REVIEW

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The role of ROS1 mutation in non-small cell lung cancer

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ABSTRACT

Lung cancer is a malignancy of the lung organs consisting of primary lung cancer originating from lung epithelial cells and metastatic lung cancer originating from other organ cancers that spread. In lung cancer, the vast of recent studies investigated the role of molecular alterations in patients. Molecular characterizations of lung cancer give further information in order to better diagnosis, prognostic, and therapeutic implications in patients. c-ROS oncogene 1 (ROS 1) is naturally expressed by healthy and normal cells arranged in human chromosomes. The role of ROS1 in its normal development is not fully understood. Point of view in oncology ROS1 expressed normally is referred to as inactive ROS1. Mutated ROS1 due to fusion with a specific gene produces tyrosine kinase receptors on the surface of the cell that has the advantage of sending signals into the cells to induce growth factors and proliferation of ROS1. Although the prevalence of ROS1 rearrangement was low, the parallel with Non-Small Cell of Lung Cancer (NSCLC), the most dominant lung cancer, indicating the number of ROS1 mutation patients also increased. The challenge of diagnosing ROS1 mutation by Immunohistochemical (IHC) ROS1 is only a screening method and confirmed by fluorescence in situ hybridization (FISH) examination. The appropriate therapy regimen for positive ROS1 mutation will increase the survival rate in lung cancer patients.

Keywords: ROS1, Fusion, Mutation, Rearrangement, NSCLC.
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INTRODUCTION

Lung cancer is a malignancy of the lung organs consisting of primary lung cancer originating from lung epithelial cells and metastatic lung cancer originating from other organ cancers that spread.[1] Based on statistical tests, the incidence of cancer from 36 types of cancer in 185 countries in 2020, lung cancer ranks second (2,206,771 cases/11.4%) after breast cancer. Unfortunately, lung cancer ranks top in death cases (1,796,444 cases/18.0%) of all cancer-related deaths.[2] Based on the histopathological results of Non-Small Cell Carcinoma Lung Cancer (NSCLC) is the most common lung cancer, which is 80% of all cases compared to other types. Approximately 50% of lung cancer cases have metastases and extensive lung damage.[3] The 5-year life expectancy for lung cancer is 56% if the cancer is still located in the lung, but only 5% for metastatic lung tumors.[4]

Cancer cells that were previously normal cells where changes occur due to cell failure in the process of repairing Deoxyribose nucleic acid (DNA) due to various influences such as radiation, chemicals, and viruses.[3,5] The hallmark of cancer cells is a framework to guide researchers' efforts to understand the molecular mechanism.[6,7] Ten advantages of cancer cells are known including, Supporting proliferation signals, avoiding growth suppressor genes, avoiding the immune system, replicating ability, promoting tumor inflammation, invasion and metastasis, angiogenesis, mutation, resistance to apoptosis, and deregulation of cellular energy.[7] Supporting proliferative signaling (sustaining proliferative signaling) is the ability to develop constantly. Normal cells will manage production strictly to the number of cells produced, tissue structure, and function. Cancer cells on the contrary cancer cells are regulated by signals in a cascade (which is the same level or stages, where each level processes the results of the previous level),[8] which allows cancer cells to be free in unrestricted growth. One of the abilities of cancer cells to maintain proliferative signaling is that cancer cells produce growth factors and their receptor molecules suitable for autocrine stimulation[9] (molecules producing cells that also have receptors for these molecules to respond to the cell itself can thus activate or inhibit the cell).[10]

In lung cancer, the vast of recent studies investigated the role of molecular alterations in patients. Molecular characterizations of lung cancer give further information in order to better diagnosis, prognostic, and therapeutic implications in patients.[11] ROS1 is a receptor tyrosine kinase found on the surface of cancer cells that constitutively promotes the effects of autocrine-stimulated oncogenes which mostly result in rearrangements of these cancer cells to proliferate, invade, metastasis, angiogenesis and even resistance to apoptosis.[12] This gene was found to be associated with progression of numerous tumors. A previous study stated the ROS1 gene involvement, such as ROS1 rearrangement was found in 0.9 to 2.6% of NSCLC patients. In addition, most of the cases were adenocarcinoma.[13]

The ROS1 gene have capability to encode a receptor tyrosine kinase and can be identified in human tumors, including NSCLC. The detection of ROS1 rearrangement is important to determine the treatment to the NSCLC patients. It can be performed using certain techniques, such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) and molecular examination (reverse transcription-polymerase chain reaction (RT-PCR)). These methods may guide the clinician to recognize any rearrangement of ROS1 and give a better diagnosis and further decides a better treatment to the NSCLC patients.[14] The previous studies have mentioned about ROS1 mutation in lung cancer, however there is not much study discuss about ROS1 mutation in lung cancer, particularly in NSCLC. This study aims to review and give a better understanding about ROS1 mutation in NSCLC (characteristics, epidemiology, signaling pathway, NSCLC examination, diagnosis, therapy, and also ROS1 resistance).

