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ORIGINAL ARTICLE

Influence of DNA repair *RAD51* gene variants in overall survival of non-small cell lung cancer patients treated with first line chemotherapy

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Abstract
Purpose Lung cancer continues to be the most frequent cancer with approximately one million people worldwide dying of this disease each year. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. The RAD51 protein is the key protein for homologous recombination, an evolutionarily conserved mechanism for DNA damage repair and the generation of genetic diversity. We conducted this study in order to investigate the effect of the *RAD51 G135C* polymorphism in treatment response to combined platinum taxanes/gemcitabine first line chemotherapy in NSCLC patients.
Methods We analysed *RAD51 G135C* polymorphism in 243 NSCLC patients using PCR–RFLP methodology.
Results There were no statistically significant differences between the groups of NSCLC patients with the different genotypes regarding tumour stage ($p = 0.232$). Our results indicate that the mean survival rates were statistically different according to the patient's genotypes. The group of patients carrying the C allele presented a higher mean survival rate than the other patients (56.0 months vs. 41.7 months; $p = 0.024$). Moreover, regarding smoking history, our results demonstrate that overall survival time differed significantly according to the patient's genotypes in smoker and ex-smoker individuals ($p = 0.034$). No statistically significant differences were found in the genotype frequencies and overall survival rate among non-smoker NSCLC patients ($p = 0.413$).
Conclusions This is the first study evaluating the effect of the *RAD51* G135C polymorphism in NSCLC patient survival. Our results suggest that *RAD51* genotypes could be useful molecular markers for predicting the clinical outcome of NSCLC patients.

Keywords RAD51 · Non-small cell lung cancer · DNA repair · Overall survival

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Introduction

Lung cancer remains a major worldwide health problem, being the most common form of cancer in the world, both in terms of incidence, 12.3% of all cancers, and mortality, representing 17.8% of the number of deaths caused by cancer [18]. In Europe, each year more than 150,000 new cases are diagnosed, but only 10% can be cured and enjoy long-term survival, mostly because of advanced stage detection. The incidence of lung cancer is higher in men and in older individuals. However, during the past decade, the incidence of this disease in females has increased, due to the change of smoking habits in women [1, 19]. While 90% of people with lung cancer have a smoking history, only 10–15% of chronic smokers develop lung cancer, suggesting factors in addition to smoking exposure are relevant

in the aetiology of this disease [45]. Age, smoking exposure, impaired lung function and family history have been identified as independent risk factors for this disease [1].

There are two major groups of lung carcinomas: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-small cell lung cancer accounts for approximately 80% of all lung cancers and includes epidermoid (squamous cell) carcinoma (which accounts for 25–40% of all lung cancers), adenocarcinoma, undifferentiated non-small cell lung cancer and large cell carcinoma [15].

Lung carcinogenesis is a multi-step process of progressive disorganization characterized by events over latent periods of time, resulting from exposure to environmental insults [4].

Maintenance of genetic stability requires the co-ordination of a network of pathways such as cell cycle checkpoint, DNA replication, DNA repair/recombination and programmed cell death. In response to DNA damage, cells arrest their cell cycle progression, thus providing time for repair, or activate programmed cell death—both responses preventing transmission of genetic instability [21, 22]. Double-strand breaks (BSBs) are considered the principal lethal DNA damage [2]. There are two distinct mechanisms in damage repair of mammalian cells, such as homologous recombination (HR) and non-homologous end joining (NHEJ) [8].

The human *RAD51* gene has a key role in the homologous recombination and DNA repair [33]. This gene is located at chromosome position 15q15.1 [38], a region that exhibits loss of heterozygosity in a large range of tumours, including lung, colorectal and breast cancers [43]. The protein (hRAD51) encoded by this gene is highly similar to *Escherichia coli* RecA and *Saccharomyces cerevisiae RAD51* [20] and has been suggested to play a role as a tumour suppressor gene [33]. Several studies have reported that mutations in genes involved in DNA repair and in the maintenance of genome integrity may be responsible for an increase of cancer risk [34].

