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Air-Containing Space: Significantly in Predicting EGFR Mutation for Early Lung Adenocarcinoma Appearing as Subsolid Nodule

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Keywords:

Computed tomography (CT); Epidermal growth factor receptor (EGFR); Lung adenocarcinoma; Subsolid nodule; Air-containing spaces

Abbreviations: NSCLC: Non-Small Cell Lung Cancer; SSN: Subsolid Nodule; PSN: Part-Solid Nodule; EGFR: Epidermal Growth Factor Receptor; TKI: Tyrosine Kinase Inhibitors; CT: Computed Tomography; PACs: Picture Archiving and Communication System; AIS: Adenocarcinoma in Situ; MIA: Minimally Invasive Adenocarcinoma; IA: Invasive Adenocarcinoma; ROC: Receiver Operating Characteristic; AUC: Area Under Curve

1. Abstract

1.1. Background: To demonstrate the interrelation between computed tomography (CT) characteristics and epidermal growth factor receptor (EGFR) mutation status in early-stage lung adenocarcinoma manifested as subsolid nodule.

1.2. Method: A total of 202 patients with appearance as subsolid nodules on CT images and pathologically confirmed as early-stage lung adenocarcinoma were enrolled in this study. All of the patients divided in to EGFR mutation group and EGFR wild-type group. Correlation between clinical and radiological features and EGFR mutation status were analyzed with univariate and multivariate analysis. A receiver operating characteristic (ROC) curves were generated to evaluate the logistic regression model.

1.3. Results: EGFR mutation were detected in 137 of 202 patients. In univariate analysis, female gender, non-smokers, larger tumor size, lobulation, air-containing space and pleural retraction were more commonly indicated in EGFR mutated tumors than in EGFR wild-type tumors. Multivariate logistic regression analysis revealed that smoking history (OR, 0.275; 95%CI, 0.090–0.840), tumor size (OR, 4.263; 95%CI, 1.802–9.982) and air-containing space (OR, 3.055; 95%CI, 1.266–7.372) were independent predicting factor relevant to EGFR mutation. The AUC of ROC curve for predicting model reached 0.808. In addition, air-containing space with EGFR mutations were more commonly less than 5mm, solitary and mainly in an eccentric distribution.

1.4. Conclusion: Our research indicated that smoking history, tumor size and air-containing space were independent factor for

predicting EGFR mutation in early-stage lung adenocarcinoma appeared as subsolid nodule. Solitary air-containing space with≤5mm and eccentric distribution would help to determine EGFR mutation status.

2. Introduction

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases and is major cause of high morbidity and mortality in the cancer spectrum. Lung adenocarcinoma is the most common histologic subtype of NSCLC [1,2]. An increasing number of solitary lung nodules are detected since the popular application of low-dose CT for lung cancer screening. A recent study revealed that 95.5% of the early-stage lung cancer detected at screening presented as subsolid nodules [3]. In 2011, new international multidisciplinary classification for lung adenocarcinoma was proposed and widely applied [4]. Epidermal growth factor receptor (EGFR), the most frequently mutated gene, was reported to promote the progress of that lung adenocarcinoma developed from pre-, minimally invasive into invasive adenocarcinoma [5,6]. Molecular-targeted therapies have improved the prognosis of lung cancer patients with gene mutations. Thereinto, patients with EGFR mutation showed striking response to EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib [7,8]. Consequently, it is essential to demonstrate gene mutation status prior to administer target therapies. However, adequate tumor tissue for EGFR mutation analysis is neither always available or gene status detection always affordable and easy to access for all patients with lung adenocarcinoma. In recent decades, several researches have reported some relationships between CT characteristics and EGFR mutations, which provided a potential pattern for predicting effective EGFR status [9-11]. For patients with early lung adenocarcinoma, predicting the EGFR mutation is not only crucial for better understanding in progress of adenocarcinoma, but also valuable for management of subsolid nodule. Nevertheless, there are little studies about CT features of EGFR mutated lung adenocarcinoma at their early stage [12]. Thus, in this study, we identified the particular CT features associated with EGFR mutation in early lung adenocarcinoma, which may provide clinician valuable reference for optimizing treatments.

