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ORIGINAL ARTICLE

Cytological and histological diagnosis of lung cancer in Sardinia and Italy in the 1990s

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ABSTRACT: ***Cytological and histological diagnosis of lung cancer in Sardinia and Italy in the 1990s. P. Pirina, M. Budroni, S. Esposito, S. Ostera, M.F. Polo, L. Santoru, G. Madeddu, A.G. Fois, G.C. Ginesu, G. Padua, F. Tanda, F. Ginesu.***

Background. **Up to 30-50% of all lung cancer cases remain without cyto-histological characterisation. The aim of our study was to evaluate retrospectively the proportion of histological and/or cytological diagnosis in patients with lung cancer in Sardinia.**

Methods. **Data was gathered by consulting the hospital registers and case notes of individual patients released from hospital with a diagnosis of Lung Cancer at all medical centres throughout Sardinia. In gathering patients' data, we focused our attention on cytological and histological procedures through which allowed the lung cancer was diagnosed. Cancer Registries data was utilised to compare our data with national and Sassari province data.**

Results. **From 1991 to 1996 there was a total of 3146 lung cancer patients registered in Sardinia. 1902 patients (60.5%) had a histological diagnosis, 142 patients (4.5%) a cytological diagnosis while in 1102 patients (35%) the diagnosis was performed without any pathological validation.**

Conclusions. **Our study has shown that lung cancer diagnosis is supported by pathological verification in 65% of cases while in remaining 35% of patients the diagnosis is based only on clinical and radiological reports. In Italy data from Cancer Registries report the percentage of cyto-histological diagnosis to be 70% with the percentage of cytological diagnosis being higher than in Sardinia.**
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Keywords: Lung cancer, Histological diagnosis, Cytological diagnosis.

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Introduction

Lung cancer is the most frequently diagnosed cancer and the most common cause of cancer mortality in males worldwide. It is largely due to cigarette smoking [1]. In Italy data from Cancer Registries between the period 1993-1998 demonstrate the rates of incidences to be 86.7 for males and 18.2 for females per 100,000 inhabitants per year (age-standardised rates to Italian 1981 population census) [2, 3]. The most widely adopted lung tumour classification is that of the World Health Organization (WHO). On the basis of this histologic classification the most relevant categories of lung cancer are small cell (SCLC) and non-small cell (NSCLC: adenocarcinoma, squamous cell carcinoma, large cell carcinoma) carcinoma [4]. Therapy and prognosis are closely related to histological type of lung cancer.

The goal of all diagnostic techniques is, first of all, to establish lung cancer presence and then, in order to decide the suitable treatment, to establish to which histological type the tumour belongs. For this purpose histological samples provide a greater degree of accuracy than cytological techniques, which require expert cytologists. Despite about 75% of all lung cancer cases being diagnosed in the advanced stage of the disease, up to 30-50% of cases have still not undergone histological characterisation. In fact Italian Cancer Registries show that lung cancer is positioned among tumours which cyto-histological diagnosis present difficulties (table 1) [3, 5-8].

The routine cyto-histological techniques, performed during fibreoptic bronchoscopy (FOB), comprise of bronchial brushings, washings and biopsies, transbronchial needle aspiration (TBNA) and biopsy (TBx), and bronchoalveolar lavage (BAL) [9]. A high level of diagnostic accuracy (diagnosis in more than 90% of cases) can be achieved by taking 3-5 biopsy samples and a combination of bronchial brushing and washing.

Yield from sputum cytology increases with subsequent specimens and the highest yields are obtained from large tumours with central locations, such as squamous and small cell carcinoma [10]. Specimens collected 1-4 hours post bronchoscopy and during the following morning may produce diagnostic information even if the bronchoscopy is normal [11].

