Clinical prognostic significance of xeroderma pigmentosum group C and IFN-γ in non-small cell lung cancer

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Abstract. Lung cancer is the most common cancer in the world due to its high incidence and recurrence. Genetic instability is one of the main factors leading to its occurrence, development and poor prognosis. Decreased xeroderma pigmentosum group C (XPC) expression notably enhances the stem cell properties of lung cancer cells and increases their proliferation and migration. Additionally, patients with lung cancer and low XPC expression had a poor prognosis. The purpose of the present study was to analyze the effect of XPC and IFN-γ on the clinical prognosis of patients with non-small cell lung cancer (NSCLC). Lung adenocarcinoma specimens were collected from a total of 140 patients with NSCLC. Additionally, from these 140 patients, 48 paracarcinoma tissue specimens were also collected, which were later used to construct tissue microarrays. The expression of XPC and IFN-γ in cancer tissues and in paraneoplastic tissues was detected using immunohistochemistry. The prognosis and overall survival of patients were determined through telephone follow-up. The results showed a positive correlation between expression of XPC and IFN-γ in NSCLC. Additionally, high expression of both markers was associated with a favorable prognosis in patients with NSCLC. The aforementioned findings suggest that the expression of XPC and IFN-γ has prognostic value in clinical practice and is expected to become a marker for clinical application.

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Introduction

Lung cancer causes 25% of cancer-related deaths and has a high incidence rate despite significant advances in therapies made in recent years, representing 11.6% of new cancer cases worldwide (1,2). Genomic instability is one of the main factors leading to tumor occurrence, progression and poor outcomes (2). Xeroderma pigmentosum group C (XPC) is a DNA damage recognition factor and a promoter of nucleotide excision repair that plays an important role in maintaining DNA stability (3). XPC is a key factor in the development of a number of tumor types including lung cancer (4-7). Our previous study revealed that a reduction in XPC expression can markedly promote the stem cell properties of lung cancer cells and increase the proliferation and migration of lung cancer cells, and a low XPC expression in patients with lung cancer is associated with poor prognosis (8). Zhang *et al* (9) showed that the loss of XPC could increase the amount of oxidatively damaged DNA and promote Kras-mediated lung cancer development. The underlying mechanisms through which XPC affects lung cancer development remain not understood; more specifically, the mediator responsible for these processes has yet to be identified.

IFN-γ in the blood comes from monocytes, macrophages, endothelial cells and tumor cells, and considered a diagnostic and prognostic biomarker in lung cancer (10,11). Studies have shown that IFN-γ can mediate lung cancer inhibition via programmed death-ligand 1 expression (12,13). IFN-γ-induced endoplasmic reticulum stress impairs autophagy and triggers apoptosis in lung cancer cells (14).

A total of >90% of lung cancer-related deaths are due to metastasis of lung cancer cells (15). Cytological studies have shown that the expression of both XPC and IFN-γ is closely related to the metastasis of lung cancer (8,16).

A study by Wu *et al* (17) revealed that XPC expression levels were linked to prognosis and metastasis in patients with lung cancer. In a study by Ahn *et al* (18) investigating the relationship between the expression level of IFN-γ, and the prognosis and metastasis status of patients with adenocarcinoma, it was found that patients with low *in vitro* production of IFN-γ by peripheral immune cells had a markedly lower 1-year overall survival rate than patients with high IFN-γ production.

However, the expression of XPC and IFN-γ in lung cancer tissue has yet to be studied. In the present study, 140 lung cancer tissue samples were collected, and the correlation between the expression of XPC and IFN-γ in lung cancer tissue and patient prognosis was analysed. In addition, the differences in the expression of XPC and IFN-γ were investigated according to the histopathological characteristics of different patients with lung cancer.

Materials and methods

The Cancer Genome Atlas (TCGA) analysis. Using the relevant clinical data of TCGA database, the relationship between the expression of XPC and the clinicopathological characteristics of patients with lung cancer was statistically analysed. There are no data on IFN-γ in TCGA database. The present study complied with the National Institutes of Health TCGA Human Guidelines Subject Protection and Data Access Policy, and the results shown are in whole or part based upon data generated by the TCGA Research Network: cancer.gov/tcga (19).

