LITERATURE REVIEW

Diagnostic Approach of Lung Cancer: A Literature Review

Jesi Hana[1*], Novia Nurul Faizah[2]
[1]Department of Emergency, Serui Public Hospital, Yapen Island Regency, Papua, Indonesia.
[2]Division of Cardiovascular Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan.

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ABSTRACT

Lung cancer is the second most commonly diagnosed malignancy with the highest mortality rate. It can be classified into small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). At the early stage of the disease, lung cancer rarely gives apparent symptoms. Patients are usually diagnosed at an advanced stage. Lung cancer is closely related to tobacco smoking. The increasing prevalence of tobacco smoking in Indonesia should be an alarm. During the last decades, knowledge and technology regarding lung cancer screening and diagnosis have vastly increased. Proper screening for high-risk individuals will help to increase the survival rate from the disease. Diagnosis of lung cancer using various radiologic modalities, histopathology, and biomolecular tests will also determine a specific treatment approach for the patient. A proper diagnostic test will also help predict the patient's prognosis. This literature review aimed to provide foundation knowledge from recent guidelines for screening and diagnosing lung cancer.

INTRODUCTION

Lung cancer has the highest incidence of mortality compared to other malignancies. A global 2020 cancer statistic reported that lung cancer is the second most commonly diagnosed malignancy after breast cancer. It has the highest mortality rate, with 1.8 million deaths reported in 2020.[1] The Global Burden of Cancer Study (GLOBOCAN) reported that lung cancer is the third highest cancer in Indonesia (8.8%), following breast (16.6%) and cervical cancer (9.2%).[1]

Lung cancer is closely linked to tobacco smoking. In industrialized countries, lung cancer peaked in 1970-1980 because of the increasing smoking prevalence in the '40s.[2] However, the incidence of lung cancer slowly decreased in the 1990s following the decreasing number of tobacco smokers.[2] High prevalence of tobacco smoking in Indonesia should alarm the country. The number of smokers in Indonesia in 2018 among youth aged 10–19 years old was 9.1%, a rapid increase from 7.2% in 2013.[3]

Considering the high prevalence of morbidity and mortality in lung cancer, the screening and diagnostic steps approach should be concise and applicable. During the last decades, knowledge and technology regarding lung cancer screening and diagnosis have vastly increased. This literature review aimed to provide foundation knowledge from recent guidelines for screening and diagnosing lung cancer.

*Corresponding author: jesiprilly@gmail.com

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Clinical Manifestation of Lung Cancer

At the early stage of the disease, lung cancer rarely gives apparent signs and symptoms. As the disease progress, patients will develop various symptoms related to the primary tumor, the metastases, or the paraneoplastic syndromes. Early symptoms such as cough, hemoptysis, and shortness of breath might be seen because of airway obstruction or compression, tumor necrosis, and cavitation.[4] The presence and severity of the symptoms also depend on the location of the lesion. Patients presenting with central bronchial tumor may show more prominent symptoms than those with peripherally located tumours.[5]

The progression of lung cancer might lead to intrathoracic spread and distant metastases. The symptoms might vary depending on the pattern of spread and metastases. Bone, followed by brain and liver, is the most common metastases site from an advanced lung cancer stage.[6] General symptoms such as headache, anorexia, weakness, unintended weight loss, and osteodynia might be seen.[4]

Paraneoplastic syndrome from lung cancer is frequently associated with the endocrine system. Hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and ectopic Cushing syndrome are some endocrine paraneoplastic syndromes that might be seen in lung cancer.[7]

Screening

Early-stage lung cancer is usually asymptomatic or only produces unspecific signs and symptoms. This is one reason patients typically visit medical facilities later in the disease.[4] Other reasons, such as limitations in accessing appropriate diagnostic technology, might lead to delayed diagnosis and treatment.[8]

The World Health Organization (WHO) stated that, in the USA, over 60% of patients present with evidence of distant metastasis at the time of diagnosis.[4] Some studies in Indonesian oncology referral hospitals showed that over 90% of patients present with advanced stage of lung cancer.[9,10] Lung cancer prognosis is massively dependent on the disease stage. Hence, screening for lung cancer is needed as an effort to increase the survival rate. Data from the National Cancer Institute (2000-2018) in the USA showed a significant survival rate difference between early and advanced stages of lung cancer after diagnosis.[11]