Table 1. - Proportion (%) of cancer cases with histological verification (data from Italian Cancer Registries)

Site	Male (%)	Female (%)
Pancreas	38.4	32.6
Liver	39.9	32.6
Brain	54.2	49.2
Lung	57.3	49.5
Prostate	84.6	
Colon	90.7	87.9
Breast		90
Rectum	92.8	90.8
Oro-rino-hypopharynx	95-96	90-92
Uterus		94-96
Skin	98	97-98

In the past, percutaneous transthoracic needle aspiration (TTNA) was abandoned because of its association with high morbidity and mortality. Fortunately the development of thin needles, image intensifiers and improved cytological techniques, has led to a reassessment of this procedure. The operator may be guided by fluoroscopy, ultrasound or CT scan and he may perform TTNA under local anaesthesia with minimal discomfort for the patients. The sensitivity of TTNA is between 70-100%, depending on the size of the lesion and is higher for lesions >2-3 cm diameter [12]. However the specificity of TTNA is low, especially for benign lesions. Therefore a non-specific or benign diagnosis does not exclude the possibility of malignancy [13]. It is probable that future advances in immunocytochemistry and molecular biology will lead to enhanced confidence in cytological verifications. The application of immunocytochemistry testing can demonstrate the presence of specific neoplastic markers, which are the neural cell adhesion molecule (N-CAM), associated with SCLC, and the epidermal growth factor receptor (EGFR), related to NSCLC.

On the basis of problems experienced in morphological confirmation of lung cancer, the aims of our study were to evaluate retrospectively the proportion of histological and/or cytological diagnosis in patients with lung cancer in Sardinia, during the 1991-1996 period, and to highlight possible hope of improvement in this cancer pathological diagnosis.

Methods

In this retrospective study we considered resident patients in Sardinia who received a lung cancer diagnosis between 1991-1996. Data was gathered by consulting the hospital registers and case notes of individual patients released from hospital with a diagnosis of lung cancer at all public and private medical centres (departments of respiratory disease, oncology, internal medicine, general surgery and thoracic surgery) throughout Sardinia.

In gathering patient data we focused our attention on the diagnostic phase, and in particular on cytological and histological procedures which allowed the lung cancer diagnosis to be achieved.

Patients with a cytological diagnosis either did not undergo histological examination or if they did, it was negative. Patients with histological verifications all had a histological diagnosis coming from either bronchoscopic biopsies, percutaneous transthoracic needle aspirations or surgical biopsies. Many of these patients with a histological diagnosis also undewent cytological examinations (sputum cytology, bronchial brushing, washing, bronchoalveolar lavage), but the spectrum of responses was very wide, ranging from subtype characterisation, generic presence of neoplastic cells, suspect neoplastic cells, to negative response.

We considered "not defined" all those cases where histological or cytological specimens showed the generic presence of neoplastic cells or allowed a diagnosis of carcinoma without any specific histological characterisation. At the same time we defined "clinical-radiological diagnosis" as being all cases diagnosed on clinical or radiological grounds without a pathological verification (where patients did not have a cyto-histological examination or, if performed, it was negative).

Cancer Registries data was utilised to compare our data, regarding the whole Sardinian Region, with National data and with Sassari Province data.

Sardinia, which is the second largest island in the Mediterranean Sea is divided, for administrative purposes, into four Provinces, whose capitals are Cagliari, Sassari, Nuoro and Oristano. Among these, only the Sassari Province has its own Cancer Register which covers 38% of the entire Sardinian population. Only major medical centres in Sardinia are provided with Pathology Institutes, while peripheral hospitals, often far from the capitals, must rely on major medical centres regarding pathological verifications of lung cancer.

Results

From 1991 to 1996 there were registred, in Sardinia, a total of 3146 patients with lung cancer. 2818 were male and 328 were female (male/female ratio 8.5:1) (table 2). Histological diagnosis was performed in 1902 patients (60.5%), while only 142 (4.5%) patients had a cytological diagnosis. Therefore in 1102 patients (35%) the diagnosis was obtained only on the basis of clinical and radiological grounds without any pathological validation.

Among the patients with clinical-radiological diagnosis, 43.9% of males and 56.6% of females were over 70 years old, 51.3% and 35.3% were 50-59 years, 4.8% and 8.1% respectively were less then 49 years old. Patients with a histological diagnosis and over 70 years old were 33.6% while 56.7% of them were 50-59 years old.