3. Materials and Methods

3.1. Patient Cohorts

This retrospective study was approved by institutional review board and informed consent was waived. We collected patients that were surgically and pathologically confirmed as lung adenocarcinoma from January 2018 to January 2020 at following hospitals, the General Hospital of the People's Liberation Army and Affiliated Qingdao Hospital of Qingdao University. The imaging data came from the picture archiving and communication system (PACS). The inclusion criteria were as follows: (a) Patients with primary stage I lung adenocarcinoma confirmed by surgical pathology; (b) At least one CT examination within 1 month before the surgery and availability of complete thin-slice images; (c) The lesion appeared as subsolid nodule with maximal diameter ≤3cm; (d) Without history of radiotherapy or chemotherapy before surgery. (Figure 1). Finally, the data of 202 patients were collected and analyzed.

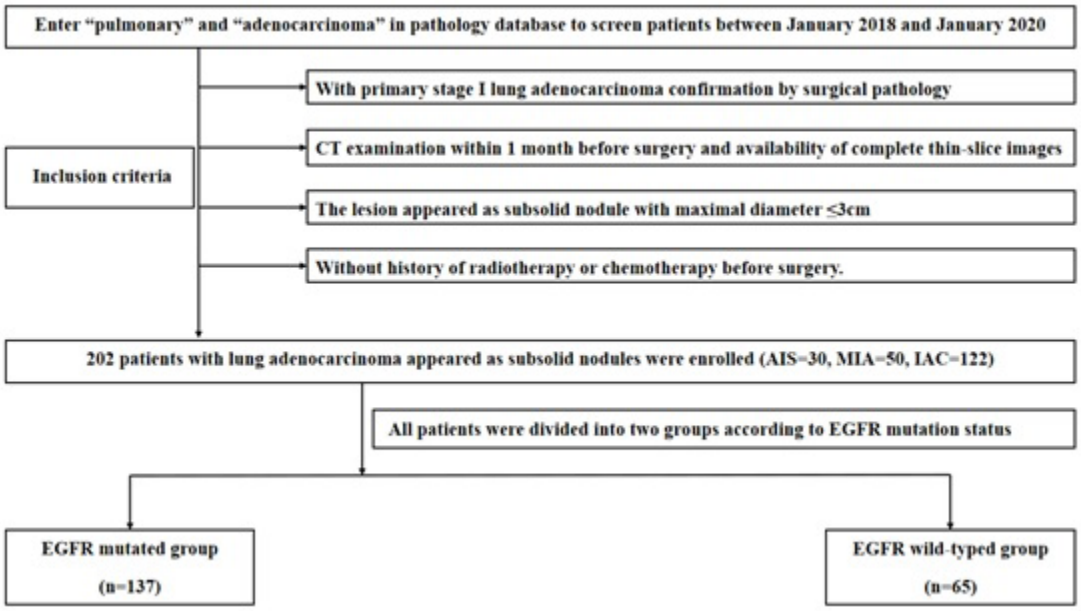

Figure 1: Inclusion flowchart shows the number of patients.

3.2. CT Examinations

All patients included in this study underwent CT examination of the chest performed with a GE Optima 660 CT scanner (GE Healthcare, Beijing, China) or a Siemens Somatom Sensation 64-Slice CT Scanner (Siemens, Forchheim, Germany). The CT scanning parameters were as follows: routine section thickness, 1.0, 1.25, or 1.5mm; section thickness after reconstruction, 1–1.25 mm; filtered back projection reconstruction method; 80–120 kV; 200–280 mAs.

3.3. CT Evaluation

Two radiologists (J.S and C.W) with more than 15 years of experience in chest radiology independently evaluated theses CT images on lung window settings (window width, 1500 Hounsfield units (HU); window level, –600HU) and mediastinal windows (window width, 350HU; window level, 40 HU). Both the radiologists were blind to the histological subtype and EGFR mutation statue. Another chest radiologist (J.W) with experience of 20 years joined the discussion to reach a final consensus in case of disagreement. CT characteristics were recorded for each lesion included: [1]lesion location; [2]tumor size (the mean diameter of longest and shortest axes of the primary tumor); [3] pGGN or PSN(according to presence of solid components or not); [4] lobulation (uneven lobular outline caused by variance in tumor growth); [5] Spiculation (radiating and tiny burr around the tumor margin); [6]vascular changes (dilated, rigid, convergent, or tortuous blood vessel observed on consecutive axial, coronal, or sagittal reconstruction images); [7]air-bronchogram (branching or tubular air density surrounded by tumor tissue on CT scans and could be distinguished in consecutive multiple reconstruction images); [8]air-containing space (presence of round or oval air-filled spaces in the tumor with relatively thin wall). Furthermore, the maximum diameter, number and location of air-containing spaces in tumor were assessed [9]. pleural retraction; [10] boundary of tumor.