Homologous recombination (HR) effects DNA repair through the interaction of free DNA ends with a homologous DNA sequence that is used as a template for the high-fidelity repair of the DSB. HR is thought to be particularly important in DNA repair occurring during cellular replication [34, 44, 46]. RAD51 is one of the key proteins for HR, and functions by forming nucleoprotein filaments on single-stranded DNA, mediating homologous pairing and strand exchange reactions between single- and double-strand stranded DNA during repair [41].

A single nucleotide polymorphism (SNP) in the 5′-untranslated region (5′-UTR) of the human *RAD51* gene, resulting in a G–C substitution at nucleotide 135 of the non-coding exon 1 has been described and referred to as G135C polymorphism [24]. The genetic variants of G135C polymorphism have been associated with breast [7] and gastric cancers [30].

Our purpose was to investigate the potential prognostic and predictive roles of *RAD51* G135C polymorphism in NSCLC patients treated with combined platinum taxanes/gemcitabine first line chemotherapy.

Materials and methods

Patients

We conducted a hospital-based study analysing 234 Caucasian individuals from the north region of Portugal with NSCLC, admitted in the Portuguese Institute of Oncology, Porto, Portugal, between 1999 and 2008, who underwent first line platinum and taxanes/gemcitabine-based chemotherapy regimens. Assessment of the tumour stage was based on the TNM system proposed by the American Joint Committee on Cancer (AJCC). The median age at diagnosis was 64 years with a mean age of 62.44 years (SD = 10.01). Patient clinical characteristics, obtained from medical records, are described in Table 1. Genomic DNA was extracted from blood samples by using QIAamp DNA Blood Mini Kit (QIAGEN). All samples were obtained with the informed consent of the participants prior to their inclusion in the study, according to the declaration of Helsinki.

Table 1 Patient clinical characteristics

Characteristic	No. of patients (N = 246)	%
Age		
Median, 64.00	246	100
Mean, 62.44 ± 10.01		
Gender		
Female	52	21.1
Male	194	78.9
Tobacco		
Non-smoker	65	26.4
Smoker/ex-smoker	181	73.6
Histologic type		
NSCLC epidermoid	92	37.4
NSCLC non-epidermoid	151	61.4
Others	3	1.2
Stage		
I	14	5.7
II	17	6.9
III	125	50.8
IV	90	36.6

PCR–RFPL assay for detection of *RAD51* G135C polymorphism

For detection of the *RAD51* G135C polymorphism, we used polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) according to a previously published protocol [24]. The PCR amplification was performed by using the following primers: forward (5′ TGGG AACTGCAACTCATCTGG-3′) and reverse (5′ GCGC TCCTCTCTCCAGCAG-3′). Conditions for PCR were an initial denaturation at 95°C for 5 min, followed by 35 cycles at 94°C for 1 min, 53°C for 30 s (annealing temperature), 72°C for 1 min, and ending with 72°C for 10 min. The resulting 157-bp product was incubated at 37°C/12–16 h (overnight) with 1 U of the restriction enzyme MvaI (Fermentas, ER0551). The restriction fragments were then visualized by 4% (p/v) agarose gel electrophoresis, with ethidium bromide staining. Three types of band patterns were obtained: will type homozygote (G/G), two bands corresponding to 71 and 86 bp; heterozygote (C/G), three bands corresponding to 157, 86 and 71 bp; and polymorphic homozygote (C/C), only one band with 157 bp (Fig. 1).

Statistical analysis

Analysis of data was performed using the computer software Statistical Package for Social Sciences (SPSS) for Windows (version 17.0). Differences in proportions were evaluated by the χ^2 test.

The probabilities of survival were calculated, and the means and life tables were computed using the product-limit estimate of Kaplan and Meier. The curves were analysed by the Breslow (generalized Wilcoxon) test, a statistical test for equality of survival distributions. A level of $P < 0.05$ was considered statistically significant. Survival duration was defined as the time between diagnosis and either death or time of the last clinical evaluation of the patient.

