



## Early View

Research letter

### **Cannabis use and lung cancer: time to stop overlooking the problem?**

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## **Title: Cannabis use and lung cancer: time to stop overlooking the problem?**

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### **Introduction**

After tobacco, cannabis is the most widely used drug worldwide, and the move to legalize it is growing in more and more countries. The literature about the involvement of cannabis smoking on the development of lung cancer is scarce and most often reassuring<sup>1-3</sup>, even though the concentration of carcinogens in cannabis smoke is unquestionably greater than that in tobacco smoke<sup>4</sup>. Moreover, recent studies on cannabis tend to focus on possible therapeutic effects<sup>5</sup>. Studies of the carcinogenic impact of cannabis are indeed limited by its frequent association with tobacco smoking and by its illegal status in most countries<sup>6</sup>.

Our study aimed at describing the prevalence and studying the clinical impact of cannabis use among young patients who underwent surgical resection for primary lung cancer.

## **Methods**

**Study design:** All patients aged 50 years or less who underwent resection for primary lung cancer in three French University hospitals between 2018 and 2020 were prospectively included in an administrative database and retrospectively reviewed. Patients were stratified into three groups: cannabis and tobacco smokers (CTS), tobacco smokers only (TS) and never smokers (NS).

**Data collection.** Each patient was contacted by phone: information on demographics, smoking history, recreational drug use, passive smoking exposure, alcohol consumption and family history of malignancy was collected. In case of cannabis and/or tobacco use, patients were asked about starting age, quantity, frequency and duration of use, and the characteristics of smoking. We also retrospectively analyzed all medical files to find whether cannabis use was reported. Tumor characteristics (localization, histology, molecular profile and staging according to the eighth edition of the TNM Classification of Malignant Tumors), surgical plan, post-operative outcomes, presence of emphysema on thoracic CT scan, and oncological follow-up were also collected.

**Ethical aspects.** All patients gave informed consent to allow medical data prospective collection and retrospective analysis. Data collection was declared to the French National Committee for Informatics and Freedom (CNIL, 2219959). Study protocol was approved by the Ethic Committee of the French Society of Thoracic and Cardio-vascular Surgery (CERC-SFCTCV, 2020-09-08-02-PRAD).

## **Statistical analysis**

Group comparison for categorical and continuous variables was performed with Fisher's exact (or chi-square) and Mann-Whitney U (or Kruskal-Wallis) tests, respectively. Statistical analyses were performed using GraphPad Prism 8.0 (San Diego, CA).  $P$ -value  $<0.05$  was considered statistically significant.

## **Results**

Between 2018 and 2020, 1329 patients underwent lung resection for primary lung cancer, in all cases non-small-cell cancer (NSCLC). Among them, 77 patients were aged 50 years or less and accounted for the study group. 71 patients (92%) answered our phone interview. The data of the remaining 6 patients were collected through contact with their general practitioner and referent oncologist. 43% (n=33) of patients were cannabis and tobacco users (CTS group), 34% (n=26) were tobacco only users (TS group) and 23% (n=18) were never smokers (NS group). Results are summarized in **Table 1**.

**Population Characteristics.** As compared with the TS and NS groups, the CTS group was characterized by a younger age (44 years versus 47 in TS and 45 in NS,  $p=0.01$ ), a higher proportion of

men (76% in CTS, 35% in TS, 11% in NS,  $p < 0.001$ ), and a higher frequency of emphysema (91% in CTS, 50% in TS, 11% in NS,  $p < 0.0001$ ). In the CTS group, joints of cannabis resin mixed with tobacco (“spliffs”) was the single method of cannabis delivery used by all patients, with a median cannabis use of 150 joints per month (range 4-300), and a median duration of cannabis use of 20 years (range 4-34 years). Cannabis use was not mentioned in the medical file of 61% of patients using cannabis.

**Tumor characteristics.** Adenocarcinoma was the most common histological subtype (84% of patients). Large cell carcinoma was more frequent in the CTS group (21% versus 4% in TS and 0% in NS,  $p = 0.02$ ). In the 40 tumors with available molecular profile, we identified alterations of KRAS (n=6), TP53 (n=6), CDKN2A (n=1), STK11 (n=1), and MET (n=1) in the CTS group; KRAS (n=6), EGFR (n=4), TP53 (n=2), ALK (n=1), NFE2L2 (n=1), and NRAS (n=1) in the TS group; EGFR (n=7), ALK (n=2), KRAS (n=1), and ROS1 (n=1) in the NS group.

**Surgical procedure.** As compared with the NS and TS groups, CTS group was characterized by larger tumors (T3-T4 tumors in 0%, 15%, and 43%, respectively,  $p < 0.0001$ ) requiring extended resection involving chest wall, superior vena cava, pericardium, or spine in 21% of the cases. As a consequence, VATS was performed less frequently in the CTS than in the TS and NS groups (36%, 50%, and 72%, respectively,  $p = 0.049$ ).

**Outcome.** CTS group was characterized by longer postoperative air leak duration (3 days versus 2 days in TS and NS groups,  $p = 0.04$ ) and hospital stay (7 days versus 5.5 in TS and 5 days in NS,  $p = 0.03$ ). After a median follow-up of 14.6 months, relapse occurred in respectively 21%, 27%, and 6% in the CTS, TS, and NS groups (ns).

