

research article

## Is there any progress in routine management of lung cancer patients? A comparative analysis of an institution in 1996 and 2006.

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**Background.** The aim of the study was to establish eventual progress in routine management of lung cancer patients over a ten-year period at University Clinic for Respiratory and Allergic Diseases Golnik, Slovenia, comparing the results of analysis of 345 patients, diagnosed in 1996 (with analysis performed in 2002), and 405 patients, diagnosed in 2006 (with analysis performed in 2008).

**Patients and methods.** The patients of both analysed groups were of comparable age and number of patients in stage I and II, but there were relatively more females, patients with better performance status, more precise clinical staging and tumour histology in the 2006 group. The parameters used for assessing the progress of management were as follows: time period from admittance to diagnosis and to surgery; precision of staging; accordance of clinical and pathological staging in resected patients; percentage of exploratory thoracotomy; and use of new treatment modalities. The proportion of patients in selected/actual primary treatment modality and survival rate could also be used for assessing the progress.

**Results.** Although unessential longer time from admittance to microscopic confirmed diagnosis increased from a mean 7.4 to 8.6 days in 2006 progress was established by the following: more precise clinical staging (stage I and II also A and B stage, TNM staging also in small-cell lung cancer patients); improved accordance with clinical and pathological staging in resected patients (46% against 58%); decreased percentage of exploratory thoracotomy (13% against 4%); increased use of multimodality therapy as primary treatment modality (radiotherapy/chemotherapy, neoadjuvant chemotherapy); newly performed radio frequency tumour ablation. The proportion in selected/actual surgery increased from 76% to 93% and median survival rate of all patients from 6.2 to 10.6 months. One-year survival increased from 33.6% to 45.8% and two-year survival from 17.4% to 23%.

**Conclusions.** Progress in routine lung cancer management was proved by better staging, lower percentage of exploratory thoracotomy, use of new treatment modalities, minor discordance between selected and actual therapy, and improved short-term survival rate.

*Key words:* lung cancer; diagnostics; therapy; survival

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## Introduction

Much new information on epidemiology, pathogenesis, early detection, better diagnostics, accurate staging, and different treatment options is presented at the lung cancer conferences and published in literature, resulting in better outcomes: improved survival rates and sometimes better quality of life, as supported by some clinical studies. From the clinician's point of view the most important concrete progress in routine management of patients has been achieved through wide use of multi-slice CT scanning and MRI, CT and US-guided sampling, FDG-PET and PET/CT, videothoracoscopy and videothoroscopic surgery, new multidrug chemotherapy, more accurate radiation therapy, bronchoscopic interventional therapy (cauterisation, laser, cryo-ablation, argon plasma coagulation, stenting) and endobronchial brachytherapy, radio frequency tumour ablation, target therapies, and better palliative care. Key questions are which of the new findings are implemented into routine management of lung cancer patients at a particular institution, how they are implemented, and how much they influence survival.

The aim of the study was to establish eventual progress in routine management of all lung cancer patients over a ten-year period at the University Clinic for Respiratory and Allergic Diseases Golnik (Clinic Golnik), Slovenia, comparing the results of analysis of 345 patients diagnosed in 1996 (with analysis performed in 2002)<sup>1</sup>, and 405 patients diagnosed in 2006 (with analysis performed in 2008).

## Patients and methods

All patients, hospitalised or ambulatory, firstly diagnosed for lung cancer from January 1<sup>st</sup> to December 31<sup>st</sup>, 1996 and

2006 were included in the analysis. Patients from abroad were excluded due to lost of follow-up and unavailable survival data. The characteristics of patients and tumours are presented on Table 1. The patients of both analysed groups were of comparable age and number of patients in stage I and II, but there were relatively more females, patients with better performance status, more precise clinical staging, tumour histology and also estimated comorbidity in the 2006 group.

The parameters used for assessing the progress of management were:

- time period from admittance to diagnosis and to surgery;
- precision of staging;
- accordance of clinical and pathological staging in resected patients;
- percentage of patients undergoing exploratory thoracotomy;
- use of new treatment modalities.

The proportion of patients in selected/actual primary treatment modality and median survival time in each group of patients could also be used for assessing progress.