Specimens. Wax blocks of lung adenocarcinoma tissues from patients with lung cancer with a pathological diagnosis were collected from Weifang Second People's Hospital (Weifang, China) between January 2011 and December 2015. Confirmation of diagnosis was conducted by two independent pathologists using H&E staining. For this, tissues were fixed using 4% paraformaldehyde at 25˚C for 24 h and embedded in paraffin. Sections were cut into 5-μm thick slices and mounted on adhesive slides using a sectioning machine. The slices were then baked at 60˚C for 2 h. Subsequently, the tissue sections were rehydrated using xylene and a gradient of 100-70% alcohol, stained with hematoxylin at room temperature for 7 min and eosin at room temperature for 1 min. Finally, the sections were dehydrated in an increasing series of alcohol (70-100%) and sealed with a neutral resin. Observations were conducted using a light microscope under a 20x objective and 10x eyepiece. Tumor specimens were collected from 140 patients, from which 48 paracancerous samples were also obtained, and made into one tissue microchip by Shanghai Outdo Biotech Co., Ltd. The tissue microchip was used for subsequent experiments. Patient prognosis and survival time were obtained via telephone follow-up.

The present study protocols were reviewed and approved by the ethics committee of Weifang Second People's Hospital (YX2020-001-01). The study complied with the relevant regulations of the Declaration of Helsinki and was conducted under the supervision of the hospital ethics committee.

Tissue microarray and immunohistochemistry (IHC). Immunohistochemical staining with XPC and IFN-γ antibodies was performed on a microchip to analyse the protein expression in NSCLC tissues. The tissues embedded in paraffin, which were used for HE staining in the previous step, were processed into a tissue chip using a tissue microarray spotter. The tissue chip was then baked at 55˚C for 4 h to fix the tissue. Subsequently, the tissue chip was sliced into 4-μm wax slices using a tissue slicer and affixed to adhesive slides. After xylene and gradient alcohol treatment to rehydrate the tissues, the tissues were repaired by microwave heating and boiling in Citrate Antigen Repair Solution (3.23 g/l; pH, 6; cat. no. ZLI-9064; Beijing Zhongshan Jinqiao Biotechnology Co.) for 30 min, followed by incubation with 3% hydrogen peroxide for 5 min at room temperature, and then incubation with 3% goat serum (cat. no. SL038; Sorabio) for 1 h. Subsequently, the tissues were incubated with either XPC Rabbit Polyclonal Primary Antibody (1:50; cat. no. ab155025; Abcam) or IFN-γ Rabbit Polyclonal Primary Antibody (1:1,000; cat. no. ab25101; Abcam) overnight (>12 h) at 4˚C. The tissue sections were then incubated with an HRP-conjugated goat-conjugated anti-rabbit secondary antibody (1:500; cat. no. ab6721; Abcam) for 4 h at room temperature. Hematoxylin staining (cat. no. H8070; Sorabio) at room temperature for 7 min. Finally, sections were dehydrated in an increasing series of alcohol (70-100%) and sealed with a neutral resin. The IHC images were collected using a Panoramic MIDI light microscope (3DHISTECH, Ltd.), and the percentage of positive IHC signals was analyzed using Density Quant version 2.3 (3DHISTECH, Ltd.). According to the IHC staining intensity, samples were grouped according to the percentage of positive cells. A positive rate >90% was considered to indicate high expression and was marked as XPC^{high} or IFN-γ^{high}; a positive rate <90% was considered to indicate low expression and was marked as XPC^{low} or IFN-γ^{low}.

Statistical analysis. SPSS (version 22; IBM Corp.) was used to perform a χ^2-test and analyze the expression of XPC and IFN-γ in NSCLC tissues, and the relationship between the expression of XPC or IFN-γ and the clinicopathological characteristics of patients with NSCLC. The association between XPC and IFN-γ was calculated using Pearson's correlation coefficient. A Kaplan-Meier survival curve was used to perform survival analysis, and the log-rank test was applied to evaluate statistical significance. A unpaired t-test was used to compare two groups of TCGA data, while one-way ANOVA was used to analyze the TCGA data from ≥3 groups. The log-rank test was used for survival curve analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

XPC is expressed at low levels in lung adenocarcinoma tissues in TCGA database. The expression of XPC, a nucleic acid splice repair gene, was significantly different in various cancers (Fig. 1A). In the present study, the relationship between the expression of XPC in 502 lung cancer tissues in TCGA database and patient prognosis was first analyzed. The