ROS1 CHARACTERISTICS

ROS1 is a human coding gene located at 6q22 on the long arm of chromosome six. ROS1 is homologous or has a common origin with chicken c-ROS, the v-ROS proto-oncogene of avian sarcoma virus UR213.[15] A full-length cDNA c-ROS1 encodes 2347 amino acids with a molecular weight of 259 kDa, the first amino acid sequence through 1861 forms the extracellular domain, and the amino acid sequence 1862-1882 forms the transmembrane domain, and 464 terminal amino acids constitutes the cytoplasmic domain (**Figure 1**).[16] ROS1 is naturally expressed by normal cells. The highest expression of ROS1 protein in adults besides in the kidney, was also found in the cerebellum, peripheral nervous tissue, stomach, small intestine, colon, and with low levels in several other tissues. ROS1 is abnormally expressed in the lung.[17] The role of ROS1 in normal development is not fully known, but in normal cell development, cells will strictly manage the progression and prevent cell differentiation. From an oncological point of view, normally-expressed ROS1 is referred to as inactive ROS1.[18]

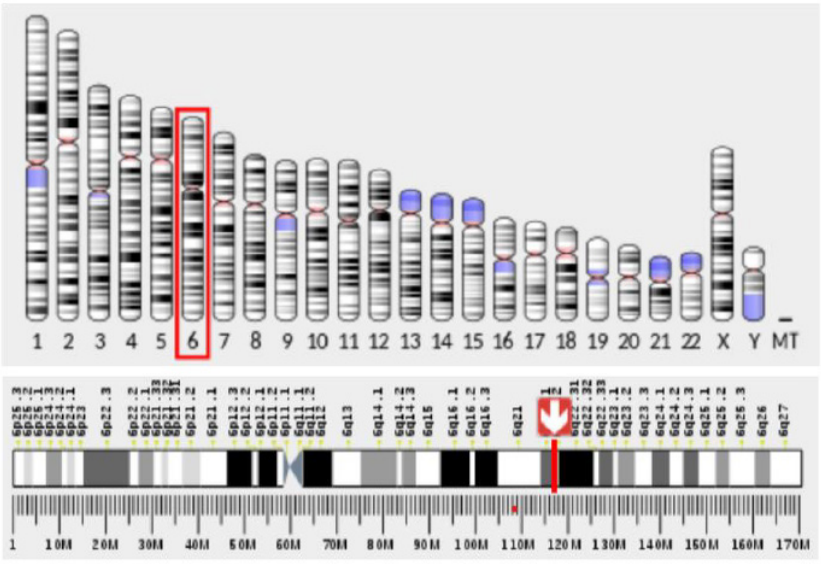


Figure 1. The location of ROS1 gene in Human Chromosome.[17]

The activation of ROS1 is if there is a fusion of pieces of other genes that match ROS1 that occurs due to mutations in DNA to the arrangement of the chromosomal chain which changes the DNA structure and is accompanied by failure of the cell in the process of repairing damaged DNA.[3,19] The ROS1 fusion gene was first discovered as FIG-ROS1 in glioblastoma cells in humans and later in cholangiocarcinoma. Several ROS1 fusion pairs have been identified in lung cancer including SLC34A2, CD74, TPM3, SDC4, EZR, LRIG3, KDEL R2, LIMA1, MSN, CLTC, CCDC6, TMEM106, FIG, GOPC, and TPD52L1, most of the ROS1 fusion pairs involve rearrangements (ROS1 rearrangement) with other chromosomes sometimes fusion pairs involve inversions within chromosome six itself (**Figure 2**). ROS1 in a wider tumor profile the number of ROS1 fusion pairs is likely to continue to increase.[12,19] The ROS1 fusion that occurs changes the structure of the genetic coding to produce enzymes. The protein or enzyme encoded by the gene is a type 1 integral membrane protein with tyrosine kinase activity that functions as a growth or differentiation factor receptor or also known as ROS1 rearrangement. This proto-oncogene is highly expressed in various tumor cell lines and is an addictive oncogenic driver associated with malignancy in lung epithelial cells.[12,15,20]