Staging was made according to TNM classification<sup>2</sup>, while the staging of small cell lung cancer (SCLC) was carried out, in 1996, with classification into limited disease (LD) and extended disease (ED). The zero time for the calculation of the survival was the date of admittance to the institution until death or until the end of the follow-up period, on 31 December 2001 for patients of 1996, and 30 April 2008 for patients of 2006. Only the date of death due to any reason was available. All living patients were confirmed in the Cancer Registry of Slovenia and by comparison with the Registry of Death of Slovenia to have been alive at this date. So the minimum follow-up time for patients of 1996 was 5 years, and for patients of 2006 was 16 months. The survival rate was calculated according to Kaplan-Meier's method,

**Table 1.** Characteristics of patients and tumours of 1996 and 2006

		1996	2006
<b>No. of patients</b>		<b>345</b>	<b>405</b>
Gender	Male	285 (83%)	301 (74%)
	Female	60 (17%)	104 (26%)
Age (years)	mean	65	67
	range	37-90	41-89
Performance status (ECOG*)			
	0 and 1	171 (49%)	300 (74%)
	2	130 (38%)	79 (20%)
	3 and 4	44 (13%)	26 (6%)
Clinical stage		NSCLC	NSCLC&SCLC
	I: 64		IA: 34
			IB: 40
	II: 32		IIA: 6
			IIB: 28
	IIIA: 48		IIIA: 56
	IIIB: 62		IIIB: 85
	IV: 85		IV: 155
	SCLC		
	LD** : 24		
	ED*** : 27		
Undeterminable stage		3	1
Microscopically	confirmed	334 (97%)	399 (98.5%)
	not confirmed	11 (3%)	6 (1.5%)
Histology			
	squamous cell	131 (39%)	162 (41%)
	adenocarcinoma	86 (26%)	120 (30%)
	large cell	63 (19%)	18 (5%)
	non-small cell	1 (0.3%)	22 (5%)
	small cel	51 (15%)	73 (18%)
	adenosquamous		1 (0.25%)
	sarcomatoid		2 (0.5%)
	LCNEC****		1 (0.25%)
	unclassified	2 (0.7%)	
Charlson comorbidity index (CI)			CI 0: 158 (39%)
			CI 1: 154 (38%)
			CI 2: 52 (12.8%)
			CI 3: 29 (7.2%)
			CI 4: 9 (2.2%)
			CI≥5: 3 (0.8%)

\* Eastern Cooperative Oncology Group

\*\* Limited Disease

\*\*\* Extended Disease

\*\*\*\* Large Cell Neuro-Endocrine Carcinoma

**Table 2.** Selected primary treatment modality of patients diagnosed in 1996 and 2006

	1996	2006
Surgery	93 (27%)	92 (23%)
Radiotherapy	110 (32%)	54(13%)
Chemotherapy	50 (15%)	121 (30%)
Supportive care	84 (24%)	49 (12%)
Radio and chemotherapy		75 (19%)
Neoadjuvant chemotherapy		9 (2%)
Radio frequency tumour ablation		2 (0.5%)
Death before treatment selection	8 (2%)	3 (0.5%)

and the survival differences were confirmed by the log-rank test using SPSS version 13.0 for statistical analysis.

## Results

### *Duration of diagnostic procedure*

The mean time period from admittance to microscopic verification of tumour was 7.4 (range 1-75) days in 1996, and 8.6 (range 1-74) days in 2006. The mean time period from microscopic confirmation of lung cancer to surgery was 27 (range 14-99) days in 2006, but in 1996 was only assessed as about one month.

### *Precision of clinical staging*

All patients in 2006 were staged according to the cTNM classification considering A and B in stage I and II, though without A and B in non-small cell lung cancer (NSCLC) stage I and II, and only LD and ED in SCLC in 1996. In 1996, a thorax CT scan was performed consistently only in candidates for surgery and in some of the remaining patients, while in 2006 it was performed in all but 15 patients. This change enabled more accurate staging.

### *Accordance of staging in resected patients*

In resected patients in 1996 clinical *vs.* pathological staging was correct in 46%,

underestimated in 44%, overestimated in 10%. For 2006, respective figures were 58%, 25%, and 17%.

### *Percentage of patients undergoing exploratory thoracotomy*

The rate of exploratory thoracotomy (thoracotomy without resection due to various causes) among patients was 12.7% in 1996 and 4.3% in 2006.

