Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2020;9(1):255-60

ERCC1 and XRCC1 single nucleotide polymorphisms can guide treatment decision in patients with metastatic non-small cell lung cancer

Mustafa Karaagac[1], Mehmet Artac[1], Caglayan Geredeli[1], Melek Karakurt Eryilmaz[1], Mahmut Selman Yildirim[2], Tuba Akkuloglu[2], Ali Inal[3], Abdurrahman Isikdogan[3], Hakan Bozcuk[4], Ahmet Demirkazik[4]

[1]Necmettin Erbakan University, Meram Medical Faculty, Department of Medical Oncology, Konya, Turkey
[2]Necmettin Erbakan University, Meram Medical Faculty, Department of Medical Genetics, Konya, Turkey
[3]Dicle University, Medical Faculty, Department of Medical Oncology, Diyarbakir, Turkey
[4]Ankara University, Medical Faculty, Department of Medical Oncology, Ankara, Turkey

Received 03 October 2019; Accepted 31 December 2019
Available online 13.03.2020 with doi: 10.5455/medscience.2019.08.9184

Abstract

Results from studies in several cancers on single nucleotide polymorphisms (SNPs) suggest that DNA repair capacity may have prognostic implication for disease recurrence, survival, and responses to treatment. This study aimed to evaluate the potential prognostic value of SNPs as biomarkers in patients with metastatic non-small cell lung cancer (mNSCLC) treated with platinum. Analysis of SNPs from peripheral blood cells was performed by polymerase chain reaction. Excision repair cross-complementing group 1 (ERCC1)-Asn118Asn, excision repair cross-complementing group 2 (ERCC2)-Lys751Gln, X-ray repair cross-complementing group 1 (XRCC1)-Arg399Gln, and tumor protein 53 (TP53)-Arg72Pro polymorphisms were evaluated in conjunction with clinical and pathological parameters, and survival. The median progression-free survival (PFS) and overall survival (OS) of 145 patients were 5.1 months and 30.9 months, respectively. In the univariate analysis ERCC1 genotype, XRCC1 genotype, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) were significant parameters for OS. In the multivariate analysis ERCC1 genotype, XRCC1 genotype, and ECOG-PS retained their significance. The median OS was 45.2 months for the ERCC1 normal (CC) and heterozygote (CT) genotypes, and 25.5 months for the ERCC1 mutant (TT) genotype. The median OS was 31.4 months for the XRCC1 normal (AA) and heterozygote (AG) genotypes, and 23.1 months for the XRCC1 mutant (GG) genotype. The median OS was 30,7 months for ECOG-PS≤ 1 and 10.2 months for ECOG-PS≥ 2. ERCC1 and XRCC1 genotypes, and ECOG-PS independently predicted OS in mNSCLC patients. Additional studies are needed for the further evaluation of potential prognostic SNPs in mNSCLC.

Keywords: Biomarker, lung cancer, platinum, single nucleotide polymorphism, survival

Introduction

Lung cancer is the second most common cancer and is the main cause of cancer death among both men and women. Although lung cancer is a molecularly heterogeneous group of diseases and new treatment methods are available, the 5-year survival rate in advanced disease is still 6% [1,2].

The treatment of lung cancer remains challenging. Platinum, the main component of cytotoxic chemotherapy (CT) used in the treatment of lung cancer, damages the DNA and causes the death of tumor cells [3]. However, platinum response rates are less than 30% in patients with metastatic non-small cell lung cancer (mNSCLC) [4]. The efficacy of platinum regimens is limited due to drug resistance. A thorough understanding of the mechanisms of resistance and the identification of new biomarkers for more accurate prognostic and predictive assessment is necessary for personalized cancer treatment and may emphasize the possibility of patient-tailored platinum-based CT for mNSCLC [5,6].

Accumulating results from the studies on single nucleotide polymorphisms (SNPs) in several cancers as well as NSCLC suggest that DNA repair capacity may have prognostic implication for disease recurrence, survival, and responses to platinum-based CT, but the results are controversial [7-9].

In this study, we aimed to evaluate the potential prognostic value of SNPs consisting of excision repair cross-complementing group 1 (ERCC1), excision repair cross-complementing group 2 (ERCC2), X-ray repair cross-complementing group 1 (XRCC1) and tumor

***Coresponding Author:** Mustafa Karaagac, Necmettin Erbakan University, Meram Medical Faculty, Department of Medical Oncology, Konya, Turkey, E-mail: mustafakaraagac55@hotmail.com

protein 53 (TP53) in mNSCLC patients treated with platinum-based chemotherapy.

Materials and Methods

This was a multicenter, cross-sectional, and retrospective study. In this study, we recruited 145 patients with mNSCLC who were treated with platinum at the Medical Oncology Departments of Necmettin Erbakan University, Ankara University, Akdeniz University, and Dicle University between April 2010 and July 2012. Data on age, gender, comorbidities, pathological diagnosis, previous treatments such as neoadjuvant and/or adjuvant chemotherapy, date of disease progression and date of death of patients were recorded. Patients were followed up every three months after completion of treatment to evaluate survival.

Ethical approval

The study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the Meram Medical School of Selcuk University and also performed with the financial support of the Scientific Research Project of Selcuk University (Project no.: 11102028).

Eligibility

Age between 18 to 80 years, having pathologically proven mNSCLC with radiologically measurable disease, being treated with platinum-based CT regimens (dose concerning the National Comprehensive Cancer Network guidelines for CT), allowing informed consent for genetic analysis were the eligibility criteria.

DNA analysis

A ten mL of a peripheral venous blood sample by the nursing staff was obtained from each patient for DNA analysis. All of these blood samples taken from participating centers were sent to Meram Medical Faculty Department of Genetics. High Pure Polymerase Chain Reaction (PCR) Template Preparation Kits (Roche Diagnostics, Mannheim, Germany) were used for DNA isolation. After DNA isolation each sample was stored for PCR analysis.

Polymerase chain reaction analysis

PCR analysis was performed with the Roche Light Cycler 480 II real-time PCR system (Roche Molecular Systems, Inc.). The polymorphisms of codon 118 (rs11615) of ERCC1, codon 751 (rs13181) of ERCC2, codon 399 (rs25487) of XRCC1, and codon 72 (rs1042522) of TP53 were genotyped. Each PCR reaction (20 µL) contained 200 ng of DNA template, 200 µM of dNTP, 1 unit of Taq DNA polymerase, and 200 µM of primers, as well as 1.5 mM of MgCl2. The PCR conditions were one cycle of 10 min at 95 ºC; 45 cycles of 10 s denaturation at 95 ºC; 10 s hybridization at 60 ºC for ERCC1, ERCC2, and XRCC1; or 58 ºC for TP53 and 15 s elongation at 72 ºC. Following PCR amplification, the results were classified as normal, heterozygote, or mutant with melting curve analysis. Genotyping was done blind, and a random 5% of the samples were repeated to validate the genotyping procedures. Two authors independently reviewed all genotyping results.

Statistical analysis

Primary statistical analysis has included descriptive statistics of the patients as age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), histological subtypes, the status of neoadjuvant CT, subtypes of the surgical procedure, the status of adjuvant CT, first-line CT regimens for metastatic disease. All patients underwent overall survival (OS) and progression-free survival (PFS) analysis.

Statistical analysis was performed by using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Univariate and multivariate Cox regression analyses and Kaplan Meier survival curves subjected to log-rank testing were utilized for the survival analyses. Forward likelihood ratio was used for the multivariate selection process. A p-value <0.05 was required for statistical significance.

Results

Characteristics of patients

A total of 145 patients were enrolled in this study. There were 126 males and 19 females. The median age was 60 years (range 34-79). The ECOG-PS of 99 patients was 0-1, while the ECOG-PS of the remaining 46 patients was 2 or more. There were 64 cases of adenocarcinoma, 55 cases of squamous cell carcinoma, and 26 cases of the other histological subtypes. All patients received platinum-based CT as the first line for metastatic disease Demografhic and cilinical parameters of patients were shown in Table 1. [Table 1 near here]