THE EPIDEMIOLOGY OF ROS1 REARRANGEMENT

Lung cancer consists of NSCLC and Small-cell Carcinoma Lung Cancer (SCLC). NSCLC accounts for 80% of all lung cancer incidence rates. With a percentage of 40% of adenocarcinoma, and 30% of squamous cell carcinoma, the rest are large cell types.[3,21] In addition to lung cancer, ROS1 rearrangement has also been identified in several other cancers such as cholangiocarcinoma, ovarian carcinoma, and gastric carcinoma, with a prevalence of 0.6%-3% ROS1-positive cancers.[12,22] A meta-analysis of epidemiological studies of ROS1 rearrangements in Asians and non-Asians consisted of 11,665 ROS1-positive of NSCLC and ROS1-positive SCLC patients either with IHK, FISH, or qRT-PCR, the study also included assessing clinical variables, age, gender, smoking history and disease stage from 20 published studies globally the prevalence of lung cancer with ROS1 positive was 2% (95% CI: 0.016-0.026) and was higher in Asia [2.2% (95% CI: 0.016-0.029)] than in non -Asian [1.9% (95% CI: 0.012–0.027)] ($p = 0.92$), with the mean ages of Asians and non-Asians being 54.5 years and 59 years, respectively. In general, rearrangement of ROS against lung cancer in stage III and IV adenocarcinoma lung cancer. Overall ROS1 positivity was higher in women than men, ROS1 rearrangements were more

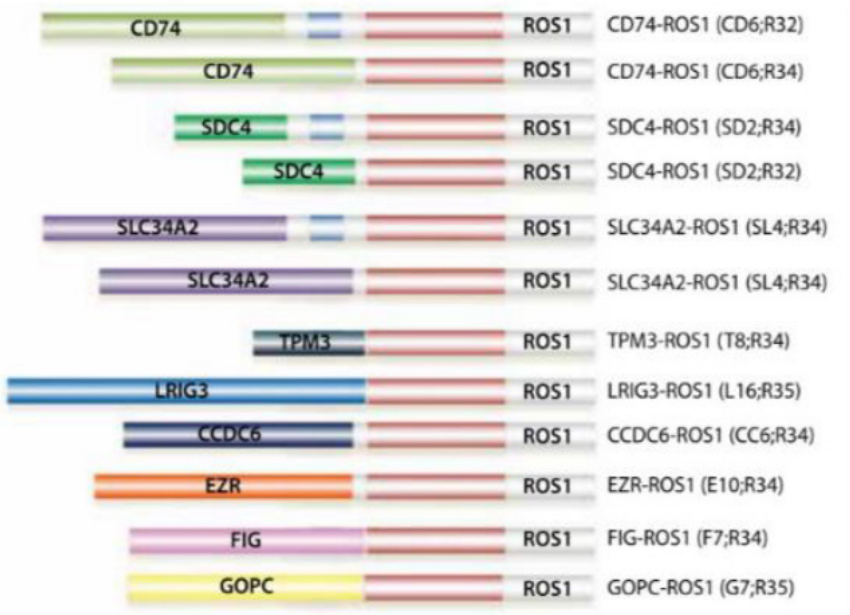


Figure 2. The fusion of ROS1 rearrangement

common in nonsmokers than in smokers, but ROS1 positivity in Asians was more common in smokers.[22]

ROS1 SIGNALING PATHWAY

ROS1 is one of 58 receptor tyrosine kinases in humans described as receptor tyrosine kinase "Orphan" whose ligand is unknown.[12,23] ROS1 is evolutionarily associated with Anaplastic Lymphoma Kinase (ALK) and Epidermal Growth Factor Receptor (EGFR). Unlike ALK, the majority of ROS1 fusions do not have a coiled domain that promotes spontaneous dimerization and kinase activation, however, some ALK inhibitors can inhibit the proliferation of the HCC-78 cell line leading to ROS1 rearrangements, in that ROS1 signaling pathway also shares similarities with ALK.[23] Several studies have been carried out with chimeric receptors containing ROS1 domains where ROS1 receptor tyrosine kinase binds to EGFR or TRKA ligands. When cells express these chimeras, they are stimulated with appropriate growth factors and activate various signaling components.[17,23] Both ROS1, ALK and activated EGFR have the same pattern in signaling to cells for transformation.

The occurrence of transformation, proliferation, increased translational capacity, ability to metastasize, angiogenesis, and resistance of cancer cells due to rearrangement of ROS1 are then followed by a signaling process below the surface of cancer cells in the nucleus by ROS1 receptor kinase which is activated and occurs in stages, in other words, the signal causes Cells to change in appearance, both form, function, and characteristics.[24] ROS1 uses several signaling pathways to exert transforming activities such as Phospholipase C gamma (PLCy) signaling, Signal transducers and activator of transcription-3 (STAT3), mitogen-activated protein kinase (MAPK), and the cytoskeleton of cell-to-cell interactions (β1-integrin tensin, , α-, β-, δ-catenin, N-catenin) for transformation, apoptosis, cancer cell proliferation for cancer cell resistance. Signaling Insulin receptor substrate 1 (IRS) signaling to Phosphoinositide 3-kinase (PI3K) is useful for increasing the translational capacity of genetic material. Vav 3 guanine nucleotide exchange factor 1 (VAV3) signaling for the ability of cancer cells to metastasis and migrate (**Figure 3**).[23,25]

In a previous study, EGFR pathways may also have a role in therapeutic implications for NSCLC patients. An interaction is found between EGFR ligands and the extracellular domain of the receptor which leads to dimerization and further promotes the activation of the tyrosine-kinase domain. When this domain is activated, the previous domain will promote the autophosphorylation of certain sites in the C-terminal domain of EGFR. The signaling pathway is then continued by the interaction of autophosphorylation sites which contains the Src homology 2 domain or phosphotyrosine binding domain within the protein. Various phosphorylation sites have been identified in the c-terminal domain of EGFR, which leads to another interaction with different types of molecules and cellular pathways, mostly occured, the MAPK pathway. The MAPK pathway is a pathway in which the adaptor protein Grb2 binds with phosphorylated tyrosine residues of EGFR, further activating the proteins. These proteins will activate the G-protein Ras, which will initiate a cascade of phosphorylation of MAPK. This pathway is specific to certain proteins such as serine/threonine kinase which lead to the activation of gene transcription that is related to some regulatory functions, such as cell adhesion, motility, and also cell progression.[26]

Another previous study also discussed the role of ALK gene mutations in NSCLC patients. There are some mutation types of the ALK gene, such as rearrangement, amplification, and point mutation. Most of the mutations are in the form of translocation with another matched gene and form a fusion oncogene. The rearrangement of the ALK gene generally forms an oncogenic tyrosine kinase that activates many downstream signaling pathways that yields an increase in cell proliferation and cell survival.[27] The first ALK mutations described in NSCLC were found in Japan and were found to be associated with EML4. The EML4-ALK rearrangement was inversion from inv.(2)(p21;p23) which indicates EML4 replaces the extracellular and intramembranous part of ALK and fusion with the domain in juxtamembrane. The translocation of the EML4-ALK fusion gene resulted in the constitutive ALK kinase activity and further induced tumor formation in a previous study conducted in mice.[27]

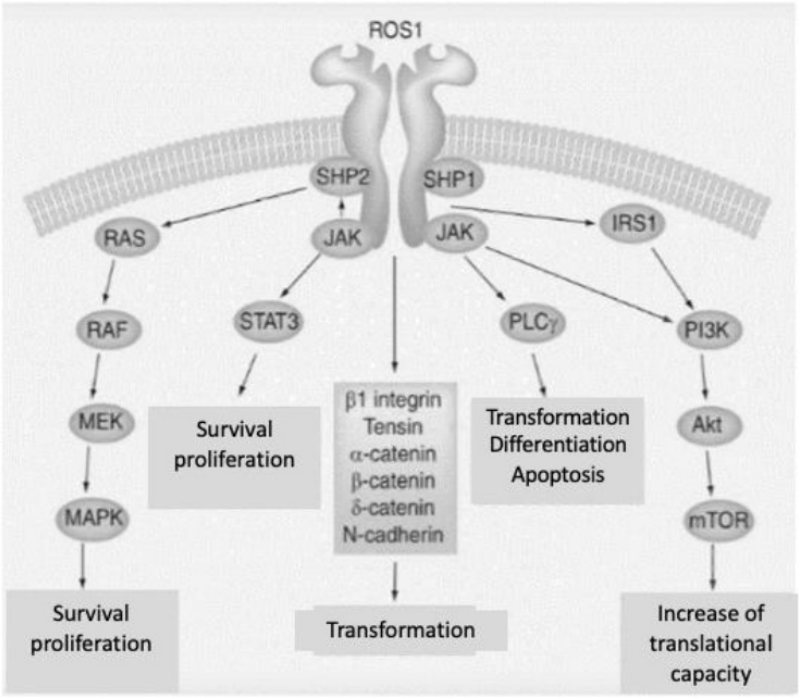


Figure 3. The transudative signaling pathway of ROS1

THE EXAMINATION OF NSCLC

Examination of the expression of the ALK and ROS1 gene rearrangements is important for selecting the appropriate therapy. The prevalence of KPKBSK patients undergoing ALK rearrangements was approximately 4% slightly lower for patients with ROS1 rearrangements with a prevalence of 2%.