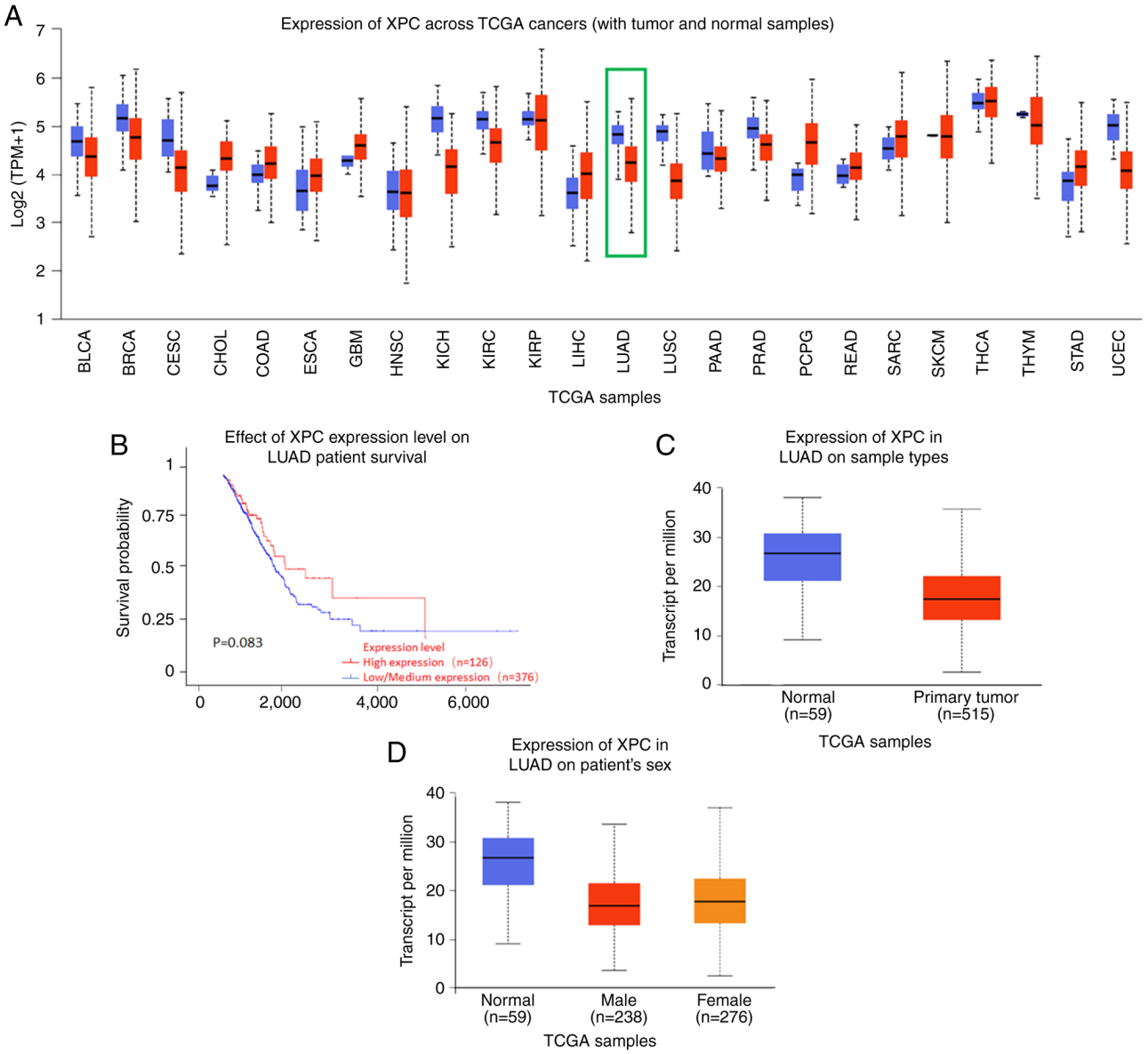

Figure 1. Expression of XPC in TCGA cohort. (A) Expression of XPC across TCGA cancer cohorts; the green box represents XPC in LUAD. There are 515 cases of tumor tissue in red and 59 cases of normal tissue in blue. (B) Effect of the XPC expression level on LUAD patient survival. (C) Expression of XPC in LUAD tissues based on sample type. (D) Expression of XPC in LUAD based on patient sex. LUAD, lung adenocarcinoma; TCGA, The Cancer Genome Atlas; XPC, xeroderma pigmetosum group C; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangio carcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; PRAD, prostate adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin C=cutaneous melanoma; THCA, thyroid carcinoma; THYM, thymoma; STAD, stomach adenocarcinoma; UCEC, uterine corpus endometrial carcinoma.

results showed that patients with high XPC expression had a better prognosis than those patients with low XPC expression; however, the difference was not significant (P=0.083; Fig. 1B).