3.4. Statistical Analysis

All statistical analyses were performed with SPSS 22.0 (IBM Statistics, Armonk, NY). Statistical differences between the groups were analyzed by using chi-square test (x2 test) or the Fisher exact text (as appropriate) for categorical variables and using unpaired t-test for continuous variables. A subsequent multivariate logistic regression model was performed to identify independent factors among variables with $p<0.1$ selected from the former stepwise. The receiver operating characteristic (ROC) curves were generated to achieve the optimal cut-off values for diameter and to evaluate differentiating performance of the logistic regression model.

4. Results

4.1. Patients Characteristics

As listed in the Table 1, a cohort of 202 subsolid nodules with lung adenocarcinoma were enrolled, including 134 (66.3%) females and 68 (33.7%) males, with mean age (56.3±9.9) years, range from 22 to 78 years. 42(20.8%) patients had smoking history. Regarding histopathological subtypes, there were adenocarcinoma in situ (AIS) in 30(14.8%) cases, minimally invasive adenocarcinoma (MIA) in 50(24.8%) cases and invasive adenocarcinoma (IA) in 122(60.4%) cases. The EGFR mutations were detected on 137(67.8%) patients, composing mutation on exon 18, 7 cases; exon 19, 41 cases; exon 20, 3 case; exon 21, 85 cases and exon 19 co-mutation with exon 21, 1 case. EGFR mutations were significantly more frequently observed in females than males (72.3% vs 27.7%, $p=0.01$), and in never-smokers than in smokers (85.4% vs 14.6%, $p=0.002$). In addition, EGFR mutation occurred more frequently in IA than in AIS/MIA (72.3% vs 27.7%, $p<0.001$).

4.2. CT Characteristics and EGFR Mutation Status

CT features of the subsolid nodule with lung adenocarcinoma and EGFR mutation status were summarized at Table 2. Univariate analysis revealed that there was significant difference between EGFR-mutated group and EGFR wild-typed group in CT characteristics including tumor size, category of subsolid nodule, lobulation, air-containing space and pleural retraction. Specifically, the size of tumor with EGFR mutation (1.50±0.52) cm was significantly larger than tumor with EGFR wild-type (1.17±0.43) cm ($p<0.01$). EGFR mutations were more frequently in PSNs than in pGGNs ($p<0.01$). Lobulation, air-containing space and pleural retraction were more commonly indicated in EGFR mutated tumors than in EGFR wild-type tumors, with significant differences ($p<0.01$). No significant differences were observed between two groups regarding location, spiculation, vascular changes. air-bronchogram and boundary of tumors.

Table 1: Characteristics of patient cohorts.

Characteristics	Number
Gender	
female	134(66.3%)
male	68(33.7%)
Age	
mean	56.3±9.9
range	22-78
Smoking history	
positive	42(20.8%)
negative	160(80.2%)
Histopathologic subtype	
AIS	30(14.8%)
MIA	50(24.8%)
IA	122(60.4%)
EGFR mutation status	
exon 18	7(3.4%)
exon 19	41(20.3%)
exon 20	3(1.5%)
exon 21	85(42.1%)
exon 19/21	1(0.5%)
wild-type	65(32.2%)

Table 2: CT features according to EGFR mutation status.