Most ALK or ROS1 rearrangements were found in lung cancer from nonsmokers or light smokers, women, young patients, and adenocarcinoma-type lung cancer. It is not clear that certain phenotypic characteristics can help in determining which patients should undergo ALK and ROS1 examinations.[12,19] The diagnosis of lung cancer is often made based on examination of small biopsy specimens via TTNA, scrapings or FNAB, cytological samples such as sputum, pleural effusion fluid, and bronchial washings, the diagnosis of histopathological examination of small biopsy specimens does not always represent the overall examination of the tumor. The non-uniformity among lung cancer studies may be related to the difficulty in diagnosing certain types of NSCLC. Therefore CAP, IASLC, and AMP suggest that ALK and ROS1 examination of histological samples from large biopsies or tissue sections are important selection criteria in establishing subtypes of lung cancer (**Figure 4**).[19,28]

*TTNA : Trans Thoracal Needle Aspiration, FNAB : Fine Needle Aspiration Biopsy, CAP : College of American Pathologists, IASLC : International Association for the Study of Lung Cancer, AMP : Association for Molecular Pathology.

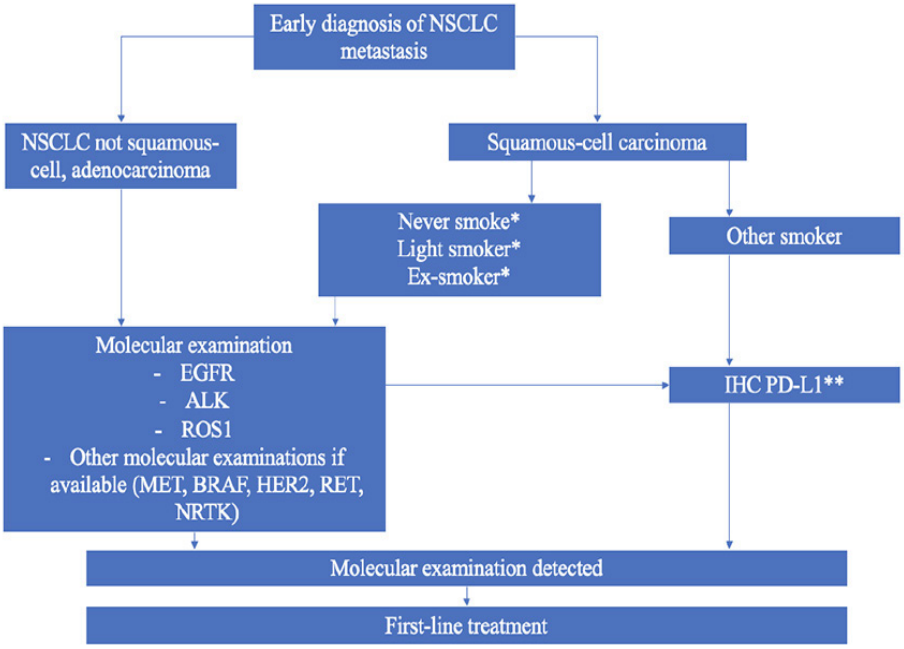
The management of NSCLC patients becomes more complex with several tests to determine oncogene subtypes. The biomarkers of NSCLC are considered standard and are part of the diagnostic algorithm to identify patients in determining treatment with chemotherapy, TKI regimens, or ICI. There are slight differences in the algorithms published in different states but generally have the same understanding. For example, based on the CAP/IASLC/AMP algorithm recommends examination of EGFR, ALK, ROS1, and PD-L1 both in non-squamous cell and squamous cell carcinomas without any conditions, the APSR algorithm recommends examination of EGFR, ALK, ROS1 and PD-L1 in NSCLC cancers non-squamous cell or squamous cell carcinoma with the condition that the patient is not a smoker, a light smoker, or a former smoker. CSCO and ESMO require examination of EGFR, ALK, ROS1, and PD-L1 in non-squamous cell patients and recommend the type of squamous cell carcinoma with the requirements of the APSR recommendation.[28] The difference is that there are differences in the prevalence of lung cancer mutations based on certain phenotypes as well as the availability of facilities in each state and region where the examination is carried out.

*TKI : Trans Kinase Inhibitor, ICI : Immuno Check Point Inhibitor, PD-L1 : Program Death Ligand 1, APSR : Asian Pacific Society of Respirology, CSCO : Algoritma Chinese Society of Clinical Oncology, ESMO : European Society of Medical Oncology.