Table 1. Demographic and clinical parameters of patients

Characteristics		(n=145) (100%)
Age (years), median (range)		60(34-79)
Gender, n (%)		
	Male	126(86.9)
	Female	19(13.1)
ECOG-PS, n (%)		
	≤1	99(68.2)
	≥2	46(31.8)
Histological subtype, n (%)		
	Adenocarcinoma	64(44.1)
	Squamos cell carcinoma	55(37.9)
	Others	26(18.0)
Neoadjuvant CT, n (%)		
	Yes	13(9.0)
	No	136(91.0)
Surgery subtype (if done), n (%)		
	Lobectomy	30(20.7)
	Pneumectomy	3(2.1)
Adjuvant CT, n (%)		
	Yes	23(15.9)
	No	122(84.1)
First line CT for metastatic disease, n (%)		
	Cisplatin+Gemcitabine	44(30.3)
	Carboplatin+Paclitaxel	33(22.8)
	Cisplatin+Docetaxel	21(14.5)
	Other Platinum-based regimens	47(32.4)

ECOG-PS; Eastern Cooperative Oncology Group Performance Status CT; Chemotherapy

Gene polymorphisms

ERCC1 was 25.1 % in CC, 52.8 % in CT heterozygosity, and 22.1 % in TT mutant alleles. ERCC2 was 23.1 % in CC, 52.8 % in CT heterozygosity, and 24.1 % in TT mutant alleles. XRCC1 polymorphism was 34.4, 41.0, and 24.6 % in AA, AG heterozygosity, and GG mutant alleles, respectively. TP53 was 14.4 % in CC, 48.2 % in CG heterozygosity, and 37.4% in GG mutant alleles.

Gene polymorphisms and survival outcomes

The median PFS and OS were 5.1 months (95% confidence interval (CI), 4.3-5.8) and 30.9 months (95% CI, 28.2-33.6), respectively.

In the univariate analysis for OS, ERCC1 genotype (hazard ratio (HR), 0.26; 95% CI, 0.12-0.57; p=0.001), XRCC1 genotype (HR, 0.37; 95% CI, 0.16-0.83; p=0.01), and ECOG-PS (HR, 5.25; 95% CI, 1.45-19.04; p=0.01) were significant parameters. Therefore, multivariate analyzes were performed, and ERCC1 genotype (HR, 0.36; 95% CI, 0.14-0.92; p=0.03), XRCC1 genotype (HR, 0.37; 95% CI, 0.14-0.98; p=0.04), and ECOG-PS (HR, 4.80; 95% CI, 1.22-18.87; p=0.02) retained their significance. In univariate analysis, there was no significant difference in PFS according to age, gender, number of metastatic organs, ERCC1, ERCC2, XRCC1, TP53, and ECOG-PS (Table 2). [Table 2 near here]

The median OS was 45.2 months (95%CI, 25.3-65.0) for the ERCC1 normal (CC) and heterozygote (CT) genotypes, and 25.5 months (95%CI, 9.5-41.5) for the ERCC1 mutant (TT) genotype (p<0.01) (Figure 1). [Figure 1 near here]

The median OS was 31.4 months (95%CI, 20.1-42.7) for the XRCC1 normal (AA) and heterozygote (AG) genotypes, and 23.1 months (95%CI, 20.0-26.3) for the XRCC1 mutant (GG) genotype (p=0.01) (Figure 2). [Figure 2 near here]

The median OS was 30,7 months (95%CI, 26.4-35.1) for ECOG-PS ≤ 1 and 10.2 months (95%CI, 3.4-16.9) for ECOG-PS≥ 2 (p<0.005) (Figure 3). [Figure 3 near here]

Table 1. The predictors of PFS and OS

Characteristics	OS (univariete)		PFS (univariete)		OS (multivariete)	
Age (years), median (range)	**HR**	p value	HR	p value	HR	p value
Age	1,01	0,40	1,00	0,82		
Gender	0,70	0,57	1,36	0,22		
Number of metastatic organs	1,60	0,30	1,01	0,96		
ERCC1 (Asn118Asn)	0,26	0,001*	0,84	0,43	0,36	0,03*
ERCC2 (Lys751Gln)	0,88	0,80	0,79	0,35		
XRCC1 (Arg399Gln)	0,37	0,01*	1,30	0,20	0,37	0,04*
TP53 (Arg72Pro)	1,31	0,69	1,10	0,70		
ECOG-PS	5,25	0,01*	3,49	0,62	4,80	0,02*

