

## Original Article

# Trends in bronchoscopic findings over a decade

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## Abstract

The incidence of lung cancer in Maltese males is higher than that in females. However trends in Maltese and other foreign populations indicate a substantial recent increment in the diagnosis of lung cancer in women. In this retrospective study we report the trends seen along the last decade in bronchoscopic findings of bronchoscopies carried out by one hospital firm in order to try and reflect the practices and results of this important endoscopic investigation on the incidence, diagnosis and treatment of lung malignancies in Malta.

## Introduction

In Malta, lung and prostate cancer are the most commonly diagnosed form of malignant tumours found in males. However, as opposed to prostate cancer, the prognosis for a newly diagnosed patient with lung cancer is alarmingly discouraging. Whereas even in the sixth year after diagnosis, prostate cancer patients have a relative survival rate of over 70%, less than 30% of patients survive the first year of lung cancer diagnosis. Mortalities due to lung cancer rank foremost amongst other common cancers.<sup>1</sup>

## Keywords

lung, cancer, bronchoscopy

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Smoking is still the most common exogenous factor influencing the onset of lung cancer. The association between smoking, the numerous carcinogens found in cigarette smoke and lung cancer has been proven in various published studies.<sup>2-5</sup> However, this is not to say that smoking is the sole factor determining the risk of developing the disease as radiation, other carcinogens such as asbestos, inhaled industrial agents and genetic polymorphisms also have a role to play in the aetiology of this malignancy. The onset of lung cancer, in all its forms, as mediated by smoking is a complex mechanism. To date, among all the components of tobacco smoke, 20 carcinogens have been found to cause lung tumours in laboratory animals and humans alike.<sup>6-9</sup> Among these components, polycyclic aromatic hydrocarbons and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone are likely to play a pivotal role in lung cancer induction. This mechanism is also genetic in nature since it is thought that tobacco smoke carcinogens interact with DNA and induce genetic changes in the form of mutations in oncogenes and tumour suppressor genes.<sup>10-12</sup>

The incidence of lung cancer in Maltese males is higher than that in females. However, trends in Maltese and other foreign populations indicate a substantial recent increment in the diagnosis of lung cancer in women. This occurrence might be attributable to the increase in female smokers over the last decades. In 2004 a study conducted by Sant Portanier et al.<sup>13</sup> indicates that the number of Maltese female smokers has doubled from 10.2% in 1995 to 21% in 2004 and in the 40 – 45 year old age group females were more likely to be smokers and also more likely to consume more cigarettes daily than their male counterparts.

In addition, studies indicate that throughout the years, tobacco smoking patterns have altered the ranking order of the 'league table' of the histopathological types of lung cancer.<sup>14-15</sup> This started to be observed in the 1950s when the introduction of filter-tip cigarettes in combination with advancements in diagnostic techniques led to a worldwide increase in the reported incidence of pulmonary adenocarcinomas. It has been suggested that the number of adenocarcinomas has been on the increase since filter-tip cigarette smoke is inhaled more deeply than other non-filtered cigarette smoke. Such deep inhalation transports tobacco-specific carcinogens further and more distally towards the bronchoalveolar junction where adenocarcinomas often arise.<sup>16</sup> The 1950's also saw the introduction of blended reconstituted tobacco. This form of tobacco releases higher concentrations of nitrosamines from tobacco stems as opposed to products made predominantly from tobacco leaves.<sup>17,18</sup>

Nitrosamines are known to induce lung adenocarcinomas in rodents when injected systemically.<sup>18</sup>

Along the years innovative bronchoscopic sampling procedures which allowed biopsies on tumours in small, distal airways, where these tumours often arise, proved to be a milestone in adenocarcinoma diagnosis. Bronchoscopic sampling is performed by one or more of three techniques; bronchoalveolar lavage (BAL), brush biopsies and tissue biopsies. Sampling methods undertaken are selected on a

case by case basis. It is common practice to use more than one sampling method to safeguard accuracy and reliability and increase the chances of a positive diagnosis. Histological forms of lung cancer include squamous cell carcinoma, which is still the most widely diagnosed lung cancer. Adenocarcinoma and small cell carcinoma are also commonly diagnosed, the latter having a worse prognosis with a highly aggressive progression. Large cell carcinoma is another type of histopathological diagnosis of lung cancer.

**Table 1:** Bronchoscopies by gender and smoking status

	<b>1995-1996</b>	<b>Ratio (%M:%F)</b>	<b>1999-2000</b>	<b>Ratio (%M:%F)</b>	<b>2006-2007</b>	<b>Ratio (%M:%F)</b>
<i>Total no. of elective bronchoscopies</i>	108		109		116	
Males (M)	92 (85.2%)	5.76	88 (80.7%)	4.18	87 (75%)	3
Females (F)	16 (14.8%)		21 (19.3%)		29 (25%)	
<i>Total number of smokers</i>	43 (59.7%)	1.2	50 (52.1%)	1.1	44 (48.4%)	1.0
Males (M)	39 (90.7%)	9.75	46 (92.0%)	11.5	34 (77.3%)	3.41
Females (F)	4 (9.3%)		4 (8.0%)		10 (22.7%)	
<i>Total number of ex-smokers</i>	22 (30.6%)	1.0	29 (30.2%)	1.0	28 (30.8%)	1.0
Males (M)	20 (90.9%)	9.99	27 (93.1%)	13.49	27 (96.4%)	26.78
Females (F)	2 (9.1%)		2 (6.9%)		1 (3.6%)	
<i>Total number of non-smokers</i>	7 (9.7%)	0.5	17 (17.7%)	0.8	19 (20.9%)	1.0
Males (M)	5 (71.4%)	2.5	8 (47.1%)	0.89	6 (31.6%)	0.46
Females (F)	2 (28.6%)		9 (52.9%)		13 (68.4%)	

**Table 2:** Mode of presentation of lung tumours

<b>Mode of presentation in Males &amp; Females resulted positive for cancer</b>	<b>1995/1996 (n= 33) (%)</b>	<b>1999/2000 (n=45) (%)</b>	<b>2006/2007 (n=36) (%)</b>
Hemoptysis	9.1	28.9	19.4
Chest pain	15.2	11.1	16.7
Weight loss	15.2	20.0	13.9
Hoarseness	3.0	4.4	5.6
Pyrexia of Unknown Origin	3.0	4.4	0.0
Persistent cough	12.1	15.6	22.2
Shortness Of Breath	24.2	20.0	16.7
Unresolving pneumonia	6.1	4.4	5.6
Brain metastasis	12.1	6.7	2.8
Past history of Cancers*	0.0	4.4	8.3
Abnormal Chest X-Ray	87.9	97.8	83.3
Abnormal CT Scan	12.1	2.2	16.7
Others**	15.2	20.0	25.0

[\* colon, larynx and squamous cell carcinoma of the skin]

\*\*pleural effusion, past history of rheumatoid arthritis, past history of extrinsic allergic alveolitis, high Erythrocyte sedimentation rate (ESR), fainting, back pain, bone pain, lymphadenopathy, neuropathy, herpes zoster, Syndrome of Inappropriate ADH secretion, superior vena caval obstruction]

In this paper we report the trends seen along the last decade in bronchoscopic findings of bronchoscopies carried out by one hospital firm in order to try and reflect the practices and results of this important endoscopic investigation on the incidence, diagnosis and treatment of lung malignancies in Malta.

## Methods

This retrospective study aimed to compare the indications, findings and sampling methods used in diagnostic fibreoptic bronchoscopies carried out at three different time-points spaced over a decade.

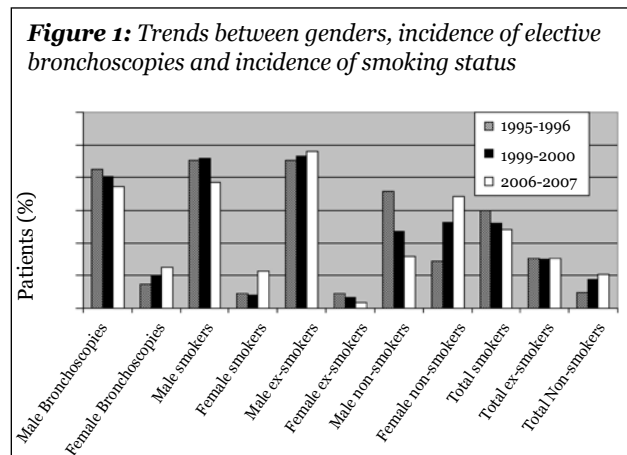
The reports of the diagnostic bronchoscopies carried out by the firm headed by a single respiratory physician [SM] in the periods 1995/96, 1999/2000 and 2006/7 were utilised. The records audited were sampled from the middle of the year till 120 bronchoscopies were reached at each time-point. Therapeutic bronchoscopies carried out mostly in intensive care setting were then excluded as these were beyond the scope of this study. As these bronchoscopies were decided on and carried out by the same respiratory physician, the policies for choice of patients requiring bronchoscopy and the protocol and sampling methods used were all similar across the decade in question. The analysis carried out on the data involved:

- demography of the patients bronchoscoped including their smoking status,
- indications for the fibreoptic bronchoscopy,
- diagnosis of bronchial malignancy if any and any gender-related or smoking-related differences which might be present,
- the histological types of malignancies diagnosed, and
- the sampling methods used and which were most sensitive and useful in detecting a malignant lesion.

As the sampling periods were irregular and the aim of the study was comparative, statistical analysis was carried out mostly on percentage values; Fisher's exact test was used.

## Results

The numbers of patients studied in this retrospective study were relatively small and thus there was not enough power for statistical significance to be reached in any of the analysis carried out. However, some clear trends were apparent and we thought that these should lead to interesting speculative discussion.

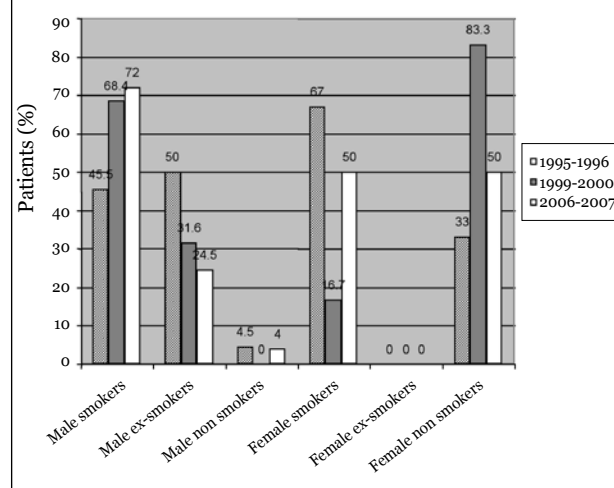


## Demography

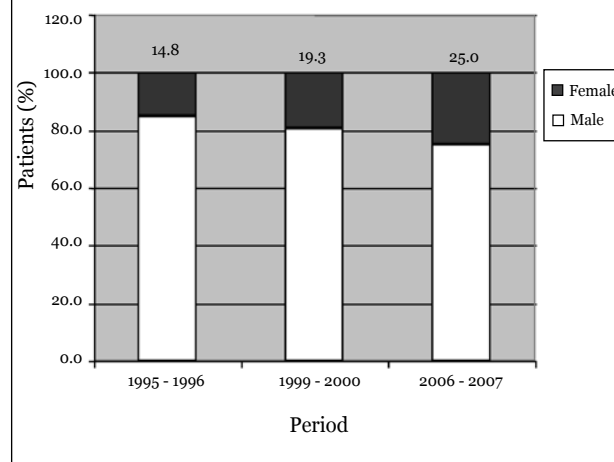
The numbers of elective bronchoscopies carried out in the three sampled time-periods were: 1995/96: 108 bronchoscopies; 1999/2000: 109 bronchoscopies and 2006/7: 116 bronchoscopies respectively. Table 1 and Figure 1 show the various subsets of patients undergoing these bronchoscopies as subdivided into gender and smoking status for each gender i.e. current smokers, ex-smokers and non-smokers, for each period studied. The mean ages were: 61.8 yrs [range 19 – 94 yrs] in 1995/96, 62.4yrs [range 11 – 86 yrs] in 1999/2000 and 63.3yrs [range 21 – 91yrs] in 2006/7. One can note that:

- the ratio of male to female patients undergoing diagnostic bronchoscopies is decreasing from 5.76 in 1995/96 to 3 in 2006/7,
- a similar trend is also seen when one compares male and female smokers undergoing bronchoscopies: whereas the proportion of male patients undergoing bronchoscopies who were still current smokers has remained quite stable along the years studied, the proportion of female smokers endoscoped rose from 9.5% in 1995/96 to 22.7% in 2006/7, and

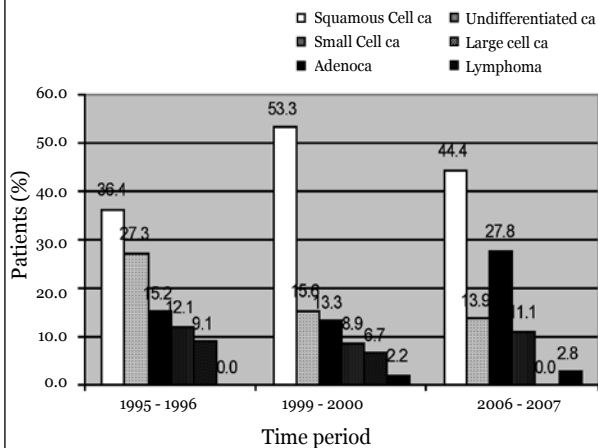
**Figure 2: Number of Malignancies detected by Gender and Smoking Status**



**Figure 3: Bronchoscopies with a diagnosis of malignancy, by period and gender**



**Figure 4:** Trends in histological results throughout the three different time points



**Table 3.** Histological types of lung tumours

**Males**

Histological Types	% of total	% of total	% of total
Squamous cell carcinoma	36.7	51.3	44.8
Small cell carcinoma	30	15.3	10.3
Adenocarcinoma	13.3	15.3	31
Undifferentiated carcinoma	13.3	7.7	10.3
Large cell carcinoma	6.7	7.7	0
Lymphoma	0	2.6	3.4

**Females**

Histological Types	% of total	% of total	% of total
Squamous cell carcinoma	33.3	66.7	42.9
Small cell carcinoma	0	16.7	28.6
Adenocarcinoma	33.3	0	14.3
Undifferentiated carcinoma	0	16.7	14.3
Large cell carcinoma	33.3	0	0
Lymphoma	0	0	0

**Table 4.** The three main bronchial investigative sampling methods used and their yield

Total	1995/ 1996	+VE	%	1999/2000	+VE	%	2006/2007	+VE	%
<b>Lavage</b>	31	23	74.2	44	29	65.9	35	19	54.3
<b>Brush</b>	32	29	90.6	43	41	95.3	34	29	85.3
<b>Biopsy</b>	14	11	78.6	10	9	90.0	10	7	70.0

c] this increase is also seen in female non-smokers [28.6% in 1995/6 vs 68.4% in 2006/7]. Although this reflects the general increase in the total number of non-smokers studied, the rise in females is greater and is more impressive because in the case of the males there has been a sustained decrease in their need for a bronchoscopy. No such changes are seen in female ex-smokers, though here the numbers are very small.