The most common subtypes of lung cancer (table 3) in male patients with histological verification, descending order, were squamous cell carcinoma with 737 cases (42.7%), adenocarcinoma 349 cases (20.2%), SCLC 212 cases (12.3%) and, finally, large cell carcinoma with 98 cases (5.7%). In 304 (17.6%) male patients there was a not defined

Table 2. - Proportion (%) of lung cancer cases with histological or cytological verification in Sardinia in the period 1991-1996

Diagnostic method	Male N° (%)	Female N° (%)	Total N° (%)
Histological	1728 (61.3%)	174 (53%)	1902 (60.5%)
Cytological	125 (4.4%)	17 (5.2%)	142 (4.5%)
Clinical-radiological	965 (34.2%)	137 (41.8%)	1102 (35%)
Total	2818 (100%)	328 (100%)	3146 (100%)

Table 3. - Proportion (%) of lung cancer subtypes in patients with histological verification in Sardinia in the period 1991-1996

Subtype	Male N° (%)	Female N° (%)	Total N° (%)
Squamous cell carcinoma	737 (42.7%)	20 (11.5%)	757 (39.8%)
SCLC	212 (12.3%)	30 (17.2%)	242 (12.7%)
Adenocarcinoma	349 (20.2%)	74 (42.5%)	423 (22.2%)
Large cell carcinoma	98 (5.7%)	11 (6.3%)	109 (5.7%)
Not defined	304 (17.6%)	39 (22.4%)	343 (18%)
Mixed	7 (0.4%)		7 (0.4%)
Others	21 (1.2%)		21(1.1%)
Total	1728 (100%)	174 (100%)	1902 (100%)

diagnosis of lung carcinoma without a histological subtype. Conversely in female patients the most common subtype were adenocarcinoma with 74 cases (42.5%), SCLC 30 cases (17.2%), squamous cell carcinoma 20 cases (11.5%) and then large cell carcinoma with 11 cases (6.3%). The female with a non-defined diagnosis were 39 (22.4%).

206 patients (6.5%) with histological diagnosis also had a subtype characterisation on cytological examination. In the remaining cases the cytological examinations, when performed, did not allow for diagnostic confirmation. Table 4 shows the low number of histological diagnoses obtained by TTNA, confirming the poor use of this diagnostic technique in Sardinia in the 1990s.

In male patients with cytological diagnosis we have found (table 5): 146 cases (50%) of squamous cell carcinoma, 46 cases (15.8%) of adenocarcino-

Table 4. - Distribution (N°) of lung cancer subtypes on the basis of bioptic technique used. Patients with histological verification in Sardinia in the period 1991-1996

Subtype	Br. Biopsies N°	TTNA N°	Surgical biopsies N°	Total N°
Squamous cell carcinoma	532	87	138	757
SCLC	173	33	36	242
Adenocarcinoma	232	62	129	423
Large cell carcinoma	52	24	33	109
Not defined	256	68	19	343
Mixed	4	3	0	7
Others	9	4	8	21
Total	1258	281	363	1902

Br. Biopsies: Bronchoscopic Lung Biopsies; TTNA: percutaneous transthoracic needle aspiration; Surgical biopsies include also lymph node biopsy.

Table 5. - Proportion (%) of lung cancer subtypes in patients with cytological verification in Sardinia in the period 1991-1996

Subtype	Male N° (%)	Female N° (%)	Total N° (%)
Squamous cell carcinoma	146 (50%)	5 (12.2%)	151 (45.3%)
SCLC	22 (7.5%)	2 (4.8%)	24 (7.2%)
Adenocarcinoma	46 (15.8%)	14 (34.2%)	60 (18.1%)
Large cell carcinoma	10 (3.4%)	3 (7.3%)	13 (3.9%)
Not defined	66 (22.6%)	17 (41.5%)	83 (24.9%)
Others	2 (0.7%)	—	2 (0.6%)
Total	292 (100%)	41 (100%)	333 (100%)

ma, 22 cases (7.5%) of SCLC, 10 cases (3.4%) of large cell carcinoma and 66 cases (22.6%) of not defined cases. Finally females with cytological verification showed 14 cases (34.2%) of adenocarcinoma, 5 cases (12.2%) of squamous cell carcinoma, 3 cases (7.3%) of large cell carcinoma and even 17 cases (41.5%) of not defined cases.