In addition, the expression of XPC in 574 lung cancer tissues including 515 lung cancer tissues and 59 adjacent normal tissues was analysed. Box plots revealed that the expression of XPC in lung tumor tissues was significantly different; compared with the XPC expression in normal tissues, XPC expression was significantly lower in lung tumor tissues (Fig. 1C). In addition, the expression of XPC in lung tumor tissues was not related to sex (Fig. 1D).

Expression of XPC and IFN-γ is positively correlated in the tumor tissues of patients with NSCLC. Immunohistochemical images of samples from all patients are presented in Fig. 2. The area encircled by the black box represents a sample of paracancerous tissue. Based on the calculation method of Pearson's correlation coefficient mentioned by Akoglu H (20), after Pearson's correlation coefficient, the results showed a correlation between XPC and IFN-γ in the tissues of patients with NSCLC. To investigate whether the expression of XPC was associated with that of IFN-γ in the tissues of patients with NSCLC, immunohistochemical analysis using cancer tissues from 140 patients with NSCLC was performed. There was a

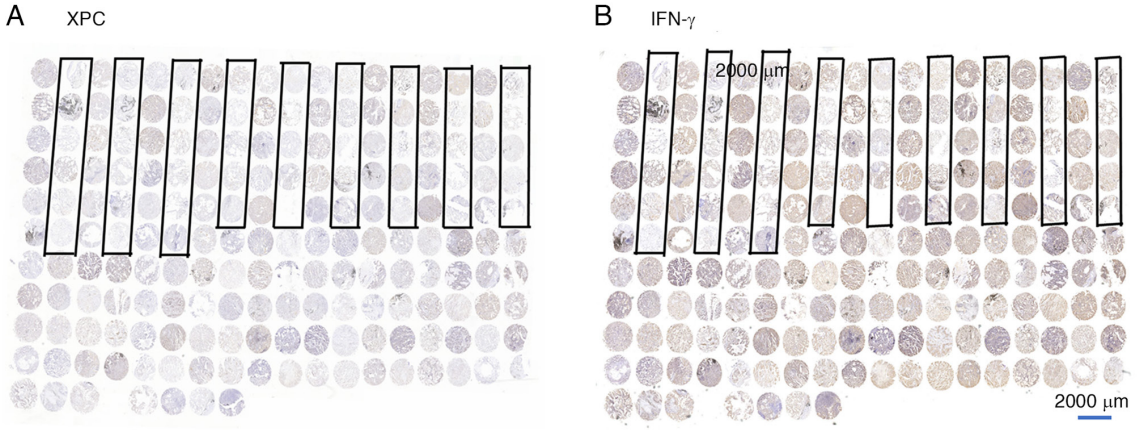

Figure 2. Establishment of tissue microarrays to investigate the expression of XPC and IFN-γ in lung cancer tissues and paracancerous tissues. (A) Expression of XPC in lung cancer tissues. (B) Expression of IFN-γ in lung cancer tissues. Paracancerous tissues shown in black box. XPC, xeroderma pigmentosum group C.