FS; Progression free survival, OS; Overall survival, HR; Hazard ratio, ERCC1: Excision repair cross-complementing group 1, ERCC2: Excision repair cross-complementing group 2, XRCC1: X-ray repair cross-complementing group 1, TP53: Tumor protein 53, ECOG-PS; Eastern Cooperative Oncology Group Performance Status *;statistically significant (p value<0,05)

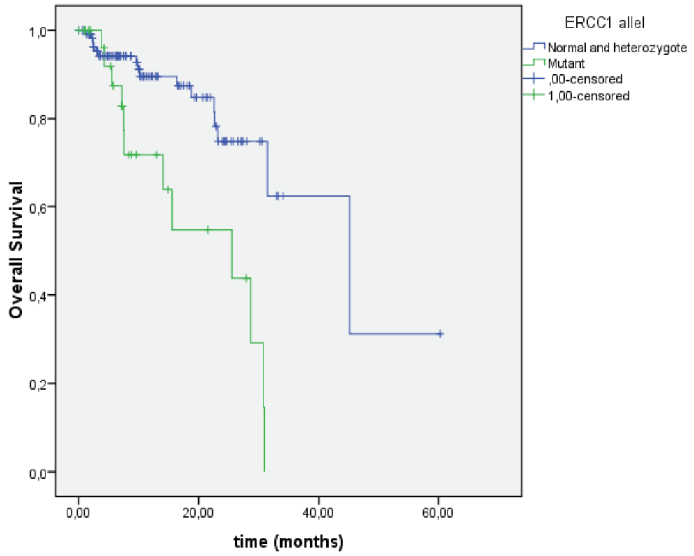

Figure 1. The overall survival with respect to ERCC1 genotypes

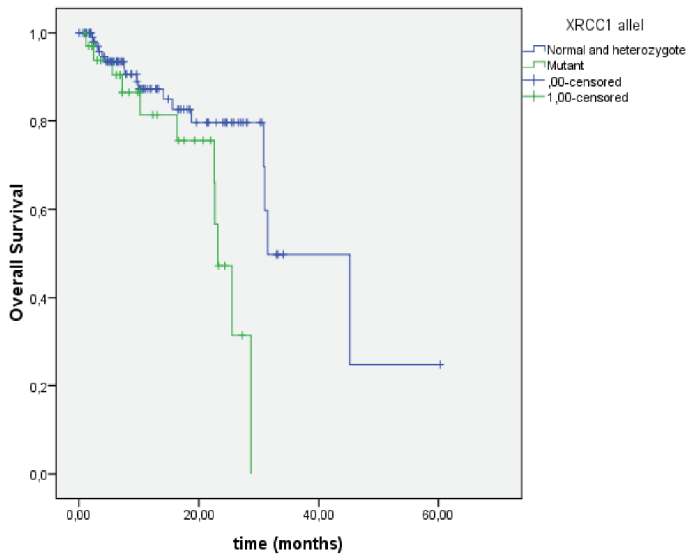

Figure 2. The overall survival with respect to XRCC1 genotypes

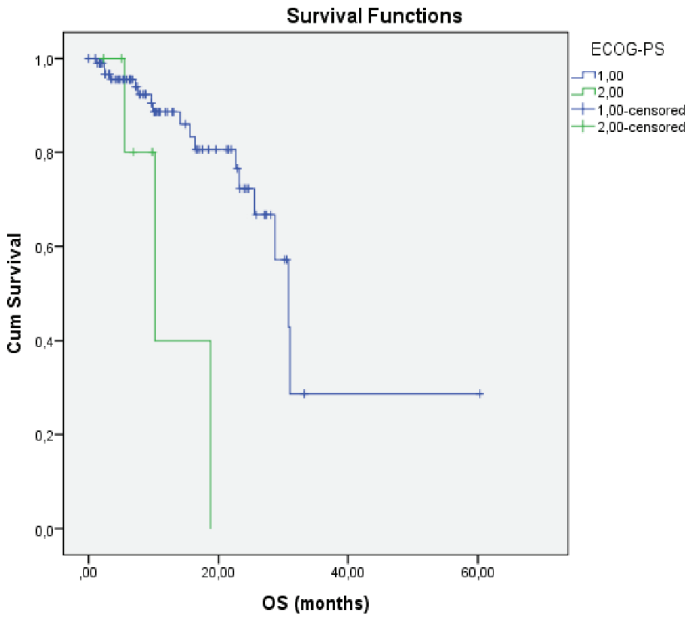

Figure 3. The overall survival with respect to ECOG-PS

Discussion

This was the first study investigating the prognostic role of SNPs in patients with mNSCLC in Turkish cohort. In this study, we demonstrated that ERCC1 and XRCC1 gene polymorphisms and ECOG-PS predicted OS in mNSCLC patients, but ERCC2 and TP53 were not significant in this regard.

Although many newer treatment methods that target mutations and rearrangements in oncogenes are available and have excellent clinical benefit and minimum toxicity, the majority of patients with mNSCLC are not appropriate for these drugs due to the lack of target mutations or rearrangements in these oncogenes [10]. Currently, platinum-based CT is still the primary treatment modality for most of the patients with mNSCLC. But, the platinum response rate is not high in patients with advanced NSCLC [4]. The efficacy of platinum regimens is limited due to drug resistance. Decreased accumulation of platinum, increased drug inactivation, enhancement of tumor cells' tolerance to platinum-DNA adducts, and enhancement of the repair of the damaged DNA by nucleotide excision repair (NER) pathway which consists of many polypeptides, including ERCC1 and ERCC2 are thought to be the cause of this critical problem [11,12]. Explaining the mechanisms of resistance and the identification of prognostic and predictive biomarkers are necessary for personalized treatment of mNSCLC.

ERCC1 plays a critical role in the NER pathway and simplifies the excision of damaged DNA, and thus, can be used as a prognostic biomarker to reestablish the therapeutic sensitivity to platinum-based agents in chemoresistant patients [5,6,13,14]. Also, ERCC2, where the gene product has ATP-dependent helicase activity, participates in NER [15]. SNPs, which have been shown to induce amino acid changes such as Asp312Asn and Lys751G1n, have been identified in some exons of ERCC2 [16]. Several studies demonstrated the relationship between ERCC2 SNPs and platinum activity in many different types of cancer, but the relationship between ERCC2 levels and treatment results in patients treated with platinum-based CT is still controversial [17-19]. Kang et al. demonstrated that upregulation of ERCC1 in metastatic lymph nodes was a poor prognostic factor in N1 patients but not in N2 patients who underwent surgical resection followed by platinum-based adjuvant CT [20]. In several studies, it has been demonstrated that the suppression of ERCC1 can regenerate or increase platinum sensitivity and the low level of ERCC1 was associated with significantly improved OS in lung cancer patients treated with platinum-based CT [21-23]. Olaussen et al. demonstrated that ERCC1 expression is a possible marker for the effect of postoperative adjuvant CT in patients with resected tumors. Adjuvant platinum-based CT was reported to be beneficial for survival in ERCC1-negative patients, but no benefit was observed in ERCC1-positive patients [22]. In another study, Geredeli et al. evaluated ERCC1 and ERCC2 polymorphisms in surgically treated NSCLC patients, and an increase in relapse-free survival (RFS) was observed, but was not statistically significant [24]. Kalikaki et al. showed that ERCC1 polymorphic variants were independent prognostic factors for improved OS and ERCC1 genotype was significantly associated with response to platinum-based treatment in advanced NSCLC patients treated with platinum-based CT [25]. On the other hand, Yin et al. performed a meta-analysis in patients who received platinum-based treatment and demonstrated that the rate of ERCC1 and ERCC2 polymorphisms did not have a predictive or prognostic value for RFS and OS [26]. Besides all these, in this study, we evaluated the association between ERCC1 and ERCC2 polymorphisms and survival in mNSCLC treated with platinum-based CT. So here we showed that the median OS was longer for the ERCC1 normal and heterozygote genotypes, and shorter for the ERCC1 mutant genotype and it was statistically significant. These results confirmed the positive data related to ERCC1 in the literature and revealed that platinum-based CT may be more benefical in patients with ERCC1 normal and heterozygote genotypes. And, for the first time, these results showed that ERRC1 had a prognostic role also in the Turkish cohort. However, unlike ERCC1, we demonstrated no significant difference between ERCC2 polymorphism and survival in mNSCLC.

XRCC1 is another protein involving NER and a member of the base excision pathway in DNA repair paths. XRCC1 gene polymorphism is associated with suboptimal DNA repair, and as a result of this inadequate process, the tumors may become more biologically aggressive [16,27]. XRCC1 T-77C polymorphisms are associated with increased risk of NSCLC [28]. Kim et al. showed that non-mNSCLC patients with AA homozygous variants of XRCC1 gene polymorphism had better survival rates [29]. Besides, the polymorphisms of XRCC1 399 and XRCC3 241 have been reported to be a prognostic factor in survival [25,30,31]. However, Yao et al. examined XRCC1 polymorphism in advanced-stage NSCLC patients, but no statistically significant correlation was observed [32]. Also, Gurubhagavatula et al. demonstrated that XRCC1 variant alleles were associated with short-term survival in NSCLC patients treated with platinum-based CT [33]. Moreover, XRCC1 was found not to be associated with prognosis and survival in another study on T-77C polymorphism [7]. In this study, we also evaluated the relationship between XRCC1 polymorphism and survival in mNSCLC. So here we demonstrated that the median OS was shorter in XRCC1 mutant genotype and it was statistically significant. This result suggested that polymorphism of XRCC1 may play an essential role as a prognostic marker in the survival

of mNSCLC patients and should be considered as a predictive marker for treatment outcome of platinum-based CT.

As in lung cancer, the most commonly mutated gene in cancer is the TP53 tumor suppressor gene, which, as a result of these mutations, has acquired oncogenic properties to promote invasion, metastasis, proliferation and cell survival [34,35]. Many studies have demonstrated that TP53 mutations have a potential prognostic role for disease recurrence and shorter survival in non-mNSCLC [36-38]. Although Fukuyama et al. demonstrated that the NSCLC patients with TP53 mutations had a worse prognosis in early-stage cases, there was no statistically significant difference when advanced-stage cases or all patients were considered [39]. To the best of our knowledge, few studies in the literature investigated the relationship between TP53 polymorphism and prognosis and survival in patients with mNSCLC. In this study, we evaluated the relationship between TP53 polymorphism and survival in mNSCLC and found no statistically significant difference. This result is consistent with the current literature.

Performance status is one of the most critical criteria in the choice of treatment in patients with mNSCLC and is an independent predictor of poor prognosis in patients with advanced or mNSCLC receiving CT [40-42]. Also, we demonstrated that a good ECOG-PS was statistically significant on prolonged survival.

Conclusion

We showed that ERCC1 and XRCC1 gene polymorphisms and ECOG-PS are prognostic markers in survival and should be considered as predictive markers for the treatment decision of patients with mNSCLC. Our results may provide insight and guidance on prospective studies of the assessment of potential predictive and prognostic biomarkers in patients with mNSCLC.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
The study was approved by the Ethical Board of the Meram Medical School of Selcuk University and performed with the financial support of the Scientific Research Project of Selcuk University (Project no: 11102028)

Ethical approval
The study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the Meram Medical School of Selcuk University and also performed with the financial support of the Scientific Research Project of Selcuk University (Project no.: 11102028).

Mustafa Karaagac ORCID: 0000-0003-4533-0620
Mehmet Artac ORCID: 0000-0003-2335-3354
Caglayan Geredeli ORCID: 0000-0002-3982-7465
Melek Karakurt Eryılmaz ORCID: 0000-0003-2597-5931
Mahmut Selman Yildirim ORCID: 0000-0002-3986-5517
Tuba Akkuloglu ORCID: 0000-000-2398-65517
Ali Inal ORCID: 0000-0002-7451-2786
Abdurrahman Isikdogan ORCID: 0000-0002-7451-2786
Hakan Bozcuk ORCID: 0000-0001-7809-1721
Ahmet Demirkazik ORCID: 0000-0002-2917-7999

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.

2. Inamura K. Lung Cancer: Understanding Its Molecular Pathology and the 2015 WHO Classification. Front Oncol. 2017;28:7:193.

3. Yamaguchi M, Sugio K. Current status of induction treatment for N2-Stage III non-small cell lung cancer. Gen Thorac Cardiovasc Surg. 2014; 62: 651-9.

4. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.

5. Friedberg EC. How nucleotide excision repair protects against cancer. Nat Rev Cancer. 2001;1:22-33.

6. Kelley MR, Logsdon D, Fishel ML. Targeting DNA repair pathways for cancer treatment: what's new? Future Oncol. 2014;10:1215-37.

7. Liu L, Yuan P, Wu C, et al. Assessment of XPD Lys751Gln and XRCC1 T-77C polymorphisms in advanced non-small-cell lung cancer patients treated with platinum-based chemotherapy. Lung Cancer. 2011;73:110-5.

8. Darcy KM, Tian C, Reed E. A Gynecologic Oncology Group study of platinum-DNA adducts and excision repair cross-complementation group 1 expression in optimal, stage III epithelial ovarian cancer treated with platinum-taxane chemotherapy. Cancer Res. 2007;67:4474-81.

9. Stoehlmacher J, Park DJ, Zhang W, et al. A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. Br J Cancer. 2004;91:344-54.

10. Shea M, Costa DB, Rangachari D. Management of advanced non-small cell lung cancers with known mutations or rearrangements: latest evidence and treatment approaches. Ther Adv Respir Dis. 2016;10:113-29.

11. Rosell R, Tarón M, O'Brate A. Predictive molecular markers in non-small cell lung cancer. Curr Opin Oncol. 2001;13:101-9.

12. Simon GR, Sharma S, Cantor A, et al. ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer. Chest. 2005;127:978-83.

13. 13. Marteijn JA, Lans H, Vermeulen W, et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014;15:465-81.

14. He L, Wang X, Liu K, et al. Integrative PDGF/PDGFR and focal adhesion pathways are downregulated in ERCC1-defective non-small cell lung cancer undergoing sodium glycididazole-sensitized cisplatin treatment. Gene. 2019;691:70-6.

15. Lainé JP, Mocquet V, Bonfanti M, et al. Common XPD (ERCC2) polymorphisms have no measurable effect on nucleotide excision repair and basal transcription. DNA Repair (Amst). 2007;6:1264-70.

16. Vineis P, Manuguerra M, Kavvoura FK, et al. A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. J Natl Cancer Inst. 2009;101:24-36.

17. Ott K, Rachakonda PS, Panzram B, et al. DNA repair gene and MTHFR gene polymorphisms as prognostic markers in locally advanced adenocarcinoma of the esophagus or stomach treated with cisplatin and 5-fluorouracil-based neoadjuvant chemotherapy. Ann Surg Oncol. 2011;18:2688-98.

18. Yin M, Yan J, Martinez-Balibrea E, et al. ERCC1 and ERCC2 polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: a systemic review and meta-analysis. Clin Cancer Res. 2011;17:1632-40.

19. Kim SH, Lee GW, Lee MJ, et al. Clinical significance of ERCC2 haplotype-tagging single nucleotide polymorphisms in patients with unresectable non-small cell lung cancer treated with first-line platinum-based chemotherapy. Lung Cancer. 2012;77:578-84.

20. Kang CH, Jang BG, Kim DW, et al. Differences in the expression profiles of excision repair crosscomplementation group 1, x-ray repair crosscomplementation group 1, and betaIII-tubulin between primary non-small cell lung cancer and metastatic lymph nodes and the significance in mid-term survival. J Thorac Oncol. 2009;4:1307-12.

21. Martin LP, Hamilton TC, Schilder RJ. Platinum resistance: the role of DNA repair pathways. Clin Cancer Res. 2008;14:1291-5.

22. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med. 2006;355:983-91.

23. Vilmar A, Sørensen JB. Excision repair cross-complementation group 1 (ERCC1)in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: a review of current literature. Lung Cancer. 2009;64:131-9.