**Mode of presentation**

Table 2 shows the various indications for diagnostic fibreoptic bronchoscopies. These figures show that the commonest indication for bronchoscopy along the decade studied has remained that of an abnormal chest X-ray. However, haemoptysis and persistent cough seem to have become even more common reasons for referral. These three commonest reasons for referral were all much more common in smokers when compared to ex-smokers and even more so to non-smokers.

**Bronchial malignancy diagnosed**

Around a third [34.2%] of patients who were bronchoscoped in all the three time-periods studied ended up with a diagnosis of a malignant bronchial lesion:

- in 1995/96, 33 out of 108 bronchoscopies were positive for malignancy,
- in 1999/2000, 45 out of 109 bronchoscopies were positive for malignancy, and
- in 2006/7, 36 out of 116 bronchoscopies were positive for malignancy.

These proportions of positive results for malignancy show a good degree of consistency and have not increased or decreased substantially over the decade studied.

When these figures were further subdivided into gender-related percentages [Figure 2] one could see that there was an increasing trend in bronchial malignancies in male smokers and a decrease in male ex-smokers. In the female subset there was also an increasing tendency in female non-smokers being diagnosed with a pulmonary malignancy through these bronchoscopies and a subtle decrease in the percentage of female smokers with such a diagnosis. However, one must remember that the number of female smokers increased across the studied time-period and this could explain this relative percentage decrease.

Figure 3 shows that over the studied decade the overall percentage of female patients undergoing bronchoscopy and ending up with a diagnosis of bronchial malignancy compared to the total number of patients at the three specific time-points

analysed has increased markedly from 14.8%, in 1995/96, to 19.3%, in 1999/2000, and to 25.0% in 2006/7.

### **Histological types of diagnosed malignancies**

Figure 4 shows that whereas squamous cell carcinoma remained the most common histological type of bronchial malignancy, there was an impressive increase in the rate of increase of the incidence of adenocarcinomas and a decrease in small cell and large cell carcinomas along the years. However table 3 reveals that it is in males that the greatest increase in adenocarcinoma has occurred while in females there was an increase in the number of small cell carcinomas diagnosed. Although the numbers were small one could also see that some pulmonary lymphomas being diagnosed during these bronchoscopies.

### **Sampling methods**

In table 4 one can see that bronchial brushings have remained the most reliable and sensitive mode of positive sampling for bronchial malignancies. Bronchial lavage has shown some loss of sensitivity while bronchial biopsies, which are least utilised, have remained stable in the rates of confirming a positive diagnosis of pulmonary malignant lesions.

### **Discussion**

This comparative retrospective study has showed some interesting trends, between the three chosen time-points spanning a decade, in the demography of patients undergoing diagnostic fiberoptic bronchoscopies, in the indication for the bronchoscopy, in the differing rates of diagnosis of bronchial malignancies among the different patient groups, in the histological types of tumours seen and in the pick-up rates of the various sampling modalities utilised.

The general trend of the results shows an increase in the prevalence of bronchial malignant tumours in female patients and this is also reflected in the changes seen in the male to female ratio of patients undergoing this type of endoscopy. One could note that between 1995/6 and 2006/7 the female proportion undergoing bronchoscopies rose from 14.8% to 25%. A surprising finding was that this increase was not found uniquely in female smokers but also in non-smokers. In the male patients undergoing bronchoscopies the numbers have remained quite stable over the time-span studied and this status quo was noted in all subsets of patients, whether they were smokers, ex-smokers or non-smokers.

This increase of female non-smokers requiring bronchoscopies, which runs parallel with that seen in the case of their smoking counterparts, is further echoed in the finding of an increase in bronchial malignancies diagnosed in these non-smokers along the decade. This even surpasses the rate seen in the female smoking group were there was an actual decrease in bronchial carcinomas. This finding of female non-smokers developing more bronchial malignancies when compared to their male counterparts along the years has been reported elsewhere.<sup>19,20</sup> In fact whereas it is estimated that 85% of males with lung cancer are smokers, in females this figure is only around 47% worldwide<sup>21</sup> and 70% in Europe.<sup>22</sup> Although

tobacco is still the commonest cause of lung cancer in both sexes one cannot ignore this apparent increase in risk for this type of cancer in non-smoking females. One could question whether all female patients were truthful about their smoking status but one must also speculate that they might be more sensitive to inhaled carcinogens such as those found in environmental tobacco smoke.<sup>23-27</sup> It has been suggested that females might be more susceptible to tobacco-smoke induced DNA damage and that they have a lower ability to repair such damage. In fact mutations to this DNA such as the K-Ras mutations are commoner in female than male smokers and have also been detected in non-smoking females.<sup>28-30</sup> One must remember that on the whole female smokers still smoke less than men so it does seem that they are more prone to tobacco-induced carcinogenesis. This seems to reflect the increased preponderance in women to develop liver cirrhosis when they abuse alcohol when compared to men.<sup>31</sup>

The percentage of all the patients undergoing bronchoscopies and ending up with a diagnosis of bronchial malignancies has remained quite stable along the years – at around 35%. However, as discussed above there are major differences related to gender. Whereas in 1995/6 the ratio of female to male lung cancer victims was 1:9 [14.8%], this increased to 1:7 [19.3%] in 1999/2000 and 1:4 [25%] in 2006/7. These figures compare quite well to the national female/male ratio in the incidence of lung cancer in the National cancer registry [14/111 – 12.6% in 1996; 23/121 – 19% in 2000; 27/115 – 23.5% in 2006]<sup>1</sup> and enhance the reliability of our results. From these figures one can see that in these 3 time-points the national overall figures for lung cancer has remained relatively stable 125 [1995], 144 [2000] and 142 [2006]<sup>1</sup> As in the case of other European countries this is due to an increase in lung malignancies in females and a decrease in the males at the same time.<sup>32</sup> A local study in 1987 had noted that only 9% of lung cancers in Malta were found in females,<sup>33</sup> thus showing that this incidence increased by almost three times over twenty years. This increase in females with lung cancer is becoming a more common cause of death secondary to malignancy and is catching up to the death rate secondary to breast cancer. In France, in 1985, cancer of the lung was the sixth highest cause of cancer-related deaths but in 1995 it went up to the third commonest.<sup>34,35</sup>

These pulmonary malignancies have also shown that along the years all adenocarcinomas are showing a steep rise in prevalence. In Europe, adenocarcinoma is the most common histological type of lung cancer in females while squamous cell carcinoma is still the commonest in males but, even in this sex, adenocarcinoma is on the increase.<sup>32,36,37</sup> One hypothesis for this reason is that adenocarcinomas, previously more common in non-smokers, is that higher consumption of low-tar cigarettes with better filters lead to deeper inhalations by smokers during smoking this type of cigarette. This is thought to lead to more peripheral delivery of the smoke where adenocarcinomas are more likely to develop.<sup>16</sup>

During our bronchoscopies we employed various sampling modalities according to macroscopic findings seen. In central airway lesions all three i.e. bronchial lavage, brushings and biopsies were utilised while in more peripheral lesions biopsies



were less used than the other two methods of sampling. The pick-up rate, as in the past,<sup>38</sup> turned out to be that acquired by bronchial brushings which are sometimes taken 'blindly' or under fluoroscopy for peripheral lesions and sent for cytology. Lavage seems to be less sensitive, possibly because of the dilution factor on scanty numbers of collected cells from bronchial lining and lesions, while biopsies might suffer from sampling of necrotic areas seen on the tumour surfaces apart from the obvious small size of the sampling biopsy forceps.

In conclusion we have seen that over the past decade the trends in bronchoscopies and their findings have shown an increase in female patients undergoing bronchoscopies, an increase in the general proportion of females being diagnosed with lung malignancies especially so in female non-smokers. There has also been an impressive increase in adenocarcinomas of the lung which like other pulmonary malignancies in our series, were mostly picked up by bronchial brushings carried out during bronchoscopy.

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