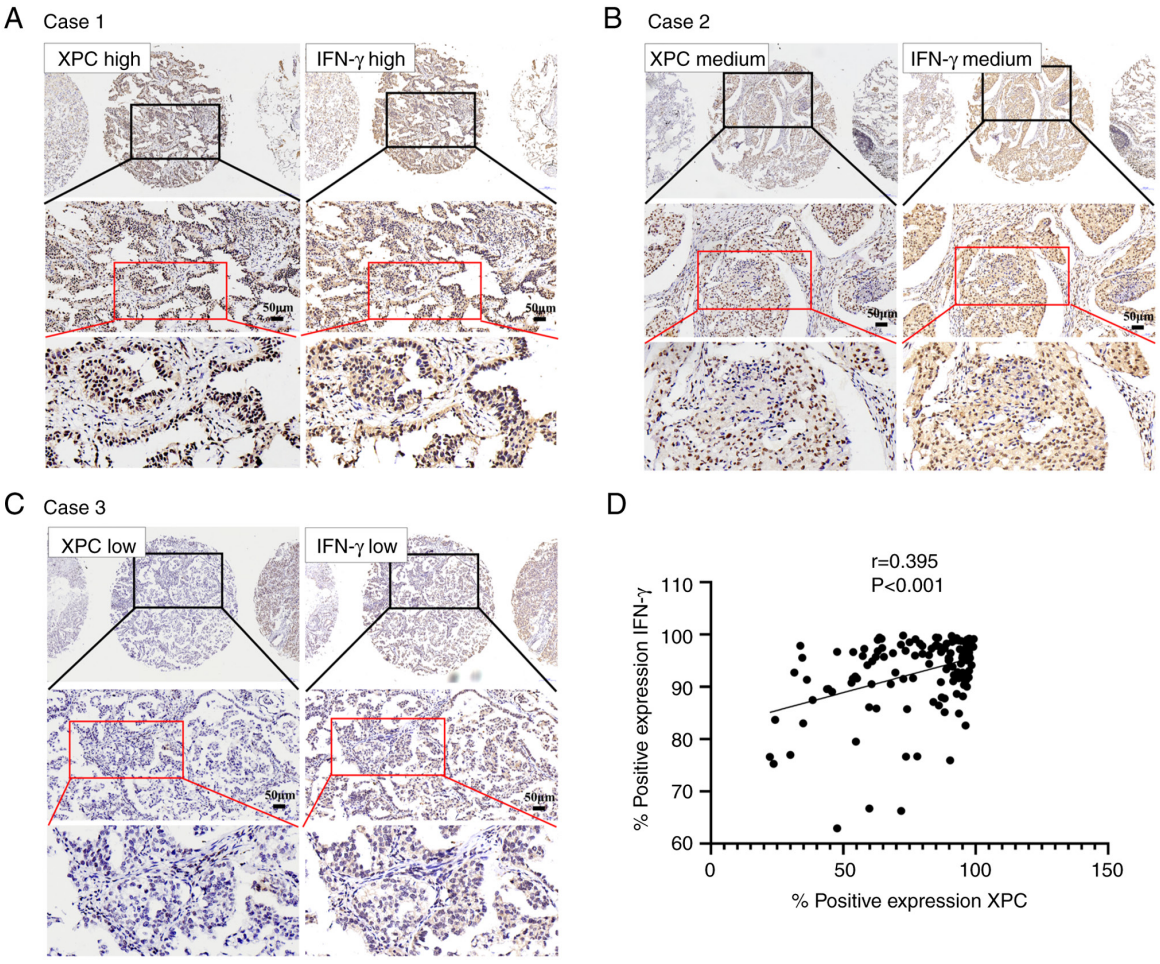

Figure 3. Correlation analysis of XPC and IFN-γ protein expression. Expression of XPC and IFN-γ in tumor tissues from three patients with non-small cell lung cancer; (A) case 1, (B) case 2 and (C) case 3. (D) Pearson's correlation coefficient for the percentage of positive XPC and IFN-γ protein expression in 140 NSCLC tumor tissues. XPC, xeroderma pigmentosum group C.

significant positive correlation between the expression of XPC and that of IFN-γ. In case 1, XPC and IFN-γ were expressed at high levels (Fig. 3A). In case 2, both XPC and IFN-γ were moderately expressed (Fig. 3B). In case 3, the expression levels of XPC and IFN-γ were weak (Fig. 3C). The expression of XPC and IFN-γ in NSCLC tissues was significantly positively correlated (r=0.395; P<0.01; Fig. 3D).

XPC and IFN-γ expression is associated with a better prognosis in patients with NSCLC. Given the correlation