There is a new method of examination where when compared to sequential single-gene testing, the Multigene OncoPANEL method test is the Next Generation Sequencing (NGS) examination, which is a biomarker that can detect 12 mutated genes in cancer cells simultaneously and ROS1 is one of them can also be used for monitoring and seeing resistance patterns. Multigene OncoPANEL can detect limited samples and use cytological examination samples and is cheaper when compared to all single-gene assays examined one by one with only one NGS assay, however, this method is not yet used in general and further studies on its efficiency and benefits are needed.[19,29]

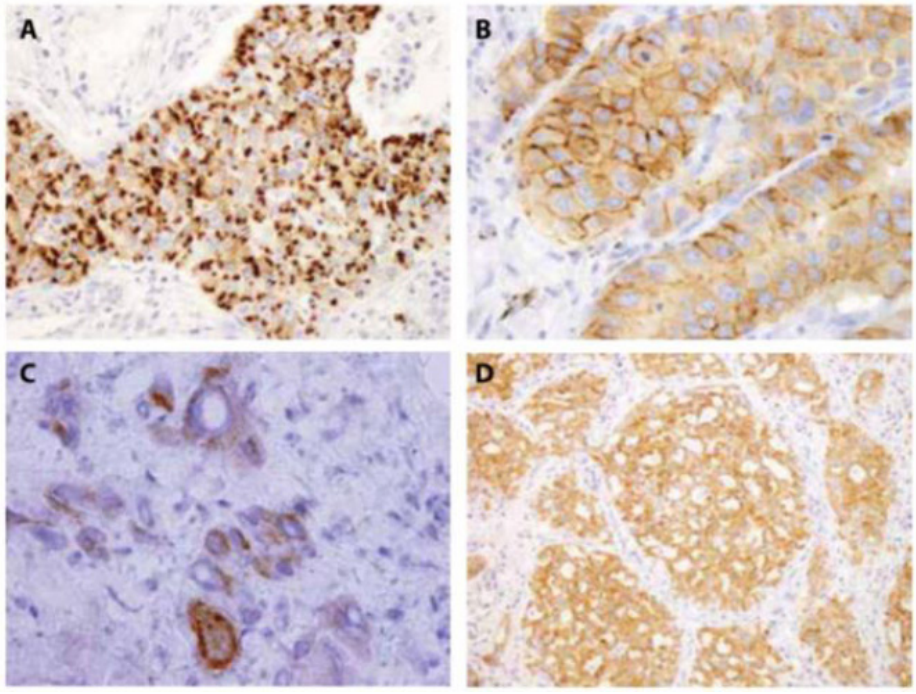
THE DIAGNOSIS OF ROS1 REARRANGEMENT

Rearrangement of ROS1 detected 1-2% of lung cancer NSCLC adenocarcinoma type. ROS1 rearrangements occur in younger, non-smoking individuals. Substantially, patients with ROS1 rearrangements have a good response to TKIs that have been approved by the Food and Drug Association (FDA) in America and Europe. Most of the ROS1 rearrangement fusions are easily detected by FISH. Considering the rare occurrence of ROS1 rearrangements plus the high cost of FISH examinations, screening tests such as IHC ROS1 examinations are needed. In its management, IHC ROS1 is used as a screening tool and if the results are positive or doubtful, then followed by FISH or



*Never smoker: Never been smoking or smoke <100 cigarettes in entire life
*Light smoker: smoke <15 packs per year
*Ex-smoker: ex-smoker >10 years
**IHC-PD-L1 examination can be performed with other molecular examination in early diagnosis.

Figure 4. The algorithm of molecular examination diagnosis.



A. Fusion of CD74-ROS1 fusion, B. EZR1-ROS1 fusion, C. SLC34A2-ROS1 and SDC4-ROS1 fusion, D. Similar to ALK CPI, ROS1 rearrangement tumors are almost always positively diffuse.

Figure 5. ROS1 fusion protein pattern on histopathological examination[16]

NGS examination as a confirmation stage.[16,19,23,25]

In published studies, IHC ROS1 examination was carried out only on tissues that had been fixed by the formalin-fixed paraffin-embedded (FFPE) method to take tissue slices and then carry out Immuno-staining which later this assessment was carried out by an anatomical pathologist25. To date, only D4D6 clones are commercially available ROS1 antibodies for application in immunostaining, however, assay techniques vary which may reflect the approach to the results obtained. Several fusions are frequently reported in histopathological examination of ROS1 rearrangements such as CD74-ROS1 is the frequently reported fusion associated with ROS1 rearrangements which have a granular cytoplasmic pattern with intense focus or diffuse spherical protein aggregates and other fusions, EZR-ROS1 appears to be correlated with weak cytoplasmic expression with membrane accentuation, SLC34A2-ROS1 and SDC4-ROS1 showed dense cytoplasmic ROS1 staining (**Figure 5**). The challenge facing IHC ROS1 assays must be confirmation of FISH or NGS, the expression of ROS1 mRNA that produces protein is generally low and sometimes can be promising in contrast to the expression of ALK rearrangements which are almost all specific with ALK IHC assay.[19,30]