## Discussion

In this study focusing on young patients with resected NSCLC, the use of cannabis was frequently underreported, but it was in fact highly prevalent and yield important consequences on tumor stage, underlying emphysema, VATS accessibility, and postoperative complications.

Our results show a high prevalence of cannabis smoking (43%), that is well above the prevalence in general population in France and in the US, estimated between 2 and 26%<sup>7,8</sup>. This high prevalence of cannabis smoking has been previously reported in the French and Moroccan setting<sup>9,10</sup>. Interestingly, most of the time cannabis consumption is not even mentioned in epidemiological studies about lung cancer<sup>11,12</sup>. For 61% of our patients, cannabis consumption was not reported in medical files, whereas tobacco-use status was always noted. Therefore, it is unlikely that we overestimated cannabis consumption. To query about cannabis addiction is not consistently done, probably because

of the illegality of cannabis and because physicians may overlook the topic; nonetheless, patients enrolled in this study answered without discomfort about their cannabis consumption.

Our study also confirms previous work on the increasing prevalence of lung cancer in women, either related to tobacco use (65%) or in never smokers (89%)<sup>13,14</sup>. Our study also finds a significant difference in the localization of the primary tumor between the groups, with more tumors in the upper lobes and more emphysema, especially in the apices, in cannabis users. These features suggest a co-carcinogen role for cannabis smoke, which contains a greater quantity than tobacco of polycyclic aromatic hydrocarbons and tar particles<sup>4</sup>. Moreover, the presence of cannabinoids and pathologic alterations have been demonstrated in the lung apex of young cannabis smokers with pneumothorax<sup>15</sup>. In our clinical experience, tumors in the CTS group are frequently diagnosed at an advanced stage. This could be due to social barriers to early diagnosis in this population, to the analgesic effects of cannabis, or to a specific natural history of NSCLC in cannabis users. Indeed, a larger proportion of poorly differentiated carcinomas have been found in this population, possibly suggesting a distinctive tumor phenotype.

In conclusion, this preliminary work suggests that cannabis consumption is largely underreported in lung cancer patients, and this is concerning since our data suggest that the co-consumption of cannabis and tobacco may lead to more severe and advanced forms of lung cancer in young male patients. Larger studies are urgently warranted to analyze the impact of cannabis use on the natural history and outcome of NSCLC in young patients. Lung oncologists and thoracic surgeons must be alert to the high prevalence of cannabis smoking in their patients and its potential consequences, to better advise them on the importance of cessation.

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Table 1

	Cannabis and tobacco smokers (CTS)	Tobacco smokers (TS)	Non smokers (NS)	p value
<b>Total (n = 77)</b>	<b>33 (43%)</b>	<b>26 (34%)</b>	<b>18 (23%)</b>	
Male sex	25/33 (76%)	9/26 (35%)	2/18 (11%)	<b>&lt;0.001</b>
Median age (years; min-max)	44 [30;50]	47 [35;50]	45 [31;49]	<b>0,01</b>
Smoking (pack years; min-max)	25 [10;65]	23 [12;79]	-	0.2
Cannabis joints (per month; min-max)	150 [4;300]	-	-	-
Lung emphysema	30/33 (91%)	13/26(50%)	2/18 (11%)	<b>&lt;0.0001</b>
Cancer history in first-degree relatives	13/32 (41%)	12/26 (46%)	7/17 (41%)	<b>0.9</b>
<b>Histological subtype</b>				
Adenocarcinoma	25/33 (76%)	23/26 (88%)	17/18 (94%)	0.2
Large cell carcinoma	7/33 (21%)	1/26 (4%)	0/18 (0%)	0.02
Squamous cell carcinoma	1/33 (3%)	1/26 (4%)	0/18 (0%)	0.7
Mucoepidermoid carcinoma	0/33 (0%)	1/26 (4%)	1/18 (6%)	0.7
<b>Tumor characteristics</b>				
Upper lobes localization	29/33 (88%)	18/26 (69%)	10/18 (56%)	<b>0.03</b>
T1-T2	19/33 (58%)	22/26 (85%)	18/18 (100%)	<b>0.001</b>
T3-T4	14/33 (42%)	4/26 (15%)	0/18 (0%)	<b>0.001</b>
N+	11/33 (33%)	8/26 (31%)	4/18 (22%)	0.7
o N1	5/11 (46%)	5/8 (63%)	1/4 (25%)	0.5
o N2	6/11 (54%)	3/8 (37%)	3/4 (75%)	0.5
<b>Surgery and post operative course</b>				
VATS	12/33 (36%)	13/26 (50%)	13/18 (72%)	<b>0.049</b>
Chest wall and/or adjacent organs resection	7/33 (21%)	1/26 (4%)	0/18 (0%)	<b>0.02</b>
Length of hospital stay	7 [3;45]	5.5 [2;21]	5 [2;19]	<b>0.03</b>
Air leak duration	3 [0;20]	2 [0;17]	2 [0;9]	<b>0.04</b>
Pneumonia	7/33 (21%)	3/26 (12%)	3/18 (16%)	0.6
Need fo reintervention	5/33 (15%)	3/26(12%)	3/18 (17%)	0.9
Relapse during follow-up	7/33 (21%)	7/26 (27%)	1/18 (6%)	0.2

VATS : Video-assisted thoracoscopic surgery