It is clear that patients who had only a cytological diagnosis had a SCLC less frequently and a higher percentage of non-defined cases. This is particularly true for women and is probably related to diagnostic difficulty in emphasizing SCLC in cytological specimens, in spite of the preferential central location of this subtype of lung cancer.

Discussion

Our study showed that lung cancer diagnosis is supported by pathological verification in only 65% of cases, therefore in the remaining 35% of cases the diagnosis is based only on clinical and radiological reports. Data from Italian Cancer Registries regarding the 1993-1998 period relates to a percentage of cyto-histological diagnosis of 70%, that is slightly higher than our reported data. In particular, data from Cancer Registries at national level showed a proportion of cases with histological verification of 57.3% in male and 49.5% in female, while at the level of Sassari province the proportions are respectively 59.9% and 51.8% (table 6) [3]. In our study the proportion of cases with histological verification were slightly higher both in male (61.3%) and in female (53%).

Moreover data from the Italian Cancer Registries reports a proportion of cytological verification in lung cancer of 17.2% in male and 19.1% in female (table 7). While data from the Cancer Register of Sassari Province showed a lesser proportion of cytological verification, respectively of 10.3% in male and 11.3% in female [3]. Our study showed even lesser proportions of cytological verification, which are 4.4% in male and 5.2% in female. This bias suggests the presence of serious problems of cytological verification in Sardinia (lack of suitable specimens, poor use of cytological specimens, inexperience of cytologists).

Both national data as well as our own has shown differences in histological verification rates between male and female, in fact the diagnosis of lung cancer in men were confirmed by biopsy in 61.3% of cases, while in women this percentage was only 53%. In fact females exhibited a higher rate of clinical-radiological diagnosis cases (41.8%). It's important that, for these cases, we can't distinguish patients who have a NSCLC or a SCLC.

Our data, regarding Sardinia, has shown a low percentage of lung cancer cytological diagnosis, that is 4.5% in respect to the National mean of 17-19%.

Our study, according to international literature regarding histological subtypes of lung cancer, has demonstrated the predominance of squamous cell carcinoma (42.7%) in males, followed by adenocarcinoma (20.2%) and SCLC (12.3%). On the other hand, the most frequently diagnosed lung cancer in females was the adenocarcinoma (42.5%), followed by SCLC (17.2%) and finally squamous cell carcinoma (11.5%). Independent of gender, the most commonly diagnosed lung cancer subtype was squamous cell carcinoma (39.8% of all cases). It must be emphasised that females showed a higher percentage of not defined cases than males, respectively 22.4% and 17.6%; in the group of not defined cases the proportions of each lung cancer subtype cannot of course be assessed.

In female patients with only cytological verification we found a diagnosis of SCLC in only 4.8% of cases, adenocarcinoma in 34.2%, squamous cell carcinoma in 12.2%, and not defined cases in 41.5%. These findings seem to contradict the widespread

Table 6. - Proportion (%) of lung cancer cases with histological verification in different cities, areas and regions of Italy (1993-1998)

	Male (%)	Female (%)
Umbria*	78.1	75.7
Macerata	67.6	60.4
Biella	65	50.4
Romagna	63.8	51.2
Parma	63.1	50.5
Veneto	62	50.8
Sassari	59.9	51.8
Modena	58.7	56.4
Turin	57.8	46.4
Ferrara	57.3	59.2
Tuscany	56.3	46.4
North-East	51.6	49.6
Varese	50.9	42.1
Genoa	48.8	38.3
Latina	40.6	43.8
Naples	38.5	35.7
Ragusa	36.6	26.8
Total	57.3	49.5
All cancers	79.1	81.1

* cytological verification are included.