FISH with set probe break apart was originally developed to detect gene fusions created by interchromosomal translocations, FISH is a reliable pro-diagnostic method with FFPE specimens. FISH was designed to mark the 3' telomere portion (approximately 300kb) with the fluorochrome representing the orange or red marker and the 5' centromere portion (approximately 442kb) with the other fluorochrome representing the green color spectrum (**Figure 6**). There are several commercial variations of such reagents that can signal specific genomic areas. The assessment of the FISH examination looks at chromosomes or genes that have been given a spectrum or markings and looks at the fusion pattern, split pattern, the isolated pattern of 3'-5' signals from a collection of cells which then the pattern is calculated based on the formula with the result of the percentage cut off point.[19,31]

THE ROS1 REARRANGEMENT THERAPY

The global prevalence of ROS1-positive lung cancer is 1-2%. In addition to lung cancer, ROS1 rearrangements have been identified in several other cancers, such as cholangiocarcinoma, ovarian carcinoma, and gastric carcinoma, with the prevalence of all ROS1-positive cancers ranging from 0.6%-3%. November 2013 Crizotinib is the first ALK inhibitor regimen approved by the FDA in the United States. The published results of a study on Crizotinib for lung cancer treatment with positive ROS1 have also received approval in the Americas and Europe so the use of Crizotinib as an anti-cancer for TKI is wider11,16,19. Entrectinib, Lorlatinib, and Brigatinib are also regimens against lung cancer with positive ROS1 from several studies proven to be beneficial in vitro, but these regimens are TKIs that are relatively new for the treatment of ROS1 positive and there is not much evidence of clinical benefit of the drug. Crizotinib at a dose of 200 mg and 250 mg per capsule is taken twice a day in ROS1-positive lung cancer patients. The most widely consumed and manufactured regimens globally are judged to be highly effective based on published research evidence.[19,32]

In a previous cohort study of 50 ROS1-positive ROS1-positive patients treated with a standard dose of Crizotinib 250 mg twice daily, the odds ratio (OR) was 72% (95% Confidence Index (CI), 58 to 84) with 3 Complete Responses patients and 33 Partial Responses patients. The median response duration to treatment was 17.6 months, and Median Progressive Free Survival (PFS) was 19.2 months (95% CI, 14.4 to not achieved). Based on the results of this study on March 11, 2016, Crizotinib was approved by the FDA as the main regimen for lung cancer with positive ROS1 rearrangements.[19,33] Oral treatment with targeted therapy is chosen in addition to being effective, and non-invasive with mild side effects. In this study, side effects of drugs for visual disturbances were the largest percentage, followed by digestive disorders such as diarrhea and nausea, which tended to be low.[33]

In practice, the provision of TKI positive ROS1 rearrangement therapy has several considerations according to current guidelines. There is no indication of giving TKI rearrangements at an early stage. The results of the anatomical pathology examination of NSCLC which are confirmed at an advanced stage can be carried out by molecular examination, of course, they must meet the agreed principles of examination analysis. The main elements of the principle of analysis include the use of an accredited laboratory. The specimen management acquisition from the type of sample received by the testing laboratory has been fixed using the FFPE method for CPI examination as a screening medium. The minimal sample will complicate the molecular examination therefore it is necessary to obtain a sufficient sample that allows for all tests with the biopsy sample being the most preferred. The last element is the availability of FISH or NGS testing methods as a medium for confirming the diagnosis.[12,19,34] Not meeting all the main elements resulted in the delay of the ROS1 rearrangement examination. First-line systemic therapy is certainly an option for the limitations faced. Delaying treatment is not recommended given the high morbidity and mortality from lung cancer. Positive ROS1 rearrangements identified

