the 20TT genotype had a better five-year OS rate than those with the 20CC genotype ($P = 0.01$). Individuals with variant alleles (CC + CT) (45.2%) had significantly poorer OS compared with wild-type (TT) carriers (60.9%) (log-rank = 4.340, $P = 0.037$).

The five-year PFS rate was 39.4% for CC, 48.4% for CT, and 60.8% for TT (log-rank = 8.510, $P = 0.014$); patients with the 20TT genotype had a better five-year PFS than those with the CC genotype ($P = 0.004$). Carriers with variant alleles (CC + CT) (41.8%) had significantly poorer PFS compared with wild-type (TT) carriers (60.8%) (log-rank = 5.963, $P = 0.015$). These results indicate that patients with NPC who carried the TT genotype had better five-year OS and PFS rates than those who carried the CC or CT genotypes (see [Figure 1](#)).

Similarly, the five-year OS rates of patients with the rs12072 2922C/T variant genotype were 67.1% for the CC

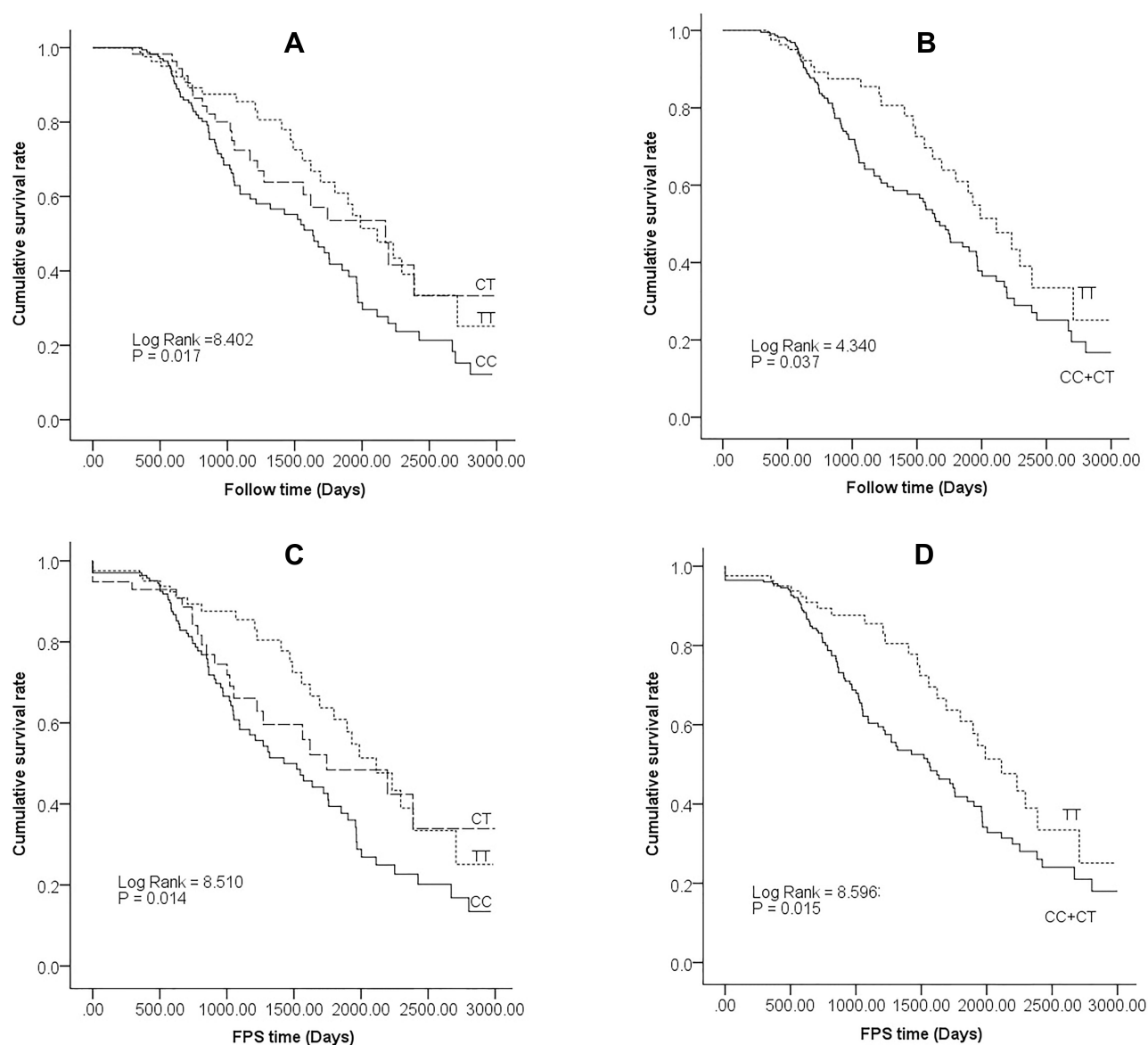


Figure 1 Survival rate curve of rs10165462 genotypes; (A) Overall survival rate curve for genotype TT, CT and CC, $P < 0.05$; (B) and wild-type TT and varied genotype CT + CC, $P < 0.05$; (C) Progression free survival rate curve for genotype TT, CT and CC, $P < 0.05$; (D) and wild-type TT and varied genotype CT + CC, $P < 0.05$.

genotype; 43.3% for the CT genotype, and 48.3% for the TT genotype (log-rank = 5.846, $P = 0.054$); however, patients with the CC genotype had a better OS rate than those with the CT genotype ($P = 0.017$). Patients with variant alleles (TT + TC) (44.8%) had significantly adverse OS rates compared with wild-type (CC) carriers (log-rank = 5.115, $P = 0.024$).

The five-year PFS rates of patients with the rs12072 2922C/T variant genotype were 62.5% for the CC genotype, 41.8% for the CT genotype, and 45.9% for the TT genotype. No significant difference was found when comparing the genotypes in the rs12072 2922C/T variant genotype (log-rank = 5.431, $P = 0.066$). Interestingly, patients with the CC genotype had a higher PFS rate than those with the CT genotype ($P = 0.022$). In addition, a significant difference was observed between those with the CC genotype and those with the TT + TC genotype (62.5% vs 42.9%) (log-rank = 4.919, $P = 0.027$). Patients with variant alleles (TT + TC) had a negative prognosis outcome compared with those with wild-type (CC) carriers (see [Supplementary Figure 2](#)). No statistically significant association with OS and PFS was observed in other Reg1a SNPs, including rs117580393 369G/T and rs768985544 1201A/G (all $P > 0.05$). This indicates that patients carrying the 20C/T and 2922T/C wild-type genotypes tend to have longer OS and PFS compared with those carrying other variant genotypes ($P < 0.05$).

Multivariate analysis showed that T stage (T1–2 vs T3–4) and rs10165462 20CT genotype were independent prognostic factors for OS (HR = 0.384, 95% CI 0.256–0.575,

$P = 0.0001$ and HR = 1.642, 95% CI 1.038–2.598, $P = 0.034$, respectively) and for PFS (HR = 0.401, 95% CI 0.269–0.599, $P = 0.0001$ and HR = 1.705, 95% CI 1.080–2.692, $P = 0.022$, respectively) when clinic-pathological characteristics, including age, gender, T stage, N stage, pathology, radiation sensitivity, rs10165462 20C/T, rs117580393 369G/T, rs768985544 1201A/G, and rs12072 2922T/C variant genotypes were entered into the Cox proportional hazards model. This suggests an association between Reg1a rs10165462 20C/T and OS and PFS and indicates that patients carrying the rs10165462 20CT genotype had significantly longer OS and PFS compared with those carrying the 20CC and 20TT genotypes (see [Table 3](#)).

Discussion

Accumulating evidence indicates that genetic variations are strongly associated with cell proliferation, disease progression, treatment response, and survival in various types of solid tumors.^{10,36} Previous studies have also observed an association between Reg1a polymorphisms and human cancers. Current research, however, is limited to the possible role of regulatory variants and some coding regions in the Reg1a gene in the development and progression of several types of pancreatic disease.³⁷ Our previous study showed that the Reg1a rs10702 2922C/T variant genotype increased the risk of developing NPC in a Cantonese population.³¹ The results of the present study indicate that Reg1a gene polymorphisms are not only involved in local invasion but also in treatment response and survival of patients with NPC.

