CHARACTERISTICS OF NON-SMALL CELL LUNG CARCINOMA AND THE RESULT OF EPIDERMAL GROWTH FACTOR RECEPTOR TEST

(KARAKTERISTIK KANKER PARU JENIS KARSINOMA BUKAN SEL KECIL DAN HASIL PEMERIKSAAN EPIDERMAL GROWTH FACTOR RECEPTOR)

Teja Koswara[1*], Jusron Iriawan[2], Fiona Surya[1]
[1]Department of Anatomical Pathology, Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi. Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi. Indonesia

*Corresponding author
tejakoswr@yahoo.com

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ABSTRACT

Lung carcinoma is cancer that develops from the abnormal proliferation of lung epithelial cells. Lung carcinoma has two forms: Non-Small Cell Lung Carcinoma (NSCLC) and Small Cell Lung Carcinoma (SCLC). NSCLC makes up 85% of lung carcinomas cases. EGFR overexpression is often seen in NSCLC. This research aims to discuss and provide information about the patient's characteristics, smoking status, functional status, clinical stage, histopathological diagnosis, and EGFR test of NSCLC. This research is a literature study that collects, manages, uses and reviews research data from scientific journals, previous research manuscripts, and textbooks. The literature review results were that most patients with NSCLC were found in the 55–65 age group. NSCLC can happen to both genders. NSCLC was found in smokers and non-smokers. The patient's functional status was mostly "very dependent". The clinical stage of NSCLC patients is often found in stages III and IV. The most common histopathological diagnosis of

NSCLC was adenocarcinoma. EGFR results can be positive or negative; most occur in the adenocarcinoma subtype. EGFR overexpression in NSCLC occurs due to somatic mutations in the tyrosine kinase domain, causing continuous signal transduction and phosphorylation.

Keywords: adenocarcinoma; EGFR; lung carcinoma; NSCLC

ABSTRAK

Karsinoma paru adalah keganasan akibat pertumbuhan baru dari sel epitel paru yang abnormal. Karsinoma paru diklasifikasikan menjadi dua tipe; Kanker Paru Karsinoma Bukan Sel Kecil dan Kanker Paru Karsinoma Sel Kecil. Tipe NSCLC ditemukan sebanyak 85% dari kasus karsinoma paru. Pada NSCLC sering ditemukan overekspresi EGFR. Tujuan penelitian ini untuk membahas dan memberikan informasi mengenai karakteristik pasien, status merokok, status fungsional, stadium klinis, diagnosis histopatologi, dan hasil pemeriksaan EGFR dari NSCLC. Penelitian ini merupakan studi kepustakaan dengan mengumpulkan, mengelola, menggunakan, dan mengkaji data penelitian yang bersumber dari jurnal penelitian ilmiah, manuskrip penelitian sebelumnya, dan buku teks. Hasil tinjauan pustaka, sebagian besar pasien NSCLC ditemukan pada kelompok usia 55-65 tahun, dapat terjadi pada kedua jenis kelamin. NSCLC ditemukan pada perokok dan bukan perokok. Status fungsional pasien NSCLC sebagian besar adalah sangat tergantung. Stadium klinis pasien NSCLC sering ditemukan pada stadium III dan IV. Diagnosis histopatologi NSCLC yang terbanyak adalah adenokarsinoma. Subtipe tumor dengan hasil pemeriksaan EGFR dapat positif dan negatif, sebagian besar terjadi pada subtipe adenokarsinoma. Overekspresi EGFR pada NSCLC terjadi akibat mutasi somatik pada domain tirosin kinase menyebabkan transduksi sinyal dan proses fosforilasi yang terus menerus.

Kata kunci: *adenokarsinoma; EGFR; karsinoma paru; NSCLC*

INTRODUCTION

Cancer is a disorder caused by changes in the function of genes that play a role in regulating the process of growth, defense, and aging in cells. Cancer cells regulate their cell replication autonomously and can avoid apoptosis, resulting in excessive and uncontrolled cell proliferation.[1] Lung carcinoma is a malignancy due to the new growth of abnormal lung epithelial cells and can infiltrate surrounding tissues.[2-4] Based on data from the Global Burden of Cancer Study, International Agency for Research on Cancer in 2020, lung cancer became the second most common carcinoma, reaching 2.2 million cases with 1.8 million deaths worldwide. Carcinoma is the most common in men (14.3%) and ranks third from carcinoma in women (8.4%).[3] Lung carcinoma is more common at the age of 55-65 years, has a smoking habit, exposure to carcinogens, and history of carcinoma lungs in the family.[5-7]