CT characteristics	EGFR mutation (n=137)	EGFR wild-type (n=65)	*P*-values
Location			
right upper lobe	46(33.6%)	31(47.7%)	
right middle lobe	11(8.0%)	4(6.2%)	
right lower lobe	29(21.2%)	6(9.2%)	
left upper lobe	39(28.5%)	16(24.6%）	
left lower lobe	12(8.7%)	8(12.3%)	0.139
Tumor size (cm)	1.50±0.52	1.17±0.43	＜0.01
Category of nodule			
pGGN	45(32.8%)	39(60.0%)	
mGGN	92(67.2%)	26(40.0%)	＜0.01
Lobulation			
positive	73(53.3%)	20(30.8%)	
negative	64(46.7%)	45(69.2%)	＜0.01
Spiculation			
positive	32(23.4%)	10(15.4%)	
negative	105(76.6%)	55(84.6%)	0.192
Vascular changes			
positive	72(52.6%)	31(47.7%)	
negative	65(47.4%)	34(52.3%)	0.518
Air-bronchogram			
positive	50(36.5%)	16(24.6%)	
negative	87(63.5%)	49(75.4%)	0.093
Air-containing space			
positive	53(38.7%)	13(20.0%)	
negative	84(61.3%)	52(80.0%)	＜0.01
Pleural retraction			
positive	72(52.6%)	18(27.7%)	
negative	65(47.4%)	47(72.3%)	＜0.01
Boundary of tumor			
clear	83(60.6%)	43(66.2%)	
obscure	54(39.4%)	22(33.8%)	0.445

4.3. Independent Factors for EGFR Mutation

Candidate variables extracted from univariate analysis were performed with multivariate logistic regression to identify predictors for EGFR mutation. The results confirmed that smoking history (OR, 0.275; 95%CI, 0.090–0.840; p=0.024), tumor size (OR, 4.263; 95%CI, 1.820–9.982; p=0.001) and air-containing space (OR, 3.055; 95%CI, 1.266–7.732; p=0.013) were independent predictive factors relevant to EGFR mutation (Table 3). Determined by the Youden index indicated in ROC, the optimal cutoff value was 1.125cm for tumor size. The ROC curves of tumor size and prediction model were both shown in Figure 2, and the area under curve (AUC) of prediction model was 0.808(95%CI, 0.744-0.871), with sensitivity in 80.3% and specificity in 73.8%. Patients then were divided into two groups (≤1.125cm and＞1.125cm), and the analysis with logistics in combination with smoking history and air-containing space after adjusted were indicated in Figure 3. Additionally, 66 patients with air-containing spaces were analyzed further. Specifically, air-containing spaces in tumors with EGFR mutation were commonly less than 5mm (n=35, 53.0%), solitary (38, 57.6%) and distributed eccentrically (n=41, 62.1%). (Figure 4 and Figure 5).

Table 3: Multivariate logistic regression analysis of independent factors of EGFR mutation in patients with lung adenocarcinoma.

Variables	Odds ratio	95% CI	p-values
Smoking history			
positive	0.275	0.090-0.840	0.024
negative	—	reference	NA
Tumor size	4.263	1.820–9.982	0.001
Air-containing space			
positive	3.055	1.266–7.732	0.013
negative	—	reference	NA

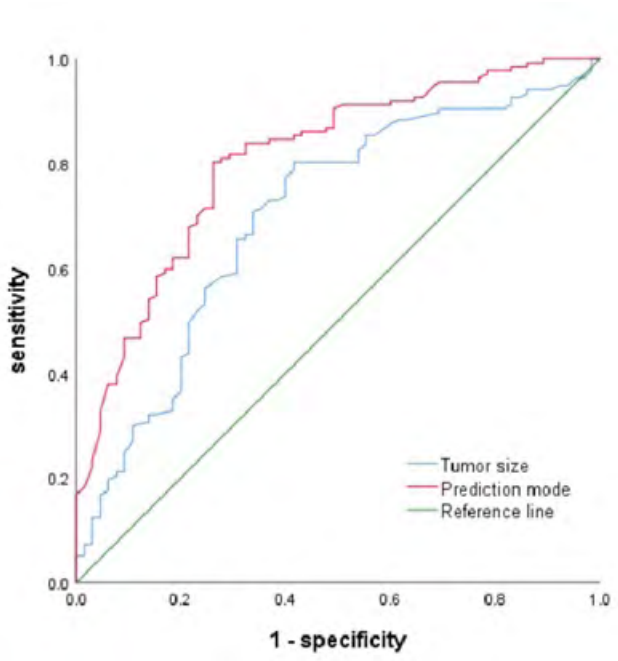

Figure 2: The receiver operating characteristic curve for prediction model. The area under the curve of logistic regression model was 0.808 (95% confidence interval, 0.744-0.871), which showed a good determination.