### *Use of new treatment modalities*

The selected primary treatment modality is presented on Table 2. In 2006, there were more patients underwent primary treatment by chemotherapy and by combined therapy (radiotherapy/chemotherapy and chemotherapy/surgery), and radiotherapy of primary tumour and/or metastases with curative and palliative intent. In two patients, the new therapy by radio frequency tumour ablation was performed. Neoadjuvant (preoperative) chemotherapy was performed in nine patients, potential candidates for surgery. Six of them were radically resected, while three patients were irradiated due to the progress assessed after the chemotherapy. In one patient with microscopically confirmed intrabronchial squamous carcinoma and subcarinal lymph node metastasis after three cycles of cisplatin/gemcitabin, the histology of the resected lobe and all lymph nodes was without cancer. In both groups

**Table 3.** Resection and exploratory thoracotomy in patients diagnosed in 1996 and 2006

	1996	2006
Selected for surgery	93	101
Realised surgery	71 (76%)	94 (93%)
Lobectomy	35	68
Bilobectomy	5	6
Pneumonectomy	22	16
Exploratory thoracotomy	9 (12.7%)	4 (4.3%)

of patients, various bronchial interventional therapies were performed. In 2006, targeted therapy was also performed, but of course not as a primary treatment modality.

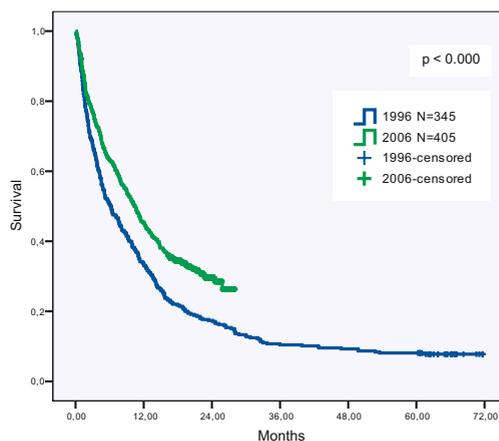
#### *Proportion in selected/actual primary treatment*

Actual surgery in both groups of patients is shown in Table 3. The percentage of realised surgery including neoadjuvant chemotherapy increased and the number of pneumonectomies decreased in 2006.

#### *Survival rate*

The overall survival of both patients group is presented in Figure 1. The median survival was 6.2 months in 1996, and 10.6 months ( $p < 0.000$ ) in 2006. One-year observed survival was 33.6% and two-year 17.4% in 1996. In 2006 one-year survival was 45.8%, calculated two-year survival was 23%.

The median survival for NSCLC for stage I, II, IIIA, IIIB, and IV was 30.1, 11.0, 8.6, 4.3 and 3.3 months, respectively in 1996. In 2006, median survival in stage I has not yet been reached, in stage II it was 14.8 ( $p = 0.064$ ), stage IIIA 12.3 ( $p = 0.077$ ), stage IIIB 8.13 ( $p = 0.002$ ), and stage IV 3.8 ( $p = 0.035$ ) months. In SCLC patients, the median survival in LD was in 1996 11.0 months and in ED 3.3 months, and in 2006 13.3 ( $p = 0.116$ ) months and 8.5 ( $p = 0.01$ ) months respectively.

**Figure 1.** Overall survival of 1996 and 2006 patients.

Median survival according to performance status in 1996 was for patients in ECOG 0 and 1 10 months, ECOG 2 4.2 months, and ECOG 3 and 4 1.7 months, and in 2006 was 13 months ( $p = 0.001$ ), 4.3 months ( $p = 0.175$ ) and 1.9 months ( $p = 0.217$ ), respectively.

## Discussion

Lung cancer management is comprised of detection, diagnostics inclusive microscopic confirmation, staging, selection and performance of therapy, follow-up of patients, as well as evaluation of results. At an institution like Clinic Golnik, it is difficult to influence the detection of lung cancer. Some patients are diagnosed while being treated for another disease. The clinic certainly has a teaching role for residents, students and through patients' follow-up also for general practitioners and other referring physicians. However, it is routinely possible to expedite the diagnostic procedure, to improve the staging, the selection of optimal treatment modality by a multi-disciplinary team meeting, the performing of therapy within the institution, and partly also the follow-up. Since all diagnostic procedures

except PET-CT, MRI and radioisotope scanning are performed at Clinic Golnik, it is understandable that a complete diagnostic procedure including microscopic confirmation of a tumour takes about one week in the majority of patients. From 2007, PET-CT scanning has been available in Ljubljana, in 2006 we referred two patients for FDG-PET to Klagenfurt, Austria.

