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Prognosis of patients with non-small cell lung cancer with isolated brain metastases undergoing combined surgical treatment☆

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Abstract

Objective: To compare survival of patients with isolated synchronous and metachronous brain metastases from non-small cell lung cancer (NSCLC) after combined surgical treatment. **Methods**: A total of 991 patients underwent surgical resection of primary NSCLC between January 1994 and November 1999. Out of these, 32 patients (21 males and 11 females) were further treated for isolated brain metastases. In a retrospective survey, the outcome of patients with either synchronous (group 1, $n = 16$) or metachronous (group 2, $n = 16$) brain metastases was evaluated. Five patients out of each group received either adjuvant or neo-adjuvant chemotherapy. Data analysis includes descriptive statistics, Wilcoxon test, Kaplan–Meier method and Cox's proportional hazards model. **Results**: There was no significant difference in local tumour stage and histology of the primary tumour between both groups. Median of the disease free interval (DFI) after primary lung surgery (group 2) was 10 months, range 3–60 months. Median survival after lung surgery was 8.5 months in group 1 and 16.4 months in group 2 ($P = 0.094$). Median survival after cerebral procedures was 9.3 and 6.2 months, respectively ($P = 0.127$). Estimated survival rates by Kaplan–Meier method after cerebral procedures operation in group 1 were 37.5% at 1 year, 25.0% at 2 years and 18.8% at 5 years; in group 2 estimated survival rates were 31.3% at 1 year, 15.6% at 2 years and 0% at 5 years ($P = 0.148$). Calculated survival rates after lung surgery were identical in group 1; in group 2 survival rates were 62.5, 43.8 and 18.8% at 1, 2 and 5 years, respectively ($P = 0.101$). In the univariate model, none of the following variables had effect on survival: sex, age, T stage of the tumour, nodal status, timing of metastatic lesions, number of cerebral metastases, complete resection of primary tumour and histological type. Multivariate analysis did not reveal any risk factor, which significantly predicted survival. DFI did not correlate with survival of patients in group 2. **Conclusions**: Once isolated synchronous or metachronous brain metastases from NSCLC have developed, there is no difference in prognosis after combined surgery between analysed groups. This questions the value of lung resection in patients with isolated synchronous brain metastases.

Keywords: Lung cancer; Brain metastasis; Surgical treatment

1. Introduction

Cerebral metastases occur most commonