

Diagnosing lung malignancy from bronchoscopy in Malta – an update

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Abstract

Introduction: A previous local study by Agius *et al.* published in MMJ in 2009¹ identified a rise in lung adenocarcinoma over a decade, as well as an increasing number of females diagnosed with lung malignancy.

Aims and Objectives: The aim of this retrospective study was to further compare trends in lung malignancy diagnosis made from bronchoscopy in Malta to previous local data.

Materials and Methods: All bronchoscopies performed by one respiratory firm at Mater Dei Hospital in 2014-2015 were analysed, excluding those performed in intensive care. Cytology and histology results were retrieved and compared to those obtained from previously studied timeframes. Patients who had a post-bronchoscopy diagnosis via other means, were noted in order to calculate the bronchoscopy pick-up rate.

Results: 118 bronchoscopies were performed, 101 of which were done for suspected malignancy. 48 patients were diagnosed with lung malignancy from bronchoscopy in 2014-2015 by this respiratory firm. When compared to 2006-2007, 83.3% were males (vs 75%) and 16.7% were females (vs 25%). The overall bronchoscopy pick-up rate for malignancy was 81.4%. The most common histological diagnoses, when compared to 8 years previously, were adenocarcinoma 35.4% vs 27.8% (males 37.5% vs 31%; females 25% vs 14.3%), squamous cell 35.4% vs 44.4% (males 37.5% vs 44.8%; females 25% vs 42.9%), and small cell 14.6% vs 13.9%.

Conclusion: Lung adenocarcinoma has shown an upward trend in both gender groups, having now reached a similar prevalence to squamous cell carcinoma, which appears to be decreasing in both males and females in the Maltese population.

Keywords

Lung Neoplasms, Bronchoscopy, Malta

Introduction

Worldwide trends in primary lung malignancy have shown a rise in adenocarcinoma. This is now the most common histological subtype worldwide², surpassing squamous cell which was historically the most frequent.

A 2009 Maltese study¹ compared trends in bronchoscopic findings over a decade by

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studying three 2-year periods: 1995-1996, 1999-2000 and 2006-2007. The study identified a local rise in adenocarcinoma reflecting international statistics; however squamous cell carcinoma remained the most common subtype.

International trends indicate a rising incidence of lung cancer in women. The 2009 local study also revealed an increasing number of females diagnosed with lung malignancy over a decade.

This 2014-2015 local project aimed to study the bronchoscopic diagnoses of lung cancer and compare them to the data from 1995-1996, 1999-2000 and 2006-2007, and to identify whether local data shadows worldwide trends in the rise of lung adenocarcinoma.

Materials and Methods

Inclusion and Exclusion Criteria

All patients who had a flexible bronchoscopy at Endoscopy Unit, Mater Dei Hospital under the care of one respiratory physician between January 2014 and December 2015 were included in the study. Patients who had a bronchoscopy in the Intensive Therapy Unit were not included.

Data Collection

Patient gender, age, smoking history and presenting symptoms were recorded from the bronchoscopy reports. The presence or absence of macroscopic abnormality on bronchoscopy was also recorded from the bronchoscopy sheet. The pre-bronchoscopy Chest X-rays and Computed Tomography (CT) scans were reviewed on Picture Archiving and Communication System (PACS®) and the results were noted.

The presence or absence of sputum studies, bronchial washings, bronchial brushings and endobronchial biopsies was

noted from iSoft Clinical Manager®. The final cytology or histology outcome was recorded for each patient, and the availability of immunohistochemistry was documented.

Patients who had a post-bronchoscopy cancer diagnosis via other means such as radiologically-assisted biopsy and surgery, were also noted in order to calculate the bronchoscopy pick-up rate.

Data Analysis

The data for malignancy patients was compared with those from a similar study recording malignancy data from 1995-1996, 1999-2000 and 2006-2007.

Results

A total of 118 bronchoscopies were performed by one respiratory firm between January 2014 and December 2015, 101 of which were done for suspected malignancy. Of these, 48 (46.7%) had a malignant diagnosis from bronchoscopy.

Demographics

The mean age of our cohort with lung malignancy was 67 years, with a range of 49 to 87, and a median of 67.5 years. 40 patients (83.3%) were male, and the remaining 8 (16.7%) were female. Fig. 1 shows the trends in gender ratio, in comparison with previous local data.

Smoking History

Of the patients diagnosed with malignancy from bronchoscopy, 23 patients (47.9%) were current smokers, 17 (35.4%) were ex-smokers, 7 (14.6%) were non-smokers, and the remaining patient had no smoking history documented. Fig. 2 shows the trends in smoking history in males and females separately over the past two decades.

Figure 1: Gender Distribution of Malignancy Patients

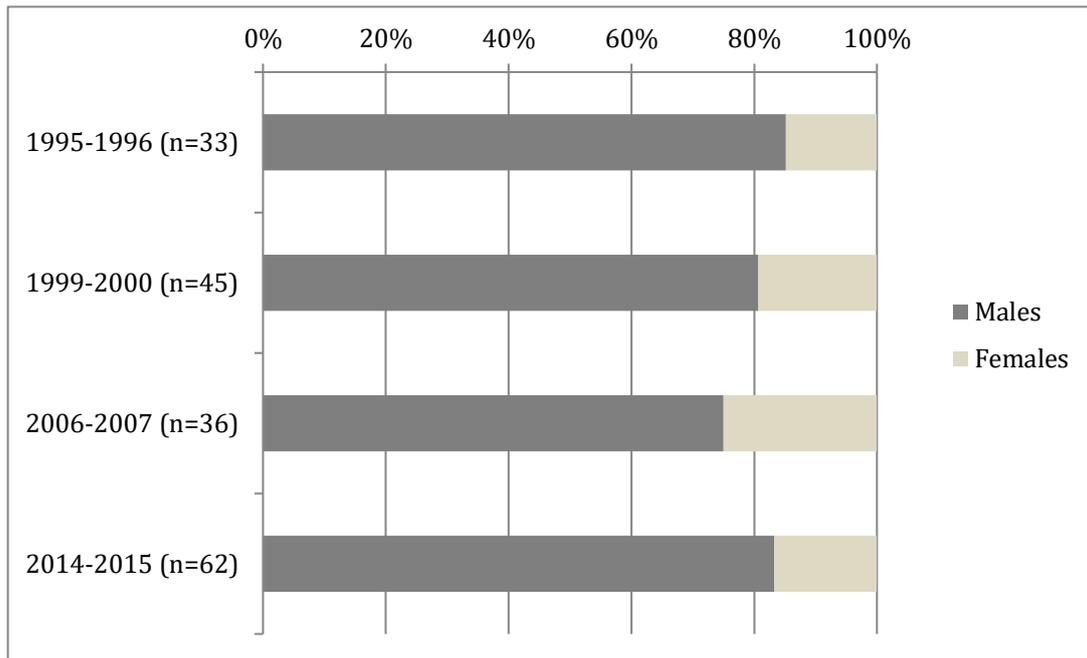


Figure 2: Smoking History of Malignancy Patients

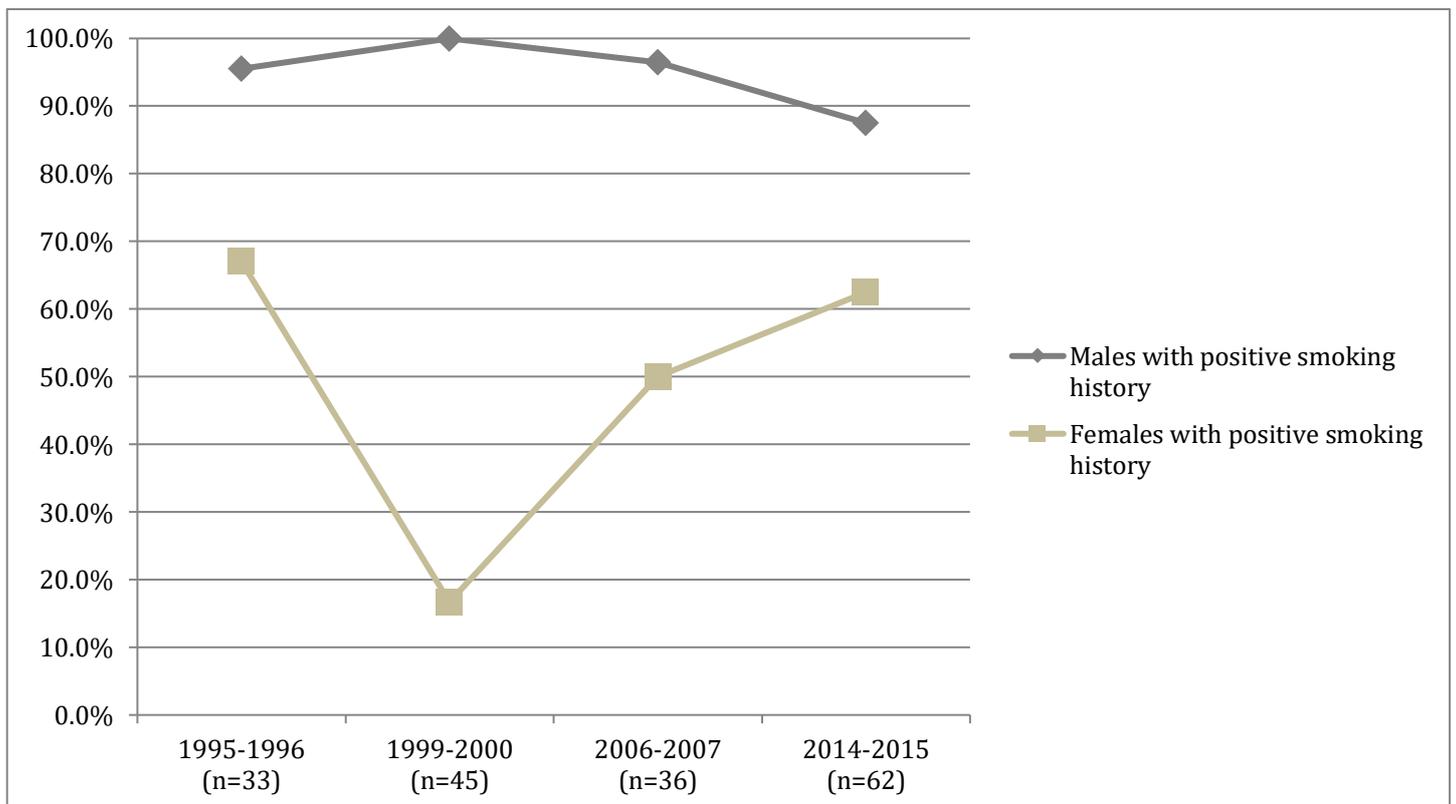
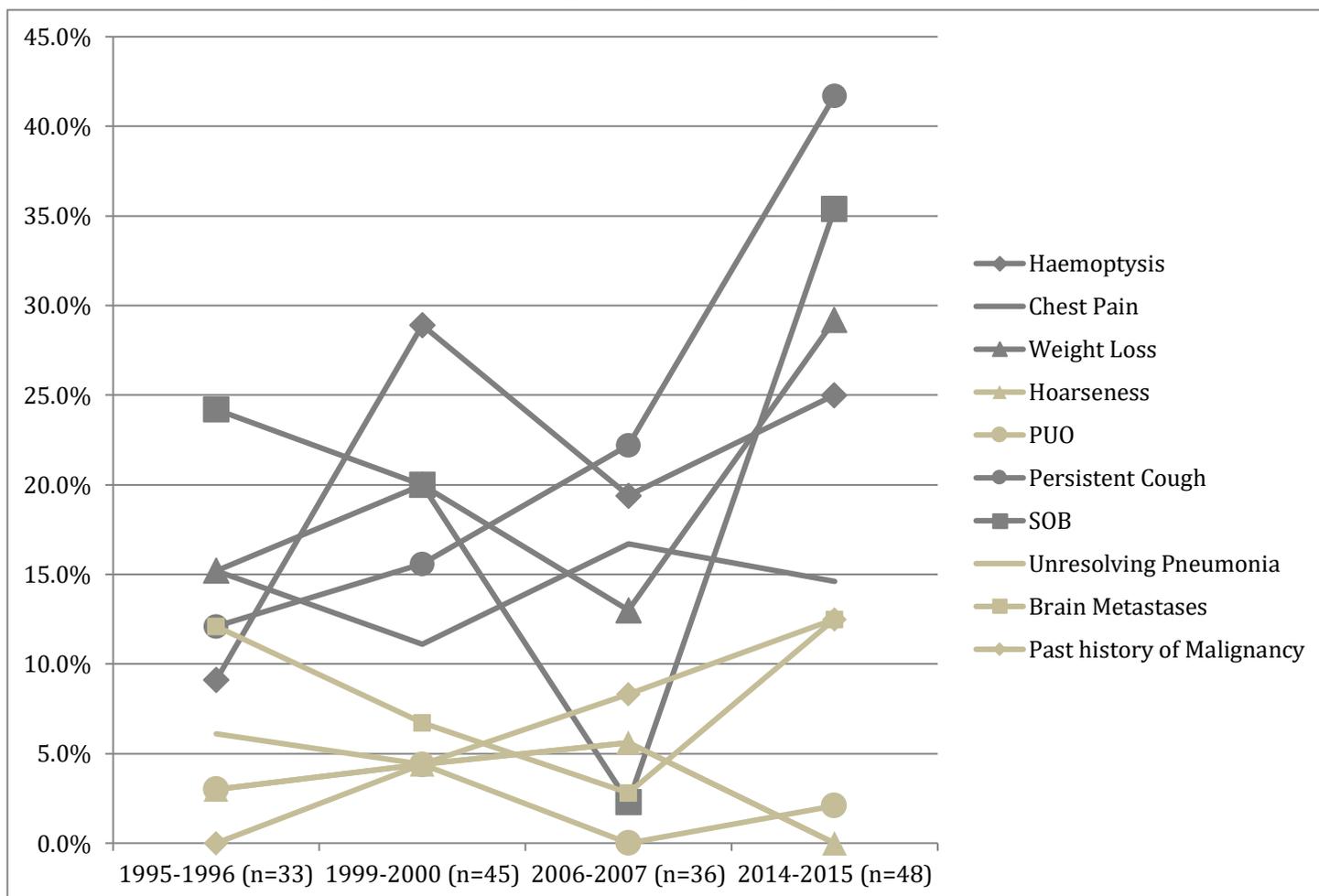


Figure 3: Presenting Symptom of Malignancy Patients

Symptoms

Fig. 3 shows the trends in presenting complaint, in comparison with previous data. Persistent cough was the most common presenting symptom in the 2014-2015 cohort, followed by shortness of breath.

Imaging results

42 patients (89.6%) had a documented abnormal chest X-ray prior to bronchoscopy. 1 patient had a normal X-ray, while 4 patients did not have a chest X-ray. All patients had an abnormal pre-bronchoscopy CT thorax.

Sputum yield

Sputum studies were largely unreliable since many samples were sub-optimal. 5

patients (10.4%) had a malignancy diagnosis from sputum cytology.

Bronchoscopic yield (Figs. 4 and 5).

Of the patients diagnosed with malignancy from bronchoscopy, 44 patients (91.7%) had a macroscopic abnormality on bronchoscopy, while the remaining 4 (8.3%) had a macroscopically normal bronchoscopy. All patients had bronchial washings or lavage taken, and 40 were positive. The positive yield of bronchial washings when considering those patients who had a malignant diagnosis made from bronchoscopy was therefore 83.3% (40 out of 48). All patients had bronchial brushings taken, 39 of which were positive. The positive yield of bronchial brushings when

considering those patients who had a malignant diagnosis made from bronchoscopy was 81.3% (39 out of 48). 35.4% (17 patients) had an endobronchial biopsy, of which 13 were positive. The

positive yield of endobronchial biopsy when considering those patients who had a malignant diagnosis made from bronchoscopy was 76.5% (13 out of 17).