Table 1. The survival rate of lung cancer after diagnosis[11]

Survival Rate	Localized Tumor	Regional Spread	Distant Metastases
5-years	57.7%	30.0%	5.4%
10-years	42.8%	19.2%	2.7%

Early detection of lung cancer could be life-saving. The United States Preventive Services Task Force (USPSTF) recommends annual screening with low-dose computed tomography (LDCT) in populations aged 50-80 years old with a 20-pack-a-year smoking history. The population might be current smokers or have a history of smoking within the past 15 years.[12] The National Lung Screen Trial (NLST) found that annual lung cancer screening by LDCT can increase the survival rate by up to 20%.[13]

Annual screening with LDCT also comes with potential risks, including:

i. False Positive

A false positive could result from a different definition of a positive result, such as the size and characteristics of a high-risk lung nodule.[12] A meta-analysis showed a risk of false-positive results from LDCT was between 4 and to 24%.[14]

ii. Overdiagnosis

Overdiagnosis of lung pathology may cause some harm ranging from unnecessary yet costly diagnostic procedures to psychosocial harm to the patients.[15] The risk of overdiagnosis from LDCT screening ranges from 19 to 69%.[15]

An individualized approach might be used because of the high risk of false-positive and overdiagnosis. Lung cancer risk assessment can be used, such as the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Model 2012 (PLCOm12).[16] Studies showed that using PLCOm12 was more efficient than the USPSTF2013 criteria to determine lung cancer screening eligibility[17] and more sensitive than NLST criteria for lung cancer detection.[18] PLCOm12 assesses 11 indicators, including age, race, level of education, body mass index (BMI), presence of chronic obstructive pulmonary disease (COPD), history of cancer, family history of cancer, smoking status, daily smoking intensity (number of cigarettes daily), duration of smoking, and duration of quitting smoking.[17]

iii. Radiation Exposure

Considering that smoking history is the only eligibility criterion, millions of healthy high-risk individuals are eligible to undergo annual LDCT.[14] Risk of radiation exposure-related cancer from LDCT is low. However, cumulative radiation exposure to LDCT should not be neglected. A study showed a cumulative effective dose of 10 years of LDCT is about 9mSv in men and 13mSv in women. For comparison, a single diagnostic CT procedure would give an equivalent

amount of 10 years of LDCT.[18] Annual LDCT is associated with a 0.2 to 0.85% increased lifetime risk of developing cancer.[19]

Table 2. Screening recommendation for lung cancer[12,20,21]

	Year	Screening technique	Inclusion criteria	Discontinuation of screening
NCCN	2022	Annual LDCT	• Age ≥ 50 years old • History of smoking ≥20 packs/year	• NA
USPSTF	2021	Annual LDCT	• 50-80 years old • Smoking ≥20 packs-year (current smokers/quit ≤ 15 years	• Quit smoking ≥ 15 years • Develop health problems that limit life expectancy
AATS	2012	Annual LDCT	• 55-79 years old with ≥30 packs-year history • 50 to 79 years with ≥20 pack-year history and cumulative risk >5% over next 5 years • Lung cancer survivors with no incidence of disease for ≥4 years	• Age > 79 years old

NNCN: National Comprehensive Cancer Network; USPSTF: The United States Preventive Services Task Force; AATS: American Association for Thoracic Surgery; NA: Not Available

Malignancy Probability of Lung Nodule

A pulmonary nodule can be defined as rounded or irregular opacity with ≤ 3cm diameter, a common radiologic finding. Physicians must determine if a nodule needs further diagnostic testing.[21] Lung nodules might be found in several pathologic processes, such as neoplasm, infections, inflammation, and congenital abnormality. Characteristics of lung nodules found through LDCT may be used as a guide to determine the probability of malignancy.[22]

Several findings of lung nodules that predict benign characteristics include (i) the presence of fat and/or calcification; (ii) a well-defined margin; and (iii) homogeneous density.[22] The Fleischner Society (2017) points out several characteristics of lung nodules as a risk factor for malignancy.[23]

(i) Nodule size and morphology

The Fleischner Society recommends a minimum nodule diameter of ≥6 mm for follow-up computed tomography (CT). Nodules <6mm in diameter do not require any follow-up test unless the nodule is high risk.[23] An analysis of data from the NELSON trial found a probability of lung cancer if the nodule is ≥10 cm in diameter.[24]

Pulmonary nodules can be classified into solid and subsolid based on morphological density. Subsolid nodules (SSN) can further be classified into pure ground glass nodules (GGN) and part-solid GGN.[25] Solid means the thickness of the nodule can conceal the underlying lung parenchyma. The density of the subsolid nodule is higher than surrounding lung parenchyma, yet lung structures such as bronchial and vascular margins are still detectable.[26] Multiple studies have shown that the chances of malignancy are higher in SSN than in solid nodules.[25]

(ii) Nodule location

The upper lobe of the right lung is the predilection site of lung cancer.[23] The upper lobes have lower perfusion than other lung regions. This results in slower lymphatic drainage and can cause higher particle concentrations, such as inhaled air pollutants.[27] A lung-to-lung metastases are usually seen in the outer third of the lung, giving a similar pattern of lung metastases from another organ.[27]

The location of the nodule might also predict the type of lung cancer, although histopathological examination is still necessary. Small and squamous cell carcinoma are usually located at the central, whilst adenocarcinoma and large cell carcinoma are generally at the periphery of the lung.[28]

(iii) Nodule multiplicity

Nodules found in CT might be solitary or multiple. NELSON trial found that the risk of lung cancer is higher in patients with 1-4 pulmonary nodules than those with >5.[24]

(iv) Nodule growth rate

Volume doubling time (VDT) is used as a parameter of the nodule growth rate and is the number of days in which the nodule grows double from its initial size. Shorter VDT shows a more aggressive malignancy, and stable nodules for over two years are usually benign.[29]

The probability of malignancy within two years of initial CT is 0.8% for VDT of ≥600 days, 4·0% for VDT of 400–600 days, and 9·9% for VDT of ≤400 days.[24,30] A retrospective study also showed that invasive adenocarcinoma has a significantly faster VDT than non-invasive adenocarcinoma.[30]

(v) Emphysema and fibrosis

Emphysema and/or idiopathic pulmonary fibrosis (IPF) is an independent indicator of malignancy.[23] Both lung cancer and emphysema are strongly related to chronic inhalation of toxic materials such as tobacco smoking. A meta-analysis study showed that the risk of lung cancer increased along with the increasing severity of emphysema.[31]

IPF is a chronic interstitial lung disease that progressively causes a decline in pulmonary function. The mechanism of changes from fibrotic into malignant cells is believed to be associated with genetic and epigenetic alteration. This alteration will then stimulate the uncontrolled proliferation of malignant cells.[32] Patients with IPF have a greater risk of lung cancer and poorer prognosis than those without IPF.[33]

The American College of Radiology (ACR) developed the Lung CT Screening Reporting and Data System (Lung-RADS) to reduce confusion in interpreting findings and probability of malignancy of nodule found on CT.[34] Category 1 is when there is no lung nodule or benign features such as calcification and fat are present.[34]

Table 3. Classification of screening findings for lung cancer[34]

Findings		Category (Lung-RADS)			
		Benign (2)	Probably Benign (3)	Suspicious (4A)	Very Suspicious (4B)
Solid nodule	Baseline	<6 mm	≥6 to <8 mm	≥8 to <15 mm OR growing <8 mm	≥ 15 mm
	New	<4 mm	4 to <6 mm	6 to <8 mm	≥8 mm or growing
Part-solid nodule	Baseline	<6 mm	≥6mm with solid component <6 mm	≥6 mm with solid component 6- 8 mm	≥8 mm solid component
	New	-	<6 mm total mean diameter	<4 mm solid component	≥4mm solid component
Non-solid nodule (GGN)	Baseline	<30 mm	≥30 mm		
	New	≥30mm or stable slow-growing	≥30 mm		