Table 3 Multivariate Cox Regression Analyses of OS and PFS

Parameters	OS						PFS					
	B	SE	Wald	P	OR	95.0% CI	B	SE	Wald	P	OR	95.0% CI
Age	0.214	0.216	0.982	0.322	1.239	0.811–1.893	0.209	0.214	0.953	0.329	1.232	0.810–1.873
Gender	0.128	0.473	0.073	0.787	1.136	0.450–2.870	0.251	0.480	0.273	0.601	1.285	0.501–3.295
T stage	−0.957	0.206	21.530	0.000	0.384	0.256–0.575	−0.913	0.204	20.050	0.000	0.401	0.269–0.599
N stage	−0.338	0.220	2.371	0.124	0.713	0.464–1.097	−0.278	0.218	1.620	0.203	0.758	0.494–1.162
Pathology	−0.024	0.331	0.005	0.942	0.976	0.510–1.867	−0.161	0.340	0.224	0.636	0.852	0.438–1.657
Radiation Sensitivity	−0.396	0.380	1.088	0.297	0.673	0.320–1.416	−0.462	0.378	1.493	0.222	0.630	0.300–1.322
rs10165462(20CC)	0.375	0.318	1.396	0.237	1.455	0.781–2.712	0.473	0.314	2.263	0.132	1.605	0.867–2.972
rs10165462(20CT)	0.496	0.234	4.488	0.034	1.642	1.038–2.598	0.534	0.233	5.246	0.022	1.705	1.080–2.692
rs117580393	1.016	0.645	2.478	0.115	2.761	0.780–9.776	0.900	0.642	1.967	0.161	2.459	0.699–8.648
rs768985544	0.546	1.245	0.192	0.661	1.726	0.150–19.811	0.651	1.252	0.270	0.603	1.917	0.165–22.314
rs12072 (2922TT)	−0.165	0.320	0.264	0.607	0.848	0.453–1.589	−0.144	0.320	0.204	0.652	0.866	0.462–1.620
rs12072 (2922TC)	0.215	0.265	0.663	0.415	1.240	0.739–2.083	0.197	0.263	0.564	0.453	1.218	0.728–2.039

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.

Liu et al reported that patients with NPC who carried the TC genotype and T-allele had a later T stage (T3–T4) than those who did not.³⁸ Hao et al suggested that IFN- γ 13-CA-repeat polymorphism impacted the metastasis of NPC and contributed to an increased risk of lymph node metastasis and distant metastasis.³⁹ Guo et al observed that two loci in the AKT1 gene (rs3803300 and rs2494738 alone or combined) were associated with reduced risk of distant failure, especially in N2–3 patients carrying at least one variant allele.⁴⁰ Another study that explored the contribution of NOS3 variants to NPC progression revealed that NOS3 T-786C can reduce the development of regional lymph node metastasis.⁴¹ The results of the present study found that carriers of the Reg1a rs10165462 20CC genotype had a later T stage (T1–2 vs T3–4), while those with the Reg1a rs10702 2992CC genotype had an earlier T stage than those with other genotypes (rs10165462 20 CT + TT and rs10702 2992 CT + TT, alone or combined).

Two loci, rs10165462 and rs10702, are related to local invasion in NPC. Our previous research indicated that the overexpression of the Reg1a protein could accelerate this local invasion and stimulate T-stage progression from early to advanced,^{30,31} suggesting that the rs10165462 20CC and rs12072 2992CC genotypes may play a role in the local invasion of NPC. Further investigation is still needed to unravel the functional significance of these polymorphisms.

Gene polymorphism is strongly related to individual variations in radiation sensitivity in various tumors.⁴² Alsbeih et al reported that MDR1 G2677T and C3435T polymorphisms can be used to assess the response to radiotherapy of patients with NPC.⁸ The wide genotype GG of XRCC1 rs25489 and the wide genotype CC of 8-oxoguanine DNA glycosylase (OGG1) rs1052133 were positively and negatively associated, respectively, with the efficacy of radiotherapy on primary tumors.⁴³ Meanwhile, ERCC1 Cys8092Ala, HDM2 promoter T/G rs2279744 and T/A rs1196333, XRCC1 Codon399 Gln/Gln allele, and cyclin-dependent kinase inhibitor gene CDKN2A rs3088440 polymorphism have all been identified as independent predictors of response to radiotherapy on the primary tumor and cervical lymph node in NPC.^{44,45}

Alsbeih et al used polygenic polymorphism to predict radiation sensitivity and identified six SNPs that were more accurate than a single SNP as biomarkers to assess the efficiency of radiotherapy.⁸ The same result was observed in the catenin beta 1 genes (CTNNB1) rs1880481 and rs3864004 and glycogen synthase kinase 3-beta gene (GSK3 β) rs3755557 polymorphisms, which were

significantly associated with poorer efficacy of radiotherapy in patients with NPC.⁴⁶ A later study suggested that a sequence polymorphism in miR-608 could predict the local recurrence rate in patients with NPC undergoing radiotherapy.⁴⁷ Our data showed that the total radiation response rate in patients with NPC was 91.23%, and that, associated with REG1a rs10165462 20C/T heterozygous genotype alone, carriers of the REG1A rs10165462 20CT genotype had a higher response rate than carriers of the 20CC or 20TT genotype or a combination of the two (CT vs CC + TT, all $P < 0.01$). This result is consistent with previous findings and indicates that the rs10165462 20CT genotype in Reg1a might stimulate a potential signaling pathway to modulate the radiotherapy response of patients with NPC.