The diagnosis of lung carcinoma is established through anamnesis, physical examination, supporting examination, anatomical pathology examination, and examination of molecular markers.[8] Lung carcinoma is classified into two types based on histopathological features: Lung Cancer Types of Non-Small Cell Carcinoma (NSCLC) and Lung Cancer Types of Cell Carcinoma Small (SCLC).[9-11] Patients with NSCLC in Asia are diagnosed at 50-74 years old.[13] In Indonesia, patients diagnosed with NSCLC are 53-59 years of age on average.[14,15] Examination of molecular markers often carried out is Epidermal Growth Factor Receptor (EGFR) which plays a role in the process of cell proliferation and differentiation, so that overexpression of EGFR will cause uncontrolled cell proliferation. EGFR overexpression was frequently found in NSCLC with adenocarcinoma subtype, stage IV. Its moderately dependent on functional status, female gender, and non-smoker.[9,16-19] The rapidness of diagnosis, determination of tumor type and stage, and the molecular markers become a reference for determining therapy and prognosis.[13, 17] As many as 50-90% of NSCLC cases with positive EGFR expression respond well to targeted therapy with EGFR Tyrosine Kinase Inhibitors (TKIs) and have a good prognosis.[16,17,20-22]

EGFR overexpression was found to be more prominent in cases of females with NSCLC and non-smokers and related to the administration of targeted therapy. So it is necessary to conduct research on patient

characteristics, smoking status, patient's functional status, clinical stage, histopathological diagnosis, and results of EGFR test.

METHOD

The design of this research is a literature review research. Literature review research design is a method used to collect data related to the formulation of the problem in research papers obtained from various literature sources such as scientific research journals, previous research manuscripts, and related textbooks and can answer the number of samples of scientific research journals used in research.

A literature search combined "NSCLC" and "EGFR Tests" was performed. The chosen descriptors in articles published on the topic and in the Medical Subject Headings (MeSH), PubMed, NCBI, Science Direct, and American Society of Clinical Oncology (ASCO) databases were accessed, covering the period from 2016-2021.

Inclusion and exclusion criteria English-language publications with the title and abstract related to the topic were included. Incomplete articles, duplicated ones, studies on animals, and those that, when read, did not fit the proposed theme were excluded from the research.

RESULT

The search resulted published papers, with potentially eligible identified after applying the inclusion and exclusion criteria. After reading these papers in full, literature remained**.**

DISCUSSION

Lung Carcinoma Classification

Lung carcinoma is divided into two types: Lung Cancer Non-Small Cell Carcinoma (NSCLC) and Lung Cancer Small Cell Carcinoma (SCLC). Lung carcinoma type NSCLC is more common (85%), while SCLC is only 5-10% of lung carcinoma cases. Although rare, SCLC is more aggressive and easily spreads to other organs. In addition, NSCLC responds better to therapeutic targets.[8,9]

Classification of NSCLC

NSCLC is classified into three subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma occurs in 40% of lung carcinoma cases. Adenocarcinoma is a malignant epithelial neoplasm with glandular differentiation and mucin production. Tumor cells form a lepidic pattern, forming an acinar (glandular), papillary, micropapillary, or solid structure.[23] The most common adenocarcinoma subtype found in NSCLC

with positive EGFR expression (95%).[7,10,16]

Squamous cell carcinoma occurs in 25-30% of lung carcinoma cases and strongly correlates with smoking.[7] This tumor is initiated by the process of squamous metaplasia and dysplasia that occurs in the bronchial epithelium.[24] Consists of squamous cells with pleomorphic, hyperchromatic, and nucleolus. In well-differentiated tumor cells, intercellular bridges are seen. In this tumor can be found keratinization, which forms a horn pearl.[10]

Large cell carcinoma occurs in 5-10% of carcinoma cases and is strongly associated with smoking risk factors. Large polygonal tumor cells are generally arranged in solid islands. There is no squamous or glandular differentiation. Tumor cells are well-demarcated, with abundant cytoplasm. Pleomorphic nuclei, vesicular or hyperchromatic, may be accompanied by nucleolus.[10,23]

Clinical Stage

The classification of the TNM system for lung cancer according to the American Joint Committee on Cancer (AJCC) 8th edition is as follows[25]:

Table 1. Stage grouping for lung carcinoma

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Previous studies have found that most NSCLCs are diagnosed at stages III, and IV.[26] NSCLC cases with positive EGFR expression are mostly patients with stage IV.[16]

Functional Status

Functional status or independence index is a parameter for the patient's ability to carry out daily activities. The functional status of the patient was determined based on the Katz Index.[27]

Table 2. Functional status of patients according to Katz Index.[27]

ACTIVITIES POINTS (1 OR 0)	INDEPENDENCE: (1 POINT) **NO** supervision, direction or personal assistance	DEPENDENCE: (0 POINTS) **WITH** supervision, direction, personal assistance or total care
BATHING POINTS:_____	(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.	(0 POINTS) Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
DRESSING POINTS:_____	(1 POINT) Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	(0 POINTS) Needs help with dressing self or needs to be completely dressed.
TOILETING POINTS:_____	(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING POINTS:_____	(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	(0 POINTS) Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE POINTS:_____	(1 POINT) Exercises complete self control over urination and defecation.	(0 POINTS) Is partially or totally incontinent of bowel or bladder.
FEEDING POINTS:_____	(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.

A total score of 6-5 indicates an independent patient, a score of 4-3 indicates a moderately dependent patient, and a score less than equal to 2 indicates a highly dependent patient.[27] Most patients with long-standing carcinoma will experience difficulty in at least one of the six daily activities listed on the Katz index. They needed assistance to carry out daily activities, or the patient had a highly dependent functional status.[28]

Risk Factor

The peak incidence of lung cancer occurs in people aged 55-65.[7.] Lung carcinoma is more common in men due to smoking behavior. But in the case of NSCLC with positive EGFR expression, it was found more in non-smoking women. Female gender is a prognostic factor for EGFR expression.[29] Smoking has a high risk for someone developing lung cancer. Carcinogenic cigarette substances can cause DNA changes, so mutations in the K-RAS and TP53 genes occur.[30] In addition to the content of cigarettes, exposure to cigarette smoke, known as Environmental Tobacco Smoke (ETS), can also cause lung cancer.[31] Risk of lung cancer caused by smoking was 91% for squamous cell carcinoma, 95% for large cell carcinoma, and 82% for adenocarcinoma. Smoking is a negative predictor of EGFR expression.[29] NSCLC occurring in non-smokers is also known as "non-smoking-associated lung cancer" and may be associated with gene mutations such as EGFR. EGFR expression was more commonly found in non-smokers compared to smokers.[32] Also, exposure to carcinogenic compounds and a family history of carcinoma can be a risk factors for lung cancer.[7.33]

Molecular Marker: EGFR

Epidermal Growth Factor Receptor is a glycoprotein gene with a receptor tyrosine kinase that plays a role in cell cycle regulation. EGFR consists of extracellular and intracellular regions. The extracellular consists of 4 domains, domains I and III for ligand binding. Domain II forms a homodimer or heterodimer. Domain IV is connected to a transmembrane domain (TM) which plays a role in dimerization. The tyrosine kinase domain plays a role in signal transduction. It is related to three processes of activation of intracellular signals: binding of ligands to receptors via the PI3K pathway, PLC-α, RAS, dimer formation, and phosphorylation.[34,35] Phosphorylation will trigger the delivery of intracellular signals to the cytoplasm and then to the nucleus via the RAS- pathway. RAF-MEK-ERK-MAPK, which controls gene transcription and cell cycle progression, STAT pathway

to induce transcriptional pathways, PI3K-Akt-mTOR pathway activating anti-apoptosis, and angiogenesis.[34-36]

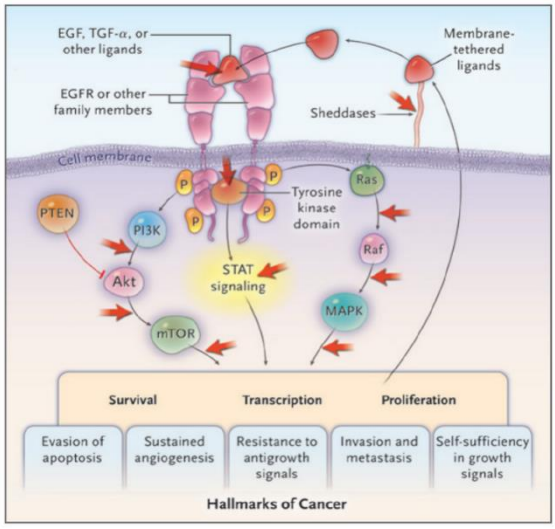

Figure 1. EGFR signal transduction pathway.[37]