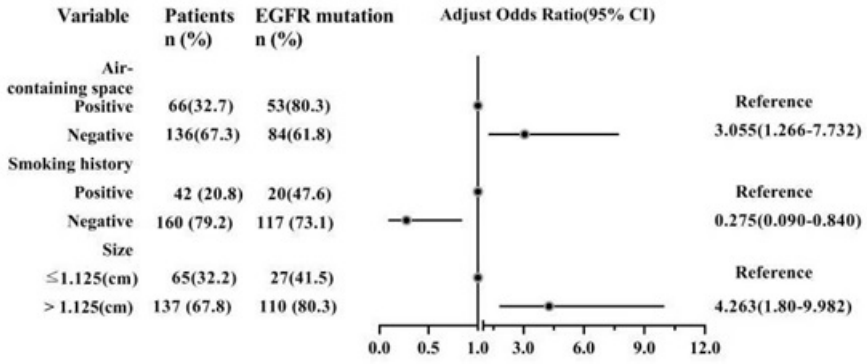

Figure 3: The odds ratios and 95% confidence intervals showed the risk of EGFR mutation among female gender, tumor diameter and air-containing space.

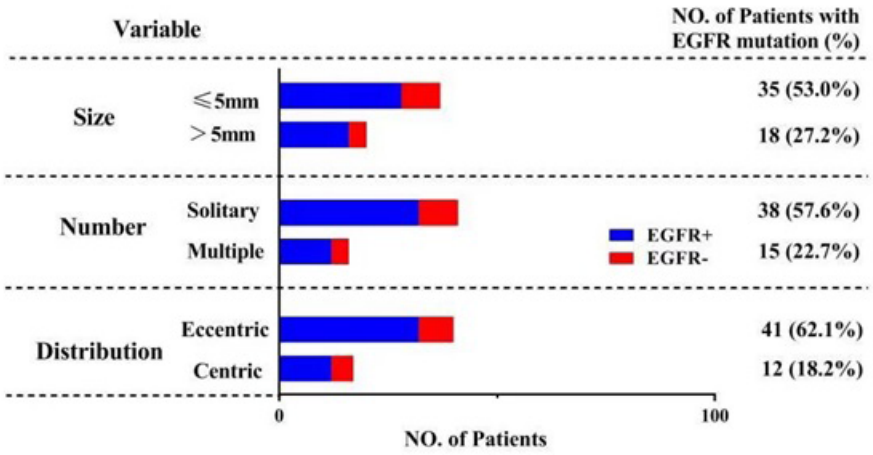

Figure 4: Distribution of number of patients with EGFR mutation among patients with air-containing space.

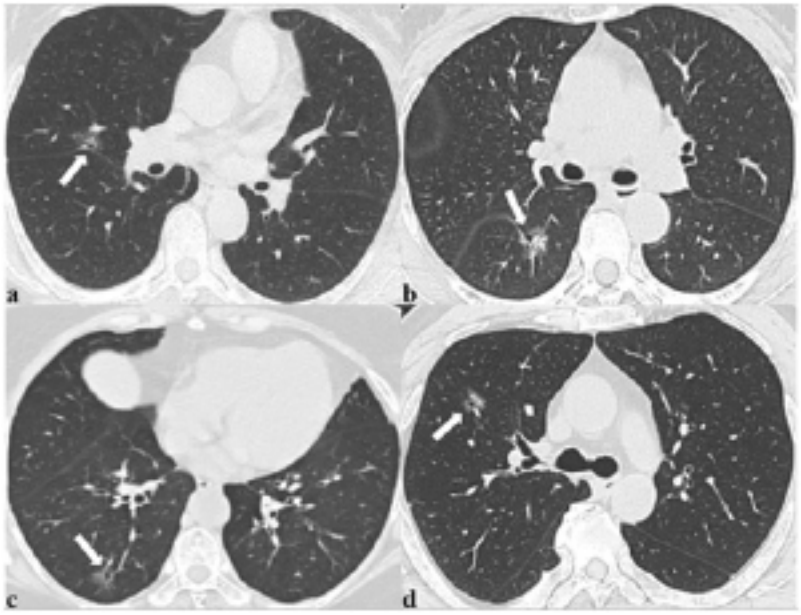

Figure 5: Axial CT images(a-d) showed solitary, smaller than 5mm and eccentric distributed air containing spaces in subsolid nodules with EGFR mutations.