Tumor load influences the efficacy of radiotherapy, regardless of local lesion or metastasis. Here, we identified the role of the rs10165462 20CC genotype in facilitating local progression and reducing radiotherapy efficacy in NPC patients. The rs10165462 genetic variations were significantly correlated with radiation response. Moreover, multivariate analysis showed that the rs10165462 20CT genotype was the only influencing factor for radiation sensitivity after adjustments for other clinic-pathological factors. Therefore, rs10165462 20CT may be a potential regulator for moderating radiotherapy efficacy and could be used as a biomarker for radiation sensitivity. The rs10165462 20CT genotype, rather than other genotypes and SNPs in the Reg1a gene, plays a key role in the NPC progression and the efficacy of radiotherapy. Therefore, the C allele of rs10165462 20C/T is implicated as a potential marker for personalized medicine, and a patient that carries it may require more aggressive radiotherapy.

A high risk of disease progression and poor radiation sensitivity both contribute to the negative prognosis and survival of patients with NPC. There is growing evidence that gene polymorphisms that help identify patients with different risks for prognosis are strongly associated with treatment outcome.⁴⁸ CXCL12 rs1801157 polymorphism has been significantly associated with distant metastasis-free survival and PFS.³ In the current study, the five-year OS and PFS rates were 49.5% and 47.1%, respectively. The rs10165462 20C/T and rs10702 2992C/C variant genotypes had different OS and PFS rates, and these differences were significant. The C allele in rs10165462 20C/T and the T allele in rs10702 2992C/C can influence the OS and PFS rates of patients with NPC. These results are in accordance with the observations of previous studies and indicate that Reg1a SNPs are associated with the efficacy of radiotherapy and

survival in patients with NPC, although the mechanism itself remains unclear.

In the multivariate analysis, it was observed that rs10165462 20 CT and T stage were associated with OS and PFS rates, and, therefore, could be used as independent predictors of survival. This provides extremely strong evidence that Reg1a plays a crucial role in NPC prognosis, with the double effect of Reg1a gene polymorphisms enhancing local invasion and regulating radiation sensitivity; this finding provides new insight into the genetic basis of tumor cellular response to radiation. Reg1a gene polymorphisms may be used as pre-treatment biomarkers for identifying highly radiosensitive patients with NPC, leading to the customization of treatment protocols and improved treatment outcomes.

Our data suggest that Reg1a gene variation is closely related to radioresponsiveness and survival of nasopharyngeal carcinoma. The potential molecular biological mechanism may be that the change of bases at polymorphic sites of REG1A gene leads in turn to the variation of the gene sequence and function, and the latter responds to radiation differently through different functional pathways in cells, manifested as proliferation or apoptosis of tumor cells, thus affecting the survival and prognosis of NPC patients. Further study with larger samples and exploration of the molecular mechanism are both needed for more accurate assessment.

The current study has some limitations. Firstly, the patient sample was small, and the candidate genetic predictors require more definitive validation in an independent cohort. Larger population-based studies in different ethnic groups are necessary to further validate the role and mechanism of Reg1a SNPs. Secondly, a single gene was identified rather than a set of genes or pathways of Reg1a involved in NPC, and, as we know, radiation sensitivity may be the result of the combined effects of genes involved in different cellular pathways. Lastly, the mechanism by which Reg1a SNPs influence the efficacy of radiotherapy and survival in patients with NPC could not be fully understood, although doing so was beyond the scope of this study. In addition, the application of CT, inferior to Magnetic resonance imaging (MRI) in soft tissue resolution, may affect the accuracy of the assessment of radiation response in this study.

Conclusion

In conclusion, our study verified that Reg1a SNPs have a reliable association with local progression, radiation response, and treatment outcome in NPC in a southern Chinese population. Reg1a rs10165462 is a significant

risk factor for local invasion and serves as a potential predictor of radiation response and prognosis in patients with NPC who are being treated with radiotherapy.

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Disclosure

The authors declare that they have no competing interests.

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