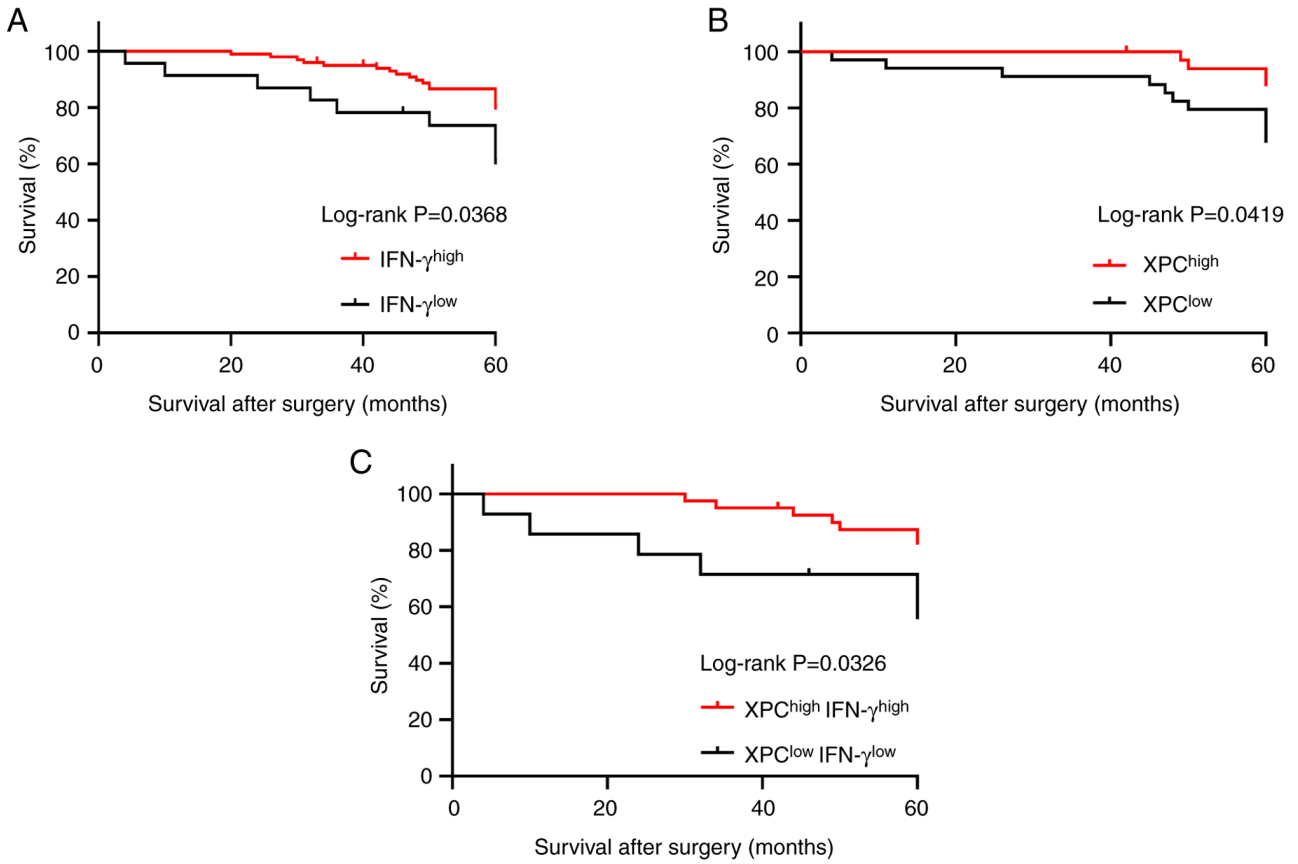

Figure 4. XPC and IFN-γ expression, and Kaplan-Meier survival analysis. (A) IFN-γ expression and Kaplan-Meier survival analysis. (B) XPC expression and Kaplan-Meier survival analysis. (C) XPC and IFN-γ co-expression and Kaplan-Meier survival analysis. XPC, xeroderma pigmentosum group C.

between the expression of XPC and IFN-γ in NSCLC tissues, the relationship between the co-expression of XPC and IFN-γ and the prognosis of patients with NSCLC was analyzed. Our previous study revealed that high XPC expression was positively correlated with a good prognosis in patients (8). High expression of IFN-γ was positively correlated with good patient prognosis (log-rank; P=0.0368, Fig. 4A), whereas analysis of XPC expression alone also showed a significant positive correlation between XPC expression and good patient prognosis (log-rank; P=0.0419, Fig. 4B). In addition, based on the expression of XPC and IFN-γ, patients were divided into the $XPC^{high}IFN\text{-}\gamma^{high}$ and $XPC^{low}IFN\text{-}\gamma^{low}$ groups and Kaplan-Meier survival analysis was carried out. The survival time of patients in the $XPC^{high}IFN\text{-}\gamma^{high}$ group was significantly longer than that of patients in the $XPC^{low}IFN\text{-}\gamma^{low}$ group (log-rank, P=0.0326; Fig. 4C).

IFN-γ expression is associated with tumor metastasis in patients with NSCLC. To further study the significance of XPC and IFN-γ expression in the occurrence, metastasis and recurrence of NSCLC, the association of XPC and IFN-γ expression with the TNM stage was investigated (21). There was no significant difference in the expression of IFN-γ at different tumor stages or N-phases (Fig. 5), but there was a significant difference in the expression of IFN-γ with tumor metastasis (P=0.036; Fig. 5H). However, XPC expression was not strongly associated with patient TNM stage.

Discussion

Lung cancer can be divided into SCLC and NSCLC according to histological classification (22). NSCLC is the most common subtype of lung cancer and can be divided into adenocarcinoma, squamous cell cancer and large-cell lung cancer. With its high incidence and recurrence, a better understanding of NSCLC is required for lung cancer treatment (23-26).