Table 7. - Proportion (%) of lung cancer cases with cytological verification in different cities, areas and regions of Italy (1993-1998)

Province	Male (%)	Female (%)
Varese	32.7	35
North-East	30.6	27.7
Ferrara	25.1	20.8
Genoa	21.8	22.8
Turin	19.7	22.4
Ragusa	19.5	15.5
Veneto	15.5	19.3
Parma	15.4	16.7
Naples	14.2	14.3
Romagna	13.8	17.4
Biella	12.3	18.9
Latina	10.8	15.4
Sassari	10.3	11.3
Modena	10.3	13.2
Macerata	10.2	13.2
Tuscany	8.4	8.1
Italian mean	**17.2**	**19.1**

opinion that the yield of cytological specimens is higher in central lung cancer compared to peripheral cancers. However making a distinction between central and peripheral lung cancer may be of little importance, considering that lung cancers are often diagnosed in the advanced stage of the disease and when they have reached greater dimensions.

On the other hand, in male patients our findings reflect literature data and confirm the high yield from cytological specimens in the diagnosis of squamous cell carcinoma, which represented the 50% of lung cancer subtypes highlighted by cytological verifications. Moreover in males our study showed a lower percentage (22.6%) of not defined cases: this is probably due to the lower incidence in male of adenocarcinoma and SCLC, which are diagnosed by cytological technique with more difficulty than squamous cell carcinoma.

It is important to highlight that for lung cancer diagnosis cytological techniques are complementary to histological ones and they should not be considered a secondary choice. In fact, excluding blood cancers, lung cancer is the most frequently diagnosed cancer by cytological techniques [3].

In fact data from Italian Cancer Registries has shown that cytological techniques allow diagnosis of lung cancer in 17.2% of males and 19.1% of females. Unfortunately there are important differences among the centres evaluated: in fact the percentage of cylogical diagnosis varies between 32.7% and 8.4% (table 7). This heterogeneity was present in our study too, where we found regional differences in cancer cytological diagnosis: this is probably due to the different resources which are distributed among the evaluated Medical Centres.

Cytological samples provided a greater degree of accuracy in the diagnosis of squamous cell carcinoma than in SCLC. This is in contrast with literature reports, which refer to a high sensitivity of cytological techniques in the diagnosis of SCLC. Our results might show that in our region the trouble was the low specificity of cytological techniques: probably the high percentage of not defined cases included more SCLC cases than NSCLC. However the low sensitivity has important implications: in fact the goal of all diagnostic techniques should be to provide a correct characterisation of the cell type for accurate therapeutic choice.

Italian Cancer Registries and our data has demonstrated an evident heterogeneity in sensitivity and specificity of cytological techniques. We noticed that the best results are reached in major Medical Centres provided with pneumological and oncological departments, compared to peripheral hospitals. The latter still have in Sardinia significant problems with sending specimens due to extensive transport time and consequently to alteration of the samples.

In conclusion, our study has shown a lower percentage of cytological and histological verifications in lung cancer diagnosis in Sardinia compared to Italian Cancer Registries data. This is probably due to:

a) Limitations both of cytological (low sensitivity) and histological specimens for the diagnosis of peripheral lesions, which are not accessible to the FOB. Percutaneous transthoracic needle aspiration may be used to diagnose peripheral lung cancer, but this technique is not widely available (see table 4) and involves a high risk of pneumothorax.
b) Persistence of some nihilism in doctors who do not believe in treatment for lung cancers and thus are unwilling to confirm it, especially in elderly people.
c) Poor diffusion of International Guide Lines, lack of Pathology Institutes and of expert and dedicated cytologists, especially in peripheral hospitals of the Island.

It is important to note that the early lung cancer diagnosis is linked with a greater spectrum of therapeutic options and then a better prognosis.

Therapeutic effectiveness and possible recovery from lung cancer depend on early diagnosis, which at the present time is hard to obtain due to the lack of political-economic support for valid protocol of screening in individuals at risk of lung cancer.

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