Of the therapy modalities chemotherapy is performed at the institution, but surgery also started in 2008. So, a shorter period from diagnosis to surgery can be expected in the future, at least for some of the patients. The Institute of Oncology Ljubljana is the only institution for radiotherapy in Slovenia where we can not influence the waiting time for radiotherapy and radiochemotherapy in both those hospitalised and out-patients. The realisation of the selected therapy modality depends on possibilities for achievement and on patients' compliance. From patients selected for surgery, 93% underwent thoracotomy in 2006, but only 76% in 1996. It is obviously that thoracotomy could be partly avoided through a more accurate preoperative staging procedure.<sup>3</sup>

Despite the many prognostic and predictive factors established<sup>4</sup>, in routine selection of treatment modality only stage, histology, performance status, technical and medical operability and age are still regarded.

The stage of lung cancer patients by the time of the diagnosis depends, beside symptomatology, also on awareness of lung cancer risk in smokers and ex-smokers, and the awareness of their physicians, especially those who treated their previous cancer. It is known that double cancers<sup>5</sup>, mainly head and neck and lung cancer, are frequent. In 2006, we registered a previous malignant tumour in 59 of 405 (15%) patients, and 15 of these had head and neck cancer.

In the literature, there is a paucity of comparable data of outcomes in routinely treated

lung cancer patients in a single institution. In our opinion, this is due to two reasons: 1. many journals seem reluctant to publish articles that report on testing management efficacy in an institution and do not directly contribute to new knowledge on disease; 2. researchers do not like to publish poor results in which they could hardly influence outcomes. In the only comparable study, of Free *et al.*<sup>6</sup> from Nottingham City Hospital, UK, over the period 1998-2001, there were similar results. In 835 lung cancer patients (87% histologically confirmed and 80% discussed at multidisciplinary team meetings) clinical stage I 25%, II 9%, IIIA 8%, IIIB 23%, IV 35% in NSCLC and, in SCLC, LD 34%, ED 50%, with 16% unknown due to missing data, surgery was undertaken in 10%, radiotherapy in 30%, chemotherapy in 16%, supportive care in 34%, and 10% unknown due to missing data. Median survival was 4.9 months (NSCLC 6.3, SCLC 4.0) and five-year survival 6.9%.

Fernandez *et al.*<sup>7</sup> reported in the period 2001-2006 a median survival time of 3 months in 124 lung cancer patients (mean age 68 years, 64% in stage IV!) in the internal medicine department in Pamplona, Spain. Otherwise, de Cos *et al.*<sup>8</sup> reported the one-year survival rate of 36.2% and three-year survival rate of 13.8% in 1,014 patients with lung cancer diagnosed in 2003 in 10 hospitals from across 8 different Spanish regions.

Erridge *et al.*<sup>9</sup> estimated improved treatment and survival for lung cancer patients in South-East Scotland, comparing data of 927 patients diagnosed in 1995 and 971 diagnosed in 2002. The median survival time increased from 4.1 to 5.2 months, and two-year overall survival from 11% to 15%. Reasons cited for the improvement in survival include greater access to CT scanning and development of scanners with improved image quality, more oncologists specialising in lung cancer, introduction of

multidisciplinary team meetings, increasing use of chemotherapy, and increased experience with 3D-conformal radiotherapy.

Leo *et al.*<sup>10</sup> studied discordance between the treatment planned by a multidisciplinary team of specialists and the administered treatment in 344 patients between July 2003 and June 2004. Discordance rate was 4.4% and median delay of treatment 20 days (surgery 22, chemotherapy 16, radiotherapy 27, chemo-radiotherapy 24).

In contrast to the modest observed survival rates cited above, cancer survival reports present the relative five-year survival rate, which was calculated according to age, sex and life tables from the population nationwide. The Cancer Registry of Slovenia reported a five-year relative survival for lung cancer in period 2000–2004 of 11% for male and 14% for female patients<sup>11</sup>, which is comparable to EUROCARE-4 data for period 2000–2002 collected from 47 of the European cancer registries, amounting to 10.9 (10.5–11.4) months.<sup>12</sup>

In conclusion, progress in lung cancer management at Clinic Golnik was proved by better staging, a lower percentage of patients undergoing exploratory thoracotomy, use of new treatment modalities, a reduced discordance between selected and actual therapy, and improved short-time survival rate, not only because of patient characteristics (better performance status, more females), but also because of more suitable management.

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