GGN: Ground-glass nodule

Histopathology Examination

Histological classification is essential to determine further diagnostic workup and specific therapy needed. Different ways to obtain a histology sample include fine needle aspiration and exfoliative specimens such as sputum or bronchial secretion, bronchial washing, and bronchoalveolar lavages.[4] Histologic assessment involves using a hematoxylin and eosin (H&E) stained tumor slide.[35]

Based on histopathology appearance under the microscope, lung cancer can be classified into small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). NSCLC can further be classified into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma.[36]

(i) Small Cell Lung Carcinoma

SCLC represents 15% of all lung cancer cases.[36] This carcinoma derives from neuroendocrine cells and usually arises in the lobar bronchus.[28] SCLC pathophysiology is closely linked with the inactivation of p53 and RB. These two genes play an essential role in regulating cell cycle progression.[36]

Under the microscope, SCLC can be identified by small round to fusiform cells with scant cytoplasm and fine granular nuclear chromatin. Extensive necrosis is often found. In a cytologic specimen, this granular chromatin can be seen as a “salt and paper” feature of SCLC.[37]

(ii) Non-Small Cell Lung Carcinoma

NSCLC represents about 85% of lung cancer with SCC as the most common subtype. The pathogenesis of NSCLC is closely associated with various genetic alterations.[38] The diagnosis of adenocarcinoma is in the presence of neoplastic gland formation, whilst the keratin production makes SCC diagnosis of tumor cells.[39]

WHO recently published a more specific histopathological classification of lung cancer, revised from the previous classification in 2015. This classification used a distinct morphological pattern of the tumor that should be reported on histopathological examination.[4]