24. Geredeli C, Artac M, Yildirim S, et al. Prognostic value of ERCC1, ERCC2, XRCC1, and TP53 single nucleotide polymorphisms in patients with early-stage non-small cell lung cancer. Tumour Biol. 2015;36:4279-85.

25. Kalikaki A, Kanaki M, Vassalou H, et al. DNA repair gene polymorphisms predict favorable clinical outcome in advanced non-small-cell lung cancer, Clin Lung Cancer. 2009;10:118-23.

26. Yin M, Yan J, Voutsina A, et al. No evidence of an association of ERCC1 and ERCC2 polymorphisms with clinical outcomes of platinum-based chemotherapies in non-small cell lung cancer: a meta-analysis. Lung Cancer. 2011;72:370-7.

27. Liang G, Xing D, Miao X, et al. Sequence variations in the DNA repair gene XPD and risk of lung cancer in a Chinese population. Int J Cancer. 2003;105:669-73.

28. Hao B, Miao X, Li Y, et al. A novel T-77C polymorphism in DNA repair gene XRCC1 contributes to diminished promoter activity and increased risk of non-small cell lung cancer. Oncogene. 2006; 25:3613-20.

29. Kim M, Kang HG, Lee SY, et al. Comprehensive analysis of DNA repair gene polymorphisms and survival in patients with early stage non-small-cell lung cancer. Cancer Sci. 2010;101:2436-42.

30. Liao WY, Shih JY, Chang GC, et al. Genetic polymorphism of XRCC1 Arg399Gln is associated with survival in non-small-cell lung cancer patients treated with gemcitabine/platinum. J Thorac Oncol. 2012;7:973-81.

31. de las Peñas R, Sanchez-Ronco M, Alberola V, et al. Polymorphisms in DNA repair genes modulate survival in cisplatin/gemcitabine-treated non-small-cell lung cancer patients. Ann Oncol. 2006;17:668-75.

32. Yao CY, Huang XE, Li C, et al. Lack of influence of XRCC1 and XPD gene polymorphisms on outcome of platinum-based chemotherapy for advanced non small cell lung cancers. Asian Pac J Cancer Prev. 2009;10:859-64.

33. Gurubhagavatula S, Liu G, Park S, et al. XPD and XRCC1 genetic polymorphisms are prognostic factors in advanced non-small-cell lung cancer patients treated with platinum chemotherapy. J Clin Oncol. 2004;22:2594-601.

34. Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. J Biomed Biotechnol. 2011;2011:583929.

35. Kastenhuber ER, Lowe SW. Putting p53 in Context. Cell. 2017;170:1062-78.

36. Tsao MS, Aviel-Ronen S, Ding K, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. J Clin Oncol. 2007;25:5240-7.

37. Ludovini V, Pistola L, Gregorc V, et al. Plasma DNA, microsatellite alterations, and p53 tumor mutations are associated with disease-free survival in radically resected non-small cell lung cancer patients: a study of the perugia multidisciplinary team for thoracic oncology. J Thorac Oncol. 2008;3:365-73.

38. 38. Lee SY, Jeon HS, Hwangbo Y, et al. The influence of TP53 mutations on the prognosis of patients with early stage non-small cell lung cancer may depend on the intratumor heterogeneity of the mutations. Mol Carcinog. 2015; 54: 93-101.

39. 39. Fukuyama Y, Mitsudomi T, Sugio K, et al. K-ras and p53 mutations are an independent unfavourable prognostic indicator in patients with non-small-cell lung cancer. Br J Cancer. 1997; 75: 1125-1130.

40. Hoang T, Xu R, Schiller JH, et al. Clinical model to predic survival in chemonaive patients with advanced non-small-cell lung cancer treated with third-generation chemotherapy regimens based on eastern cooperative oncology group data. J Clin Oncol. 2005;23:175-83.

41. Trapé J, Montesinos J, Catot S, et al. A prognostic score based on clinical factors and biomarkers for advanced non-small cell lung cancer. Int J Biol Markers. 2012;27: e257-62.

42. Gong J, Xu L, Li Z, et al. A Clinical prognostic score to predict survival of advanced or metastatic non-small cell lung cancer (NSCLC) patients receiving first-line chemotherapy: a retrospective analysis. Med Sci Monit. 2018; 24: 8264-71.