Genomic instability is the primary factor promoting the occurrence and malignant transformation of cancer (27). XPC is a protein that recognizes damage and is involved in the nucleotide excision repair pathway (7,28,29). Studies have shown that low XPC expression is associated with poor outcomes in patients with NSCLC (8,30). However, a study by Teng *et al* (31) showed that upregulation of XPC expression could increase the resistance of lung cancer cells to the chemotherapeutic drug cisplatin through the PI3K/AKT signaling pathway. This phenomenon has not been validated in animal models or clinical studies. It is hypothesized that the complex tumor microenvironment and immune microenvironment in tumor tissues can affect the physiological function of tumors. Cytological and animal experiments have shown that reduced XPC expression can promote lung cancer cell proliferation and migration (32).

IFN-γ is a key moderator of cellular immunity and is secreted by activated T lymphocytes, gd cells and natural killer cells (33,34). Studies have indicated that IFN-γ acts as an antitumor factor by activating the immune system and

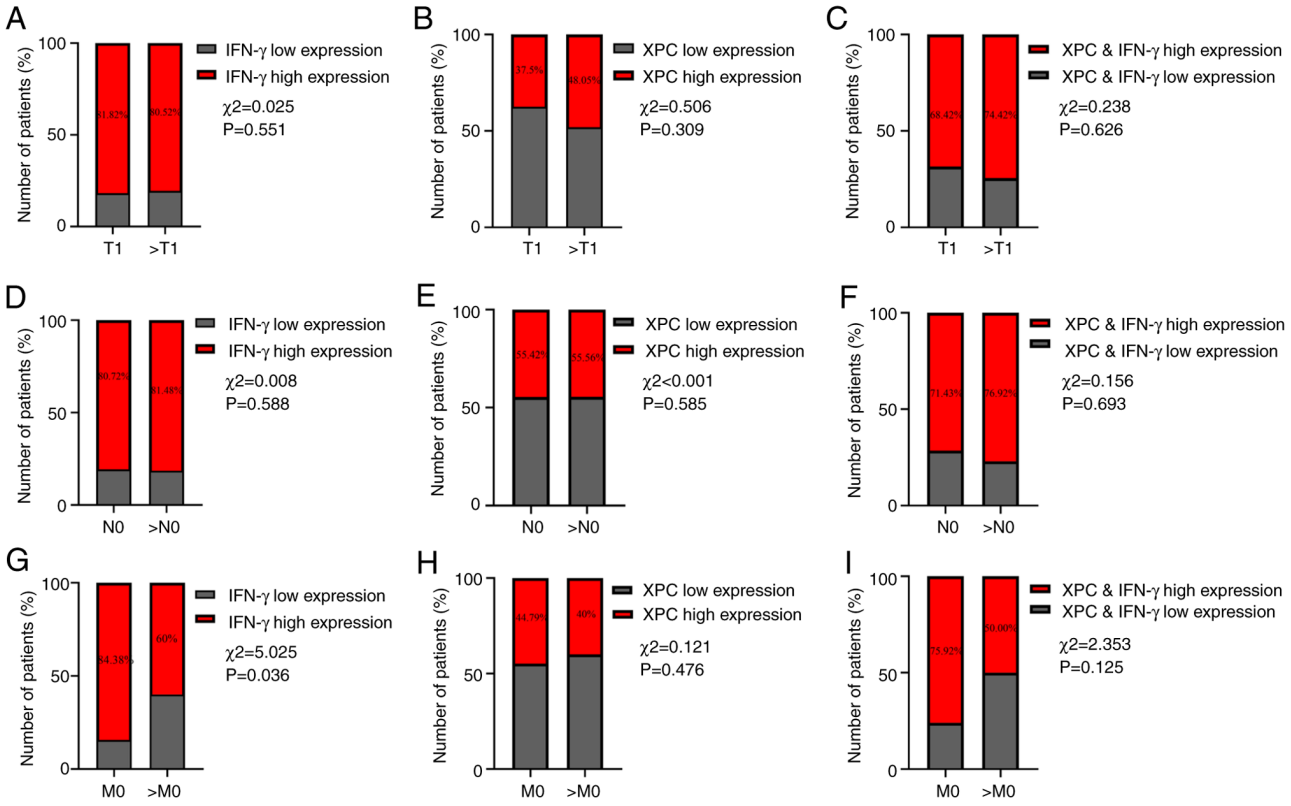

Figure 5. Association between XPC and IFN-γ expression and TNM stage. (A) Relationship between IFN-γ expression and T stage. (B) Relationship between XPC expression and T stage. (C) Relationship between IFN-γ and XPC co-expression expression and T stage. (D) Relationship between IFN-γ expression and N stage. (E) Relationship between XPC expression and N stage. (F) Relationship between IFN-γ and XPC co-expression expression and N stage. (G) Relationship between IFN-γ expression and M stage. (H) Relationship between XPC expression and M stage. (I) Relationship between IFN-γ and XPC co-expression expression and M stage. XPC, xeroderma pigmentosum group C.