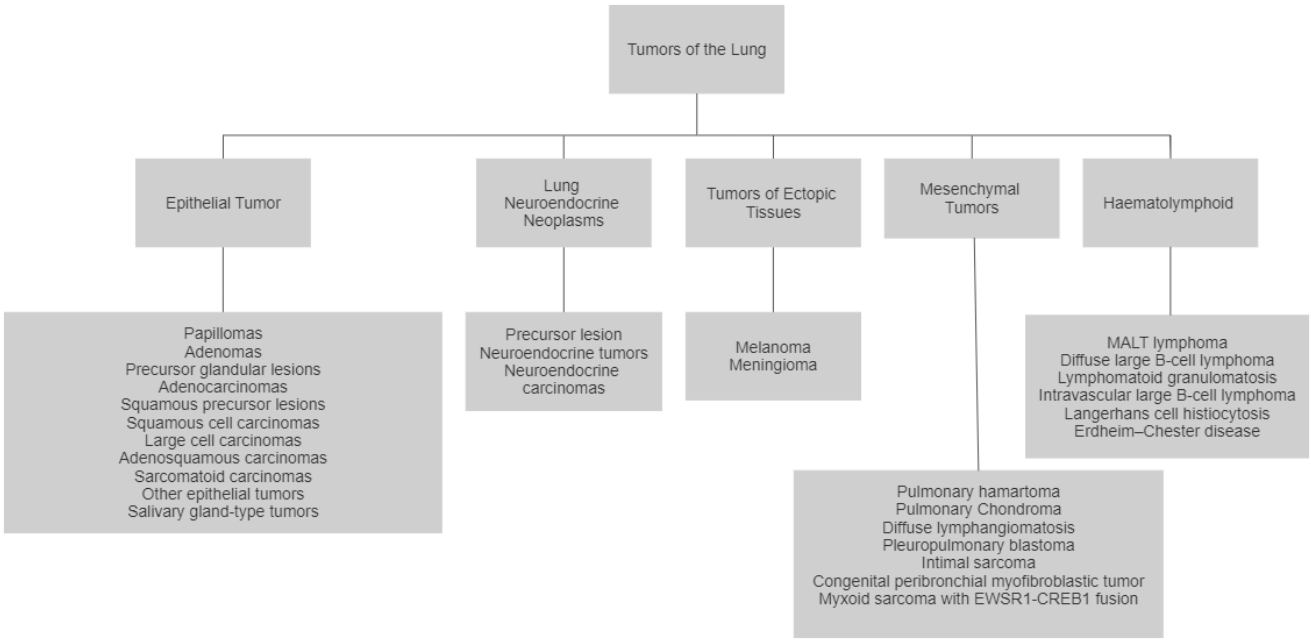

Figure 1. WHO histopathological classification of lung cancer

Biomolecular Test

Pathogenesis of genetic alteration in lung cancer can be from a mutation, gene fusion, and amplification.[40] Molecular test of these genetic alterations is the standard main consideration to determine specific patient treatment. Accurate information on cancer staging and predicted prognosis can also be gained through molecular testing.[4] Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement are strongly involved in the pathogenesis of NSCLC. These genetic alterations will lead to uncontrolled cell proliferation and inhibition of apoptosis.[41]

Various methods can be used to test specific genetic alterations in lung cancer. A molecular diagnostic determines eligibility for specific tyrosine kinase inhibitor (TKI) therapy in clinical practice.[42] Before the discovery of EGFR mutation, first-line systemic therapy for NSCLC was traditional platinum-based doublet chemotherapy. EGFR-TKI targeted the ATP-binding sites to cease the activation of downstream signaling due to EGFR mutation.[43,44] Studies have found that EGFR mutation is higher among female patients, non-smokers, and adenocarcinoma.[45]

ALK rearrangement is found in approximately 2-5% of NSCLC patients with metastases to the brain commonly found in an advanced stage.[46] A study showed that Lorlatinib, a third generation of ALK-TKI, can reduce the risk of progression or death by 72% in NSCLC patients with ALK rearrangement.[47] This finding highlights the importance of molecular targeted therapy.

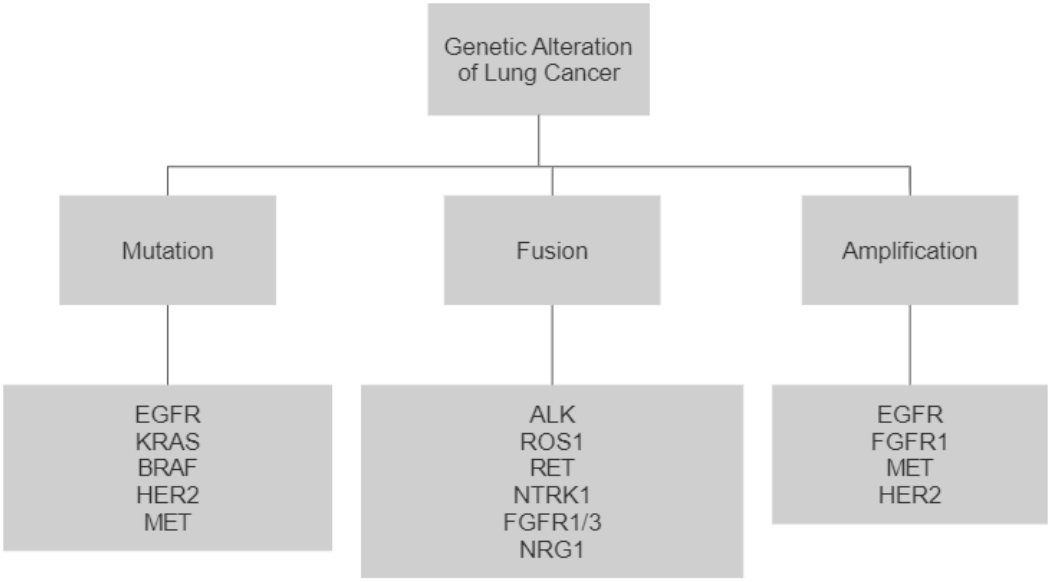

Figure 2. Genetic alteration of lung cancer

The CAP/IASLC/AMP guidelines (2013) recommend all advanced-stage lung adenocarcinoma to have molecular testing of EGFR mutation exon 18-21 and rearrangements involving ALK using fluorescence in situ hybridization (FISH).[42] EGFR assay should be able to detect the common EGFR TKI sensitizing mutation causing insensitivity to TKI.[42,48] In 2018, the guideline added ROS1 testing as a standard biomolecular test for all adenocarcinoma patients, irrespective of clinical characteristics.[42] ROS 1 (c-ros oncogene 1) is found in 1-2% of NSCLC patients and usually in young and non-smoker individuals.[48] Even though the prevalence of ROS1 rearrangement is relatively low, detection of this genetic alteration can lead to specific treatment using entrectinib or crizotinib to improve life expectancy.[49]