5. Discussion

Molecular targeted therapy has been proved to effectively prolong progression-free survival of patients with lung adenocarcinoma [13,14]. Recent studies have attempted to associate clinical, radiological features with EGFR mutations of lung adenocarcinomas with aim to determine predictors for effective EGFR status in a non-invasive way [15-17]. In our study, we found that smoking history, tumor size and air-containing space were significant independent factors relevant to EGFR mutations in patients with early-stage lung adenocarcinoma. Compared with Western population, EGFR mutation was reported to focus on Asians, especially females [18,19]. Consistent with previous studies, our research identified 137(67.8%) patients with EGFR mutations among which female patients comprised 99(72.3%) cases. It was also reported that deletion mutation on exon 19 and L858R missense mutation on exon 21 were common subtype of EGFR mutation [20,21]. The mutation rate on exon 19 and 21 of EGFR gene were 20.3% and 42.1% in our study, which was consistent with previous report. Notably, there was a patient with concurrent exon 19 and exon 21 mutation.

Tumor size is generally recognized as a dominant factor in management of subsolid nodule [22]. Several studies have associated EGFR mutation with tumor size, while there is little agreement on their results [23,25]. Sabri et al [26] and Kim et al [27] proposed that average diameter of tumor closely related to EGFR mutation. However, Hasegawa et al[28] and Zhou et al [29] reported conflicting results. Difference between previous findings may be attributed to different study cohorts or measurement for tumor size. In the present study, we validated that tumor size was an independent predicting factor for EGFR mutation with an optimal cutoff value

of 1.125cm. The AUC of tumor size reached 0.701 (95%CI, 0.623–0.780). Therefore, it is reasonable to consider that subsolid nodule with larger size (＞1.125cm) has higher probability of EGFR mutation. Additionally, we firstly explored that air-containing spaces were more frequent in subsolid nodule with EGFR mutation than those without. Previously, Liu et al. [30] revealed that bubble-like lucency was one of most important and significantly independent factors of harboring EGFR mutation. In contrast, Zou et al. [31] found that there was no significant correlation between EGFR mutation and bubble-like lucency in subsolid nodule. In our research, air-containing space was defined as presence of round or oval air-filled spaces in the tumor. Considering subsolid nodules enrolled were pathologically confirmed as early-stage adenocarcinoma and smaller than 3cm, the air-containing space in our research referred to bubble-like lucency or cystic airspace with thin wall. Bubble-like lucency was less than 5mm and reported to associate with lepidic pattern. Meanwhile cystic airspace was more often encountered in early lung cancer. Both of them had close relationship with growth pattern of early lung adenocarcinoma [32-34]. On the other hand, EGFR mutations were involved in the initial progress of tumor. Taken together, it is reasonable that our research showed close relevance between air-containing space and EGFR mutation. Furthermore, we found that air-containing spaces in tumors with EGFR mutation were commonly less than 5mm, solitary and distributed eccentrically. This could be helpful to judge whether subsolid nodule with air-containing space harbored EGFR mutation. Some researchers had reported correlation between EGFR mutation and CT characteristics, such as lobulation, air-bronchogram, vascular changes and pleural retraction [35,36]. Similarly, lobulation and pleural retraction were associated with EGFR mutation in univariate analysis while neither of them was statistically significant in multivariate logistic regression analysis. Further investigation was necessary for these results. There are several limitations in our study. Firstly, the number of patients recruited was relatively small, especially those with air-containing spaces. Secondly, CT interpretations were conducted by two radiologists while inter-observer variability was not evaluated. Thirdly, we didn't identify the correlation between CT characteristics and EGFR mutation on different exons. In conclusion, our research demonstrated that female gender, tumor size larger than 1.125cm and air-containing space were independent factor for predicting EGFR mutation in early-stage lung adenocarcinoma appeared as subsolid nodule. Additionally, solitary air-containing space with size small than 5mm and eccentric distribution would help to determine the presence of EGFR mutation.

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