triggering tumor cell apoptosis (35-37). It has also been shown that IFN-γ protects tumor cells during immune checkpoint blockade (ICB) therapy by inducing $CD4^+$ T cell apoptosis and facilitating tumor cell evasion from $CD8^+$ T cell cytotoxicity (38). It is noteworthy that IFN-γ exerts this function as a modulatory effect during the application of ICB. In general, the biological effects of IFN receptor signaling are regulated by three main factors: i) Expression profile of IFN itself; ii) profile of the receptor; and iii) expression of the target gene (39). Activated IFNs can directly initiate gene transcription and multiple downstream signaling pathways, leading to a variety of cellular responses, such as cell cycle arrest and apoptosis in tumor cells (40). Moreover, the prognostic and pathological characteristics of patients with lung cancer need to be studied further to determine the clinical significance of IFN-γ.

Both XPC and IFN-γ play important roles in cancer progression. However, the correlation between XPC and IFN-γ has not been studied. Our previous study revealed that low XPC expression could not only promote the proliferation and migration of lung cancer cells but also increase the stem cell characteristics of lung cancer cells (8). Song *et al* (41) reported that low expression of IFN-γ could confer stem cell properties to lung cancer cells through the ICAM1-PI3K-AKT-NOTCH1 pathway, while high expression of IFN-γ could induce apoptosis in NSCLC through activation of the JAK1-STAT1-caspase pathway. Low levels of XPC and IFN-γ can promote the characteristics of lung cancer stem cells. To further investigate the correlation between XPC and IFN-γ expression in lung cancer tissues in the present study, the expression of XPC and IFN-γ was investigated in the tumor tissues of 140 patients with NSCLC; it was found that the expression of XPC and IFN-γ in NSCLC was significantly positively correlated. Moreover, patients with high IFN-γ expression had a favorable prognosis. The TNM staging results indicated a decreased proportion of patients with low IFN-γ expression at stage M0, suggesting distant metastasis of tumor cells. As previously discussed, both XPC and IFN-γ can significantly influence the stemness of lung cancer cells during tumor progression. Through TNM staging analysis, it was discovered that patients with high XPC and INF-γ expression were more likely to develop distal metastases. It is hypothesized that this difference may be linked to the increased stemness of the tumor cells mentioned earlier. The significant correlation between changes in the expression of the two genes suggested a potential link between them in this process. Although the survival curves indicated that the expression of both IFN-γ and XPC significantly affects patient prognosis, the sample size limited further investigations of the correlation between the two. This limitation led to the hypothesis that a more pronounced synergistic effect was not observed. Upon analyzing the data from public databases, significant variability in XPC expression in patients was observed, with standard errors >20% in some cases. While this variability is attributed to individual patient differences, it could still potentially influence patient prognosis. In future studies, the number of clinical samples will be increased and the association between the

JAK/STAT pathway, and IFN-γ and tumor cell stemness will be investigated to elucidate the combined impact of the two on tumor cell stemness. These findings could lead to future studies investigating the interaction between XPC and IFN-γ and the mechanism through which XPC and IFN-γ affect the occurrence and recurrence of lung cancer.

In conclusion, the current study is the first to report the prognostic significance of the combination of XPC and IFN-γ detected by IHC in patients with lung cancer. The present study provides novel evidence that links XPC and IFN-γ expression in lung cancer. Evaluation of the expression of XPC and IFN-γ may lead to the identification of novel prognostic factors and therapeutic strategies for lung cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YoW and WW were responsible for collecting and preparing pathological specimens and conducting the IHC staining. HW, LQ and MZ conducted patient visits and compiled data. YZ, YuW and CH designed the experiments and provided guidance for the writing of the manuscript. MQ and GW developed the experimental protocol, funded the study and reviewed the reliability of the data. MQ and GW confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The protocols for the present study were reviewed and approved by The Ethics Committee of Weifang Second People's Hospital (Weifang, China; YX2020-001-01); all patients provided written informed consent. All analyses were conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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