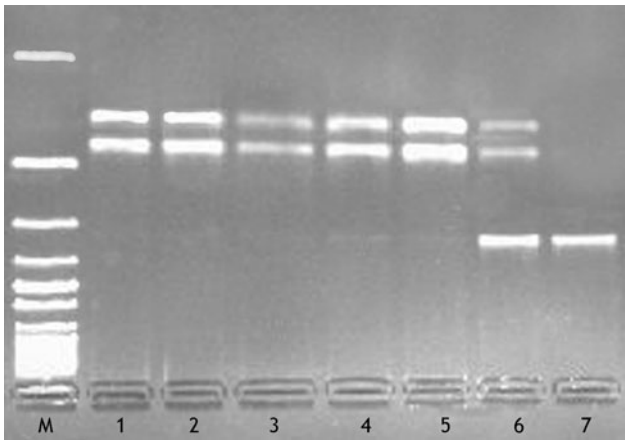

Fig. 1 Analysis of the *RAD51* G135C polymorphism genotypes: *M*, 50 bp ladder; *lanes1*, *2*, *3*, *4*, and *5* homozygote GG; *lanes6* heterozygote GC; and *lane7* polymorphic homozygote CC

Results

We analysed *RAD51* G135C polymorphism genotypes using the PCR–RFLP methodology. The genotype frequencies observed were 85.4% for GG homozygous genotype, 13.8% for CG heterozygous genotype and 0.8% for CC homozygous genotype. There were no statistically significant differences between the groups of NSCLC patients with the different genotypes regarding tumour stage ($p = 0.232$) (Table 2).

Concerning the overall survival rates found using Kaplan–Meier methodology (Fig. 2), we observed that the mean survival rates were statistically different according to the patient's genotypes. The group of patients carrying the C allele presented a higher mean survival rate than the other patients (56.0 months vs. 41.7 months; $p = 0.024$). Thus, individuals with CC/GC genotypes showed a higher overall survival, conferring a better prognosis for C allele carrier patients. Moreover, regarding smoking history, our results demonstrate that overall survival time differed significantly according to the patient's genotypes in smoker and ex-smoker individuals ($p = 0.034$). Patients carrying C allele presented a higher survival rate, comparing with the other patients (56.4 months vs. 44.7 months, $p = 0.034$) (Fig. 3a). No statistically significant differences were found in the genotype frequencies and overall survival rate among non-smoker NSCLC patients ($p = 0.413$) (Fig. 3b).

Discussion

Lung cancer is one of the most common causes of cancer-related death. Non-small cell lung cancer accounts for 75–85% of all histologic types of lung cancer. Despite

Table 2 Genotype frequencies of polymorphism in *RAD51* gene in NSCLC patients according tumour stage (Pearson χ^2 test)

	G135C polymorphism						*P*
	CC		GG		GC		
	N	%	*N*	%	*N*	%	
Stage							
I	0	0	10	71.4	4	28.6	0.232
II	0	0	14	82.4	3	17.6	
III	0	0	106	84.8	19	15.2	
IV	2	2.2	80	89.9	8	8.9	
Total	2		210		34		246

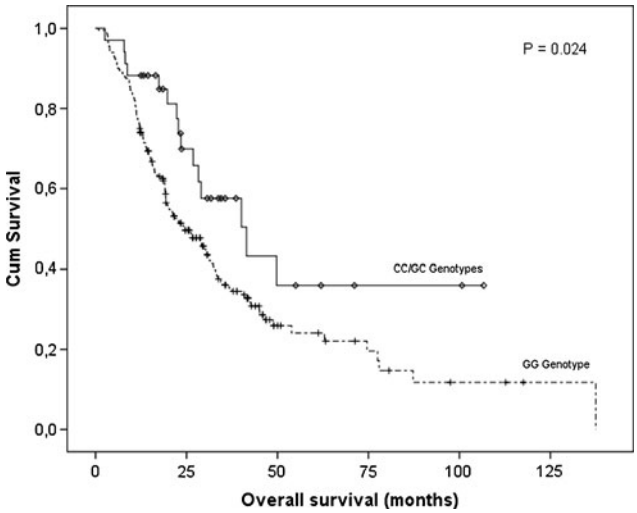

Fig. 2 Overall survival by Kaplan–Meier curves and Breslow test of NSCLC patients according to *RAD51* G135C genotypes

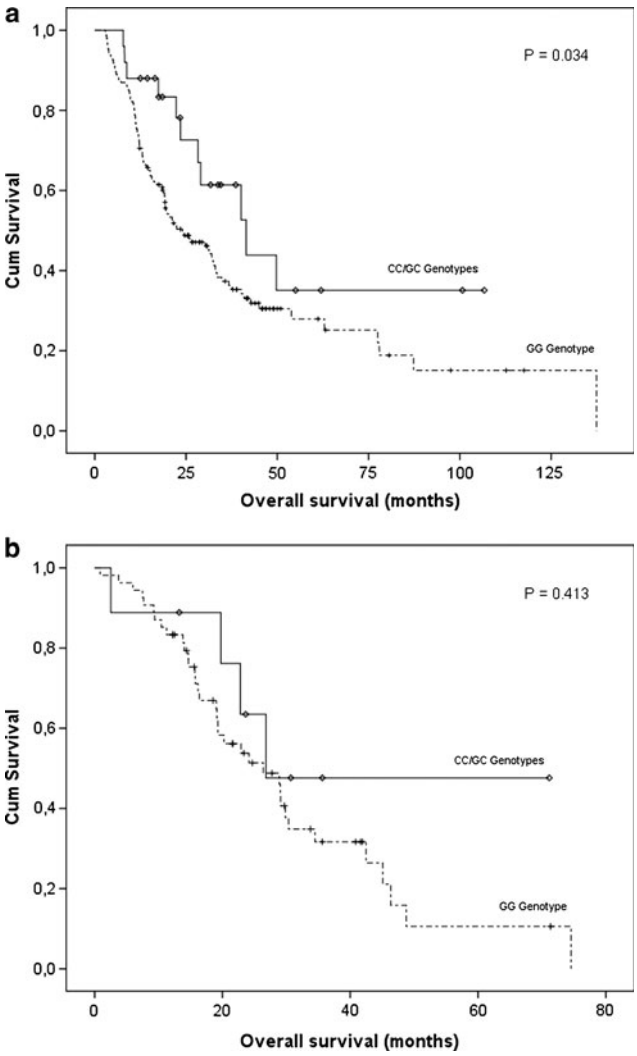

Fig. 3 Overall survival by Kaplan–Meier curves and Breslow test of NSCLC patients according to *RAD51* genotypes and smoking history. **a** Smoker and ex-smoker NSCLC patients. **b** Non-smoker patients

extensive preclinical and clinical research, the overall prognosis for patients with NSCLC remains poor, with a 5-year survival rate of only 14% [36].

Individual characteristics, such as genetic variations, are believed to be associated with an altered response to a chemotherapeutical treatment. Therefore, as predictive factors, it becomes important to study and understand the role of polymorphisms in cancer susceptibility and also in treatment response [27, 37].

The *RAD51* gene is essential for survival in the absence of exogenous DNA damaging agents [39] and has a key role in the homologous recombination and repair of DNA [33]. Overexpression of human RAD51 protein has been observed in tumour cell lines of widely different origins [31] and increased levels of the protein have been correlated with elevated recombination rates [23]. It is also required for resistance to ionizing radiation [5, 28], and high levels of RAD51 have been correlated with resistance to chemotherapeutic agents [12, 35]. According to previous studies in other tumour models, the study of *RAD51* gene seems to be important for the prediction of treatment response with chemotherapeutic drugs [6].

Previous studies suggest that the aberrant overexpression of RAD51 protein could confer several advantages to tumour cells. First, the DNA repair function of *RAD51* may protect cells from DNA damage and apoptosis. Second, overstimulation of homologous recombination and chromatid exchange mechanisms by RAD51 protein may contribute to genomic instability and genetic diversity of tumour cells [31]. The increased RAD51 protein expression leads to a perturbation of the cellular state of equilibrium, reflected in alterations of gene expression patterns detectable at the mRNA level [29].