BRAF, MET, RET, and HER2 testing is not recommended if the result of routine EGFR, ALK, and ROS1 testing is negative. However, it is appropriate to perform KRAS as part of larger testing panels either initially or when the result of EGFR, ALK, and ROS1 testing is negative.[42]

Table 4. Recommendation of genetic testing for lung cancer

	Gene	Recommended Method of Testing
Absolute minimum test	EGFR	ARMS-PCR; RT-PCR; Sanger sequencing; NGS
	ALK	FISH, IHC
	ROS1	IHC; if positive, should be confirmed by a molecular or cytogenetic method
Offered if adequate material is available	BRAF	
	MET	
	RET	FISH; RT-PCR; IHC
	HER2	
	KRAS	

ARMS-PCR: Amplified refractory mutation system-polymerase chain reaction; RT-PCR: Real time-polymerase chain reaction; NGS: Next generation sequencing; IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; ROS1: c-ros oncogene 1; BRAF: B-Raf proto-oncogene; MET: Mesenchymal epithelial; RET: Rearranged during transfection; HER2: Human epidermal growth factor receptor-2; KRAS: Kirsten rat sarcoma viral oncogene homologue

Additional Examination

Once high-risk nodules have been identified, further examination might be needed to establish diagnosis, treatment and predict the patient's prognosis.

1. Additional Imaging Examination

1.1. Computed Tomography (CT scan)

CT scan is commonly used to diagnose and evaluate lung cancer, which cannot be seen on chest X-rays. A CT scan with contrast is an excellent radiology modality to identify the location, size, and growth of the tumor in a nearby intrathoracic structure.[5]

1.2 Positron emission tomography (PET)/ CT

PET/CT is essential imaging for lung cancer evaluation. This modality is considered the best for determining cancer staging, detecting metastases,

and evaluating treatment outcomes. PET/CT has higher sensitivity than other imaging modalities, such as chest X-rays and CT scans, since it can detect metabolic changes in malignancy. This ability will help to detect malignancy before any noticeable morphology changes occur.[50]

1.3 Magnetic Resonance Imaging (MRI)

MRI is not a routinely used modality for lung cancer evaluation. This is because the lung is a low-density organ. Hence, the signal-to-noise ratio (SNR) will be reduced. Therefore, a proper radiographic image of the lung could not be achieved using MRI.[51] However, MRI has higher sensitivity than CT and PET/CT identifying tumor invasion to the mediastinum and chest wall.[5] It is also more sensitive to identify tumor metastases to the brain and the spine.[50,52] MRI also can distinguish between tumor and atelectasis in which the signal of tumor is higher in T2WI.[52]

1.4. Ultrasound

Ultrasound can be used to evaluate tumor metastases to the lymph nodes, liver, kidney and other visceral organs.[52]

2. Bronchoscopy

Bronchoscopy can be used to directly localize lung cancer and obtain cytology and biopsy samples.[52]

SUMMARY

Lung cancer is a major health problem with a low survival rate. Early screening and diagnosis could be life-saving. The current recommendation for lung cancer is an annual LDCT. Biomolecular testing can help to gain accurate information about cancer staging, treatment, and prognosis. EGFR mutation, ALK rearrangement, and ROS1 alteration testing is the recommended initial test for all adenocarcinoma patients, irrespective of their clinical appearance. Additional examination using CT with contrast, PET/CT, and MRI can provide more specific information regarding the location, growth, and metastatic activity of lung cancer.

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Conflict of Interest

The author declared there is no conflict of interest.

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Authors' Contributions

Manuscript writing and gathering data: JH. Reviewing and improvising: NNF. All authors reviewed and approved the final version of the manuscript.

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