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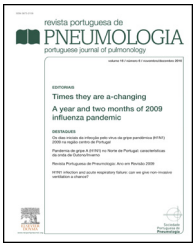

ORIGINAL ARTICLE

ERCC1 expression correlated with EGFR and clinicopathological variables in patients with non-small cell lung cancer. An immunocytochemical study on fine-needle aspiration biopsies samples

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KEYWORDS
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Abstract
Purpose: Expression of ERCC1 has not been well described in fine-needle aspiration biopsies (FNABs) in patients with non-small cell lung cancer (NSCLC). We investigated the expression of ERCC1 in correlation with EGFR expression and clinicopathological factors in patients with NSCLC in order to determine if these play a role in the prognosis of the disease.
Methods: We studied 45 patients, 34 with adenocarcinoma and 11 with squamous cell carcinoma. Of these 45 patients, 35 were males and 10 females, aged between 45 and 83 years, 30 smokers and 15 non-smokers. Eighteen (18) tumors were of stage I, twelve (12) stage II and fifteen (15) stage III. To investigate the expression of ERCC1 and EGFR (scores 0, 1, 2, 3), immunocytochemistry was performed on air dried specimens (FNABs) using monoclonal antibodies by alkaline-phosphatase (APAAP) method.
Results: ERCC1 expression was detected in tumors from 27 patients (60%) and EGFR in 10 patients (22.2%). ERCC1 was expressed more frequently in males (65.7%) in patients >65 years old (64%), in smokers (66.7%) and in stage I (66.7%). Negative ERCC1 expression was significantly associated with the presence of EGFR. EGFR was expressed only in adenocarcinomas and more frequently in women (70%) and non smokers (53.3%).
Conclusions: ERCC1 expression was identified as positive (scores 2+ and 3+) in the majority of NSCLCs and seems to be an independent prognostic marker of longer survival. In addition EGFR expression was positive (scores 2+ and 3+) in the minority of NSCLCs and only in adenocarcinomas, more frequently in ERCC1-negative (scores 0 and 1+) tumors, suggesting that it is not an independent prognostic marker for the outcome of the patients suffering from NSCLC.

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PALAVRAS-CHAVE
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Expressão ERCC1 Correlacionada com EGFR e Variáveis Clinicopatológicas em Doentes com Carcinoma Pulmonar de Não Pequenas Células. Um estudo imunocitoquímico em amostras biópsias aspirativas por agulha fina

Resumo
Objetivo: A expressão de ERCC1 não foi ainda suficientemente descrita em biópsias aspirativas por agulha fina (FNAB) em doentes com carcinoma pulmonar de não pequenas células (NSCLC). Investigámos a expressão de ERCC1 em correlação com a expressão EGFR e os fatores clinicopatológicos em doentes com NSCLC para determinar se estes desempenham um papel no prognóstico da doença.
Métodos: Estudámos 45 doentes, 34 com adenocarcinoma e 11 com carcinoma de células escamosas. Desses 45 doentes, 35 eram homens e 10 mulheres, com idades entre os 45-83 anos, 30 fumadores e 15 não fumadores. Dezoito tumores encontravam-se no estádio I, 12 no estádio II e 15 no estádio III. Para investigar a expressão de ERCC1 e EGFR (resultados 0, 1, 2, 3), foi realizada imunocitoquímica em espécimes a seco (FNAB), usando anticorpos monoclonais pelo método de fosfatase alcalina (APAAP).
Resultados: A expressão ERCC1 foi detetada em tumores de 27 doentes (60%) e a do EGFR em 10 doentes (22,2%). O ERCC1 foi expresso com maior frequência em homens (65,7%), em doentes com mais de 65 anos (64%), em fumadores (66,7%) e no estádio I (66,7%). A expressão ERCC1 negativa foi significativamente associada à presença de EGFR. O EGFR foi expresso apenas em adenocarcinomas e com maior frequência em mulheres (70%) e não fumadores (53,3%).
Conclusões: A expressão de ERCC1 foi identificada como positiva (resultados 2+ e 3+) na maioria dos NSCLC e parece ser um marcador de prognóstico independente de maior sobrevivência. Além disso, a expressão de EGFR foi positiva (resultados 2+ e 3+) numa minoria dos NSCLCs e apenas em adenocarcinomas, com maior frequência em tumores ERCC1-negativos (resultados 0 e 1+), sugerindo que não é um marcador de prognóstico independente na evolução de doentes que sofram de NSCLC.

Introduction

Primary lung cancer is the leading cause of cancer death in many countries.[1,2] Approximately 80% of primary lung cancers are non small-cell lung carcinomas (NSCLCs). Surgical resection is considered to be a curative treatment during earlier stage and adjuvant chemotherapy or radiotherapy in more advanced stage of the disease.

Excision repair cross-complementation group 1(ERCC1) is one of 16 genes that encode the proteins of the nucleotide excision in repair complex.[3,4] This multiprotein complex also links the DNA repair process with other cellular processes such as DNA transcription.

Different studies have already reported the expression of ERCC1 in human ovarian cancer cells in vitro[5] in primary gastric adenocarcinomas[6] in colorectal cancer[7] in esophageal cancer[8] and in non small cell lung cancer (NSCLC).[9]

Epidermal growth factor (EGFR) is a 17 kDa transmembrane glycoprotein which can bind and become activated by various ligands including epidermal growth factor (EGF), transforming growth factor alpha (TGFa) and certain virally encoded growth factors. EGFR overexpression is found in a variety of neoplasms such as malignant gliomas, breast and lung carcinomas. Among lung cancers, overexpression is largely due to increased transcription and is most prevalent in lung squamous cell carcinomas. Increased overexpression has also been observed in adenocarcinomas of the lung and large cell carcinomas but not in small cell carcinomas.[10] The aim of this work is to clarify and validate, in a retrospective study, the prognostic relevance of ERCC1 expression correlated with EGFR expression and other clinicopathological variables, using immunocytochemistry in cytological material (FNAB) of patients with non small cell lung cancers (NSCLCs).

Materials and methods

Forty-five patients (45) with operable NSCLC were diagnosed and studied cytologically on FNABs and had their diagnoses confirmed histologically after the operation. Diagnoses were established by both morphology and immunocytochemistry. Objective and measurable cytomorphologic differences between squamous cell carcinoma and adenocarcinoma exist. The aspirated cancer cells in adenocarcinoma are found in clusters or singly. The cytoplasm is finely vacuolated and faintly stained with indistinct cell borders. The nuclei have a delicate chromatin pattern and prominent nucleoli. In contrast tumor cells of squamous cell carcinoma have sharp cell borders, dense cytoplasm, nuclear hyperchromasia, and significant nuclear membrane irregularities. Spindle cell morphology and ''tadpole'' cells are commonly seen. However cytomorphologic differences between the two types are not always consistent. Immunocytochemistry has a significant role as an adjunct study in this context. In our settings we performed immunocytochemistry on cell block material with antibodies against TTF-1 (clone 8G7G3/1, Dako, M3575), CK7 (clone OV-TL, Dako, M7018), CK20 (clone K20.8, Dako, M7019), P63 (clone 4A4, Dako, M7247), CK5/6 (clone D5/16/B4, Dako, M7237), with the dilutions of 1:50, 1:200, 1:30, 1:60, and 1:10 respectively.