There has been, however, little comprehensive examination of DNA repair processes, which might significantly contribute to the removal of therapeutic drugs, such as cisplatin, 5-FU and taxol and/or irradiation-induced DNA damage. In general, RAD51 expression seems to be correlated with resistance to therapeutic drugs [40]. Thus, a basal level of *RAD51* appears to be required for the processing of spontaneous DNA lesions. The constitutive overproduction of RAD51 in human tumours [25, 26] and in some transformed cell lines [31] may contribute for cytotoxic drug resistance induced by RAD51 in human cancers [14].

There are some studies that investigated the role of this polymorphism in the genetic susceptibility for development breast cancer [7, 16, 17, 20, 24], gastric cancer [30] and acute myeloid leukaemia [32, 42]. However, to the best of our knowledge, this is the first study evaluating the effect of the *RAD51* G135C polymorphism in NSCLC patient survival.

Our results suggest that the *RAD51* G135C 5′-UTR genotypes may provide additional prognostic information in NSCLC patients who underwent first line-based

chemotherapy. In this study, our results demonstrate that the G135C C-allele is associated with a higher survival time, conferring a better prognosis than the GG genotype carrier patients (56.0 months vs. 41.7 months; $p = 0.024$). Thus, individuals carrying the C allele showed an overall survival of approximately 56 months after chemotherapy, compared with 42 months for individuals carrying the allele G.

This study also indicates that the influence of *RAD51* G135C polymorphism in treatment response of NSCLC patients seems to be modulated by smoking history. Our results demonstrate that smoker or ex-smoker patients carriers of *RAD51* C-allele present a higher mean overall survival time, of 56 months comparing with 45 months for patients with GG genotype ($p = 0.034$). However, this association was not observed in non-smoker patients ($p = 0.413$).

RAD51 expression was identified as an independent predictor for tumour recurrence, as well as for tumour progression. These data demonstrate RAD51 expression as a clinically significant prognostic marker. Increased RAD51 protein levels could lead to uncontrolled recombination, genome instability, prevention of apoptosis, cell cycle arrest and increased resistance of tumours to radiotherapy and chemotherapy. As down-regulation of RAD51 protein by anti-sense oligonucleotides or small molecules sensitizes cells to DNA-damaging agents [28], this may be a promising strategy for tumour therapy [14].

Polymorphisms in untranslated regions have been shown to be important for cell proliferation, differentiation, tumour suppression, and metastasis suppression on several genes [9, 10]. For this reason, *RAD51* G135C polymorphism at the 5′ UTR region can have an important role on protein expression and stability. As it is located in the 5′-untranslated region of the *RAD51* gene, this genetic variation could affect mRNA stability and/or translation efficiency, leading to altered product levels, which could alter the function of RAD51 protein [3]. Although some known regulatory elements are associated with 5′-UTRs [11], it is not clear how 135C polymorphism might affect gene function. Hasselbach et al. [13] suggested promoter activity enhancement by substituting G at the polymorphic position +135, so that the C-allele is associated with lower RAD51 expression levels.

Since increased RAD51 protein levels could lead to uncontrolled recombination, genome instability and increased tumour resistance to chemotherapy, we hypothesize that the C-allele of *RAD51* polymorphism could derive lower protein expression levels, originating sensitized tumour cells, susceptible to chemotherapy treatment.

Thus, the presence of the G135C polymorphism may have a positive influence in treatment response, decreasing RAD51 expression levels in tumour cells and originating sensitized tumour cells, with normal cell proliferation, competent for apoptosis, with reduced recombination and presenting chemotherapy sensitivity.

To the best of our knowledge, this was the first study evaluating potential prognostic and predictive role of *RAD51* G135C polymorphism in NSCLC patients treated with combined platinum taxanes/gemcitabine first line chemotherapy.

We believe that *RAD51* genotypes could be useful molecular markers for predicting the clinical outcome of NSCLC patients. Furthermore, in the attempt of optimizing responses, minimizing toxicities, and reducing the elevated costs associated with chemotherapy failure, the analysis of a wide range of molecular markers and genetic polymorphisms may contribute to the development of a pharmacogenomic profile, indicating the more appropriate chemotherapeutic protocol for each individual patient.

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Conflict of interest statement None.

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