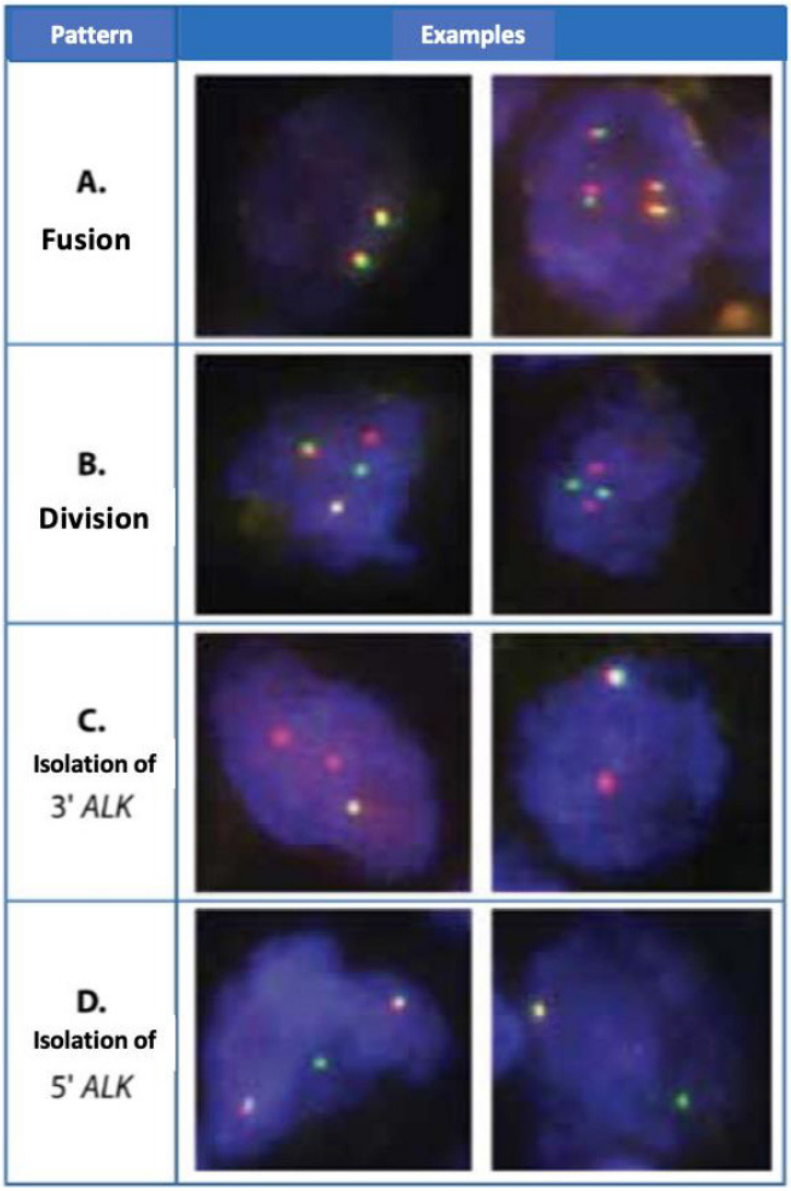


Figure 6. The pattern classification based on ALK signaling on FISH examination.[16]

before first-line therapy can be given TKI ROS1 with the choice of a regimen of crizotinib or entrectinib and ceritinib as another recommendation. However, if positive ROS1 rearrangements are identified during first-line therapy, first-line systemic therapy can be continued followed by TKI ROS1 administration with a choice of the regimen of crizotinib or entrectinib and ceritinib as another recommendation. Progressively emerging regimens may be substituted if available with lorlatinib or second-line therapy or second-line therapy plus an ICI such as nivolumab or pemolizumab or atezolizumam under consideration. The patient's performance status is also a clinician's consideration for the continuity of treatment.[34]

THE ROS1 MUTATION RESISTANCE

As in the case of lung cancer with positive EGFR and ALK mutations that can mutate to become resistant or even resistant at the beginning of diagnosis, the use of first-line regimens is no longer effective and must be changed to second-line. The rearrangement of ROS1 was considered positive in the event of fusion with certain previously described genetic material. So far, it has been reported that S1986Y/F, G2032R, D2033N, and D2155S are ROS1 fusions that lead to resistance mutations.[19,35] Platinum base doubled chemotherapy such as Carboplatin or Cisplatin in combination with Pemetrexed is currently the second-line regimen of choice. Based on clinical recommendations, you can also consider giving a regimen of Carboplatin and Paclitaxel plus Atezolizumab plus Bevacizumab.[36] Several ROS1 mutations have been described as resistance mechanisms in Crizotinib treatment of post-progressive tumor biopsies based on in vitro results and research methods and biological analysis of the process by utilizing computational technology and databases to develop further research (in silico) so that pharmacodynamic characteristics and profiles are seen. efficacy of each ROS1 inhibitor. The G2032R fusion-positive ROS1 mutation was the most common in ROS1-resistant cases. However, to date, no clinical observations have been reported.[35,37]

CONCLUSION

Rearrangement of ROS1 occurs due to the joining or fusion of ROS1 with certain genes that produce receptor kinases that lead to the proliferation of cancer cells. Cancer cell proliferation occurs due to ROS1 sending signals in the form of transformation activity to increase the resistance of cancer cells to apoptosis, increase translational capacity and metastasize. The existence of differences in candidate NSCLC patients in ROS1 examination is influenced by certain phenotype factors and the availability of facilities. IHC ROS1 assay has not been able to replace FISH in confirming the results, because the expression of mRNA that produces protein is generally low but sometimes it can be promising. TKI Crizotinib is the regimen of choice for ROS1 positive mutation NSCLC which correlates well with treatment outcome, but not in resistant ROS1 mutations.

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CONFLICT OF INTEREST

The author declares that there are no conflict of interest in this study.

AUTHOR CONTRIBUTION

All of the authors contribute in this article preparation.

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