Positive or negative EGFR can follow NSCLC. It is related to the risk factors of NSCLC on EGFR expressions, such as old age, female gender, and non-smokers.[38] NSCLC with positive EGFR expression tended to be found in women, non-smokers, and adenocarcinoma subtypes.[9] 95% of adenocarcinoma subtypes had positive EGFR expression.[16] The average EGFR expression in NSCLC was 31.6%.[39]

Pathogenesis

EGFR overexpression occurs due to abnormal signal transduction. Its excessive causes activation of ligand binding and downregulation inhibition of of EGFR protein. That occurs by endocytosis in cell membranes. In the end, it causes carcinogenesis, uncontrolled cell proliferation, angiogenesis, and inhibition of apoptosis.[40] Cell proliferation can occur due to EGFR-dependent kinase function. Cell survival is related to defenses to stay alive such as angiogenesis, resistance to apoptosis, and metastasis, due to the pro-survival Kinase Independent (KID) function of EGFR located in 3 functional domains of carcinoma cells. The cell membrane interacts with three systems; Sodium Glucose co-Transporter1 (SGLT1) to maintain active glucose uptake of cancer cells, Cystine-Glutamate (XC) antiporter system to maintain cystine, Fatty Acid Synthase (FASN) to maintain fatty acid synthesis, Mammalian Target Rapamycin Complex2 (mTORC2) complex to suppress Act. In the autophagy domain, it will interact with Lysosomal Protein Transmembrane 4 Beta (LAPTM4B), which activates pro-survival autophagy. While in the mitochondria, KID will interact with the P53 Upregulated Modulator of Apoptosis (PUMA) to inhibit apoptosis.[40,41]

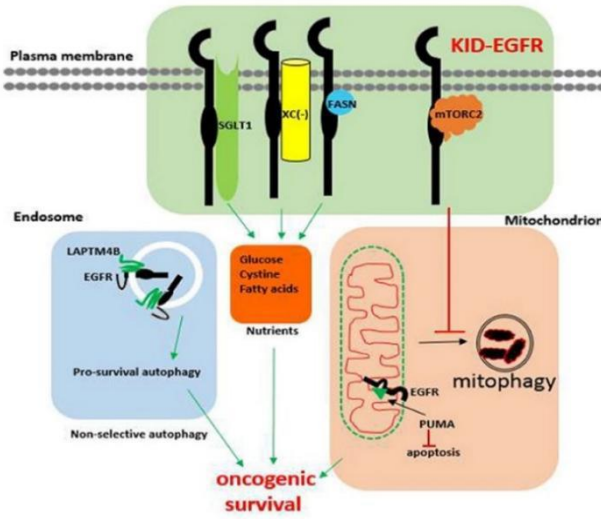

Figure 2. Kinase independent.[40]

Therapy

Therapy can be done in surgical therapy for stages I and II. Chemotherapy is the first line for patients from stage IIIA. Radiotherapy can help control tumors that are localized in certain places. Targeted therapy is a treatment that targets specific proteins in carcinoma cells in the form of chemical compounds. NSCLC patients with positive EGFR expression can be given targeted therapy, namely Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors (EGFR-TKIs).[20] EGFR-TKIs will bind to the tyrosine kinase domain of the EGFR gene, thereby inhibiting continuous signal transduction for cell proliferation. Female patients and non-smokers do better with targeted therapy than men and smokers.[29] Gefitinib and erlotinib are first-line EGFR-TKIs, while afatinib is second-line.[36] As many as 50-90% of cases of NSCLC with positive EGFR expression have a good response and prognosis.[42] The use of this therapy increases survival for more than 30 months.[43]

CONCLUSION

From the research, it can be concluded that most patients with NSCLC are found in the 55–65 year age group. NSCLC can happen to both genders. NSCLC was found in smokers and non-smokers. The functional status of most NSCLC patients was "very dependent." The clinical stage of NSCLC patients is often found in stages III and IV. The most common histopathological diagnosis of NSCLC was adenocarcinoma. EGFR results can be positive or negative; most occur in the adenocarcinoma subtype.

CONFLICT OF INTEREST

There is no conflict of interest in the scientific articles written.

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