Figure 4: Bronchoscopic Procedures Performed

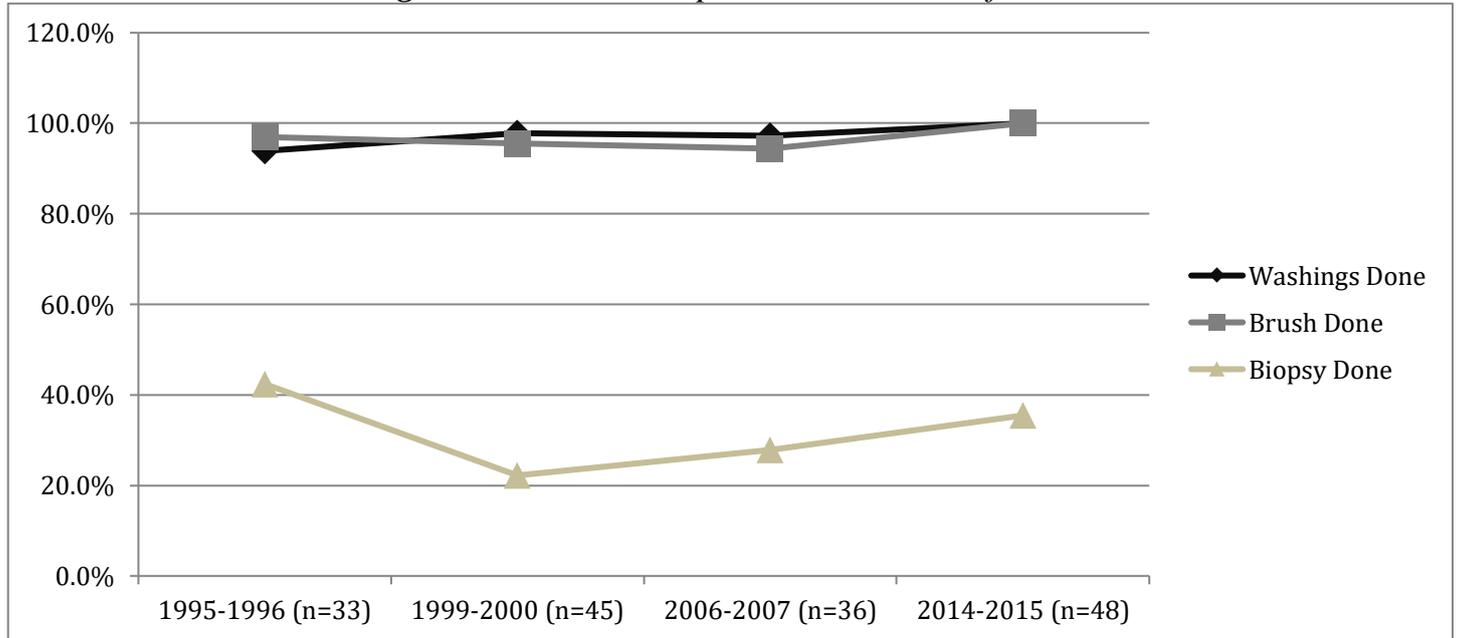
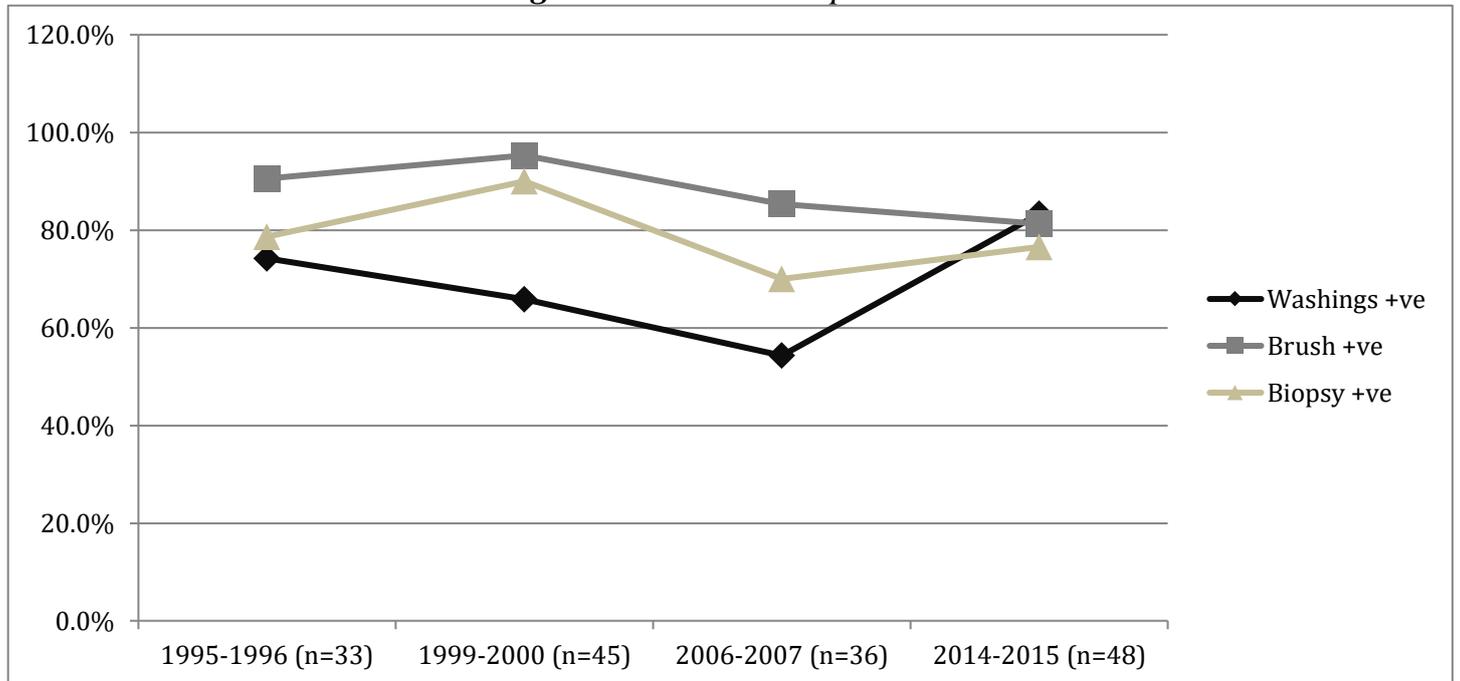


Figure 5: Bronchoscopic Yield



Bronchoscopy pickup rate

Although 48 patients were given a diagnosis of malignancy through bronchoscopic results, a further 11 patients had a negative bronchoscopy which was followed by a diagnosis of lung malignancy through other means. The overall bronchoscopy pick-up rate for malignancy was therefore 81.4% (48 out of 59 patients).

Of those patients who had a negative bronchoscopy but were eventually diagnosed with lung malignancy through alternative means, 72.7% (8 out of 11) were diagnosed with adenocarcinoma. There was one patient each for squamous cell carcinoma and small cell carcinoma, and the remaining patient had a biopsy showing necrotic cells likely originating from necrotic areas of carcinoma but no definitive diagnosis could be established. Of this same patient cohort, 72.7% (8 out of 11) presented

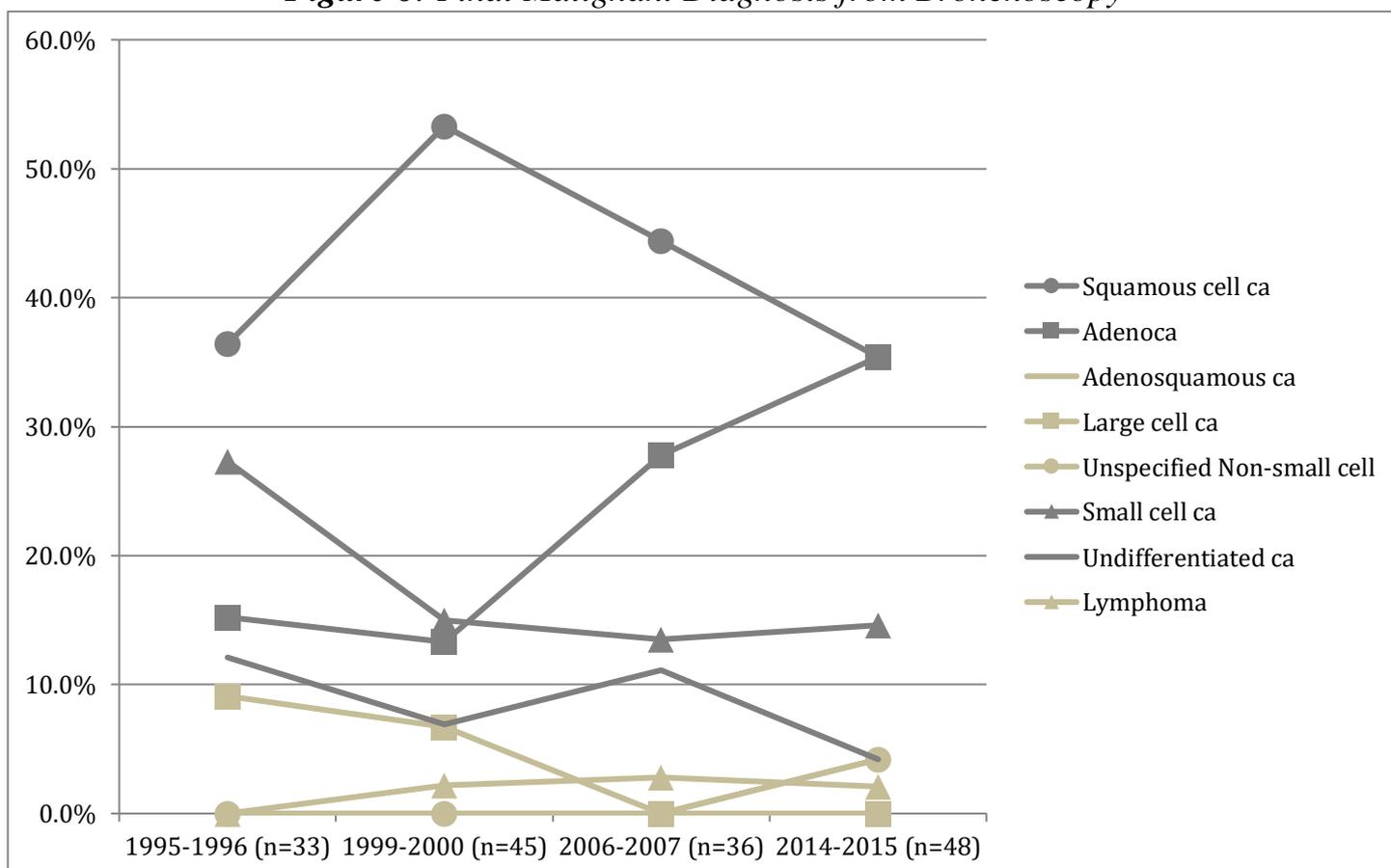
with persistent cough, while only 9.1% (1 patient) presented with dyspnoea.

The pickup rate of bronchial washings for malignancy was 67.8% (40 out of 59 patients) and that of bronchial brushings was 67.2% (39 out of 58 patients). The pickup rate of endobronchial biopsies was 68.4% (13 out of 19 patients).

Histological subtypes

Fig. 6 shows the histological subtypes diagnosed from bronchoscopy. The prevalence of adenocarcinoma is equal to that of squamous cell carcinoma in the 2014-2015 cohort. There were no patients diagnosed with large cell carcinoma in the 2014-2015 group. Immunohistochemistry results were available for 21 patients (33.9%).

Figure 6: Final Malignant Diagnosis from Bronchoscopy



In the male cohort, adenocarcinoma and squamous cell carcinoma were equally prevalent (15 patients – 37.5%). These were followed by small cell carcinoma (14.6% or 7 patients). There were no males diagnosed with adenosquamous carcinoma. The lymphoma and undifferentiated carcinoma patients were all male, and one of the patients with unspecified non-small cell carcinoma was male.

The female cohort showed an equal distribution between adenocarcinoma, squamous cell carcinoma and adenosquamous carcinoma, each accounting for 25% (2 patients). 1 patient had small cell carcinoma, and the remaining patient was diagnosed with unspecified non-small cell carcinoma.

Of those 6 patients presenting with brain metastasis who had a positive bronchoscopy, 3 patients were diagnosed with adenocarcinoma, 2 patients with squamous cell carcinoma and the remaining patient was diagnosed with unspecified non-small cell carcinoma.

Discussion

Molecular profiling studies serve to remind us that lung cancer is a complex disease, with different phenotypes that are characterized by variation in morphology as well as molecular composition. Over recent decades, there appears to be worldwide shifts in the relative frequencies of various phenotypic patterns of lung cancer, which are even more striking than changes in the overall incidence of lung cancer.³

When comparing presenting symptoms of lung malignancy over the years, it is noticeable that in our local cohort of patients, cough (41.7% of patients with a positive bronchoscopy) and dyspnoea (35.4%) have become more common, possibly explained by the fact that medical

practitioners are investigating these symptoms more thoroughly. Cough was even more common among malignancy patients with a negative bronchoscopy (72.7%); these patients most likely had peripheral tumours, and the cough suggests involvement of peripheral nerves. In contrast, patients with a positive bronchoscopy were more likely to present with dyspnoea (35.4%) than those with a negative bronchoscopy who were diagnosed with malignancy through other means (9.1%). This is probably because patients with a positive bronchoscopy had central lesions which compromise more lung function.

Unfortunately, a larger number of patients presented with brain metastasis when compared to the previous 15 years. The incidence in our local cohort (12.5%) is similar to that quoted in a study performed by Shouten *et al.*⁴ (16.3%). All cases of brain metastases occurred in conjunction with non-small cell lung cancer. Although small cell lung cancer classically carries a high risk of brain metastases, non-small cell lung cancer is also commonly associated with brain metastases and the risk can be as high as 23.2%.⁵ The absence of small cell lung cancer patients with brain metastases is probably due to the fact that small cell lung cancer was diagnosed in only a small percentage of our cohort (14.6%).

Previous local data identified a persistent decrease in the male:female ratio for lung malignancy, reflecting international trends. This trend was not reflected in our study, and the significance of the drop in females is unclear. International studies have also shown an increase in lung cancer in never-smokers, and the reasons for this remain uncertain.⁶ Our local data show a small decline in the percentage of male lung malignancy patients with a positive smoking

history over recent years, while there is no consistent trend in the female smoking history, with females having a positive smoking history varying from 16 to 67% over the last two decades.

When comparing diagnostic methods performed during bronchoscopy, a significant improvement in the lavage is noticeable. However, these results were not mirrored in the results obtained from the bronchial brushings. A plausible explanation could be the introduction of different branded bronchial brushes in our hospital, with the resulting technical difficulties associated with them. Results of endobronchial biopsies have given similar yields possibly due to that fact that more experienced staff tend to perform such a procedure, while brushings are usually carried out by respiratory trainees performing the bronchoscopy under supervision.

The bronchoscopy pick-up rate for malignancy of 81.4% was calculated by following up those patients who had a negative bronchoscopy but were diagnosed with lung malignancy through alternative means. The previous local study by Agius *et al.* did not follow up patients in this manner, and therefore do not quote any pick-up rates. Our results show that most lung cancer patients who had a negative bronchoscopy were diagnosed with adenocarcinoma (72.7%), and this is probably because adenocarcinoma tends to be peripheral and therefore less amenable to bronchoscopic techniques.

Previous results have shown that squamous cell carcinoma was the most frequent histological subtype; however, our recent study has shown that adenocarcinoma and squamous cell carcinoma are equally diagnosed. Histology trends show a persistent upward trend in the

adenocarcinoma histological subtype in both males (37.5% in our cohort vs 31% in the 2006-2007 cohort) and females (25% vs 14.3%), and a decline in the squamous cell carcinoma subtype in both gender groups (males 37.5% vs 44.8%; females 25% vs 42.9%). International studies have also identified similar trends with a significant increase in the incidence rate of adenocarcinoma and drop in the rate of squamous cell carcinoma.^{2,7-11} The increasing proportion of lung cancers classified as adenocarcinoma has been a topic of interest and research for a number of years. To date, the cause of the increase in adenocarcinomas is not clear. Two changes in cigarette design over time have been proposed to explain the rise of adenocarcinoma in females. First, ventilated filters, which have gained popularity over the last several decades, have led to compensatory smoking, where smokers inhale a greater volume of smoke more deeply, leading to increased exposure of cells on the periphery of the lung (where adenocarcinoma occurs) to carcinogens. Secondly, filtered cigarettes are richer in nitrate, increasing the exposure to N-nitrosamines, which are associated with an increased risk for adenocarcinoma but not with other types of lung cancer.⁷

A similar number of bronchoscopies has been performed during the study period compared to the previous study, despite the increasing number of CT-guided lung biopsies performed in our hospital. This implies that there is a probable overall increase in the incidence of lung malignancy locally. In our study, we also looked at patients who had suspected malignancy whose eventual malignant diagnosis was made from CT-guided biopsy following a negative bronchoscopy, whereas in the previous study, such patients were not taken

into consideration, possibly due to the fact that there were no patients who had a CT-guided biopsy performed following a normal bronchoscopy, since the procedure was not available at the time.

Limitations of the Study

Patients who never had a bronchoscopy but were diagnosed with lung malignancy through radiologically-assisted biopsy or other means, were not included in the study. This implies that the results of the study may not be totally representative of the lung malignancy trends in Malta. Only the results of one of four respiratory consultants' bronchoscopies were analysed. Since bronchoscopy results tend to depend on the operator performing the procedure, one respiratory firm was chosen in order to standardize the bronchoscopy procedure as much as possible.

Conclusion

Adenocarcinoma has increased in both males and females separately in Malta, and now has a similar prevalence to squamous cell carcinoma. On a positive note, several genetic mutations specific to lung adenocarcinomas have been found, representing attractive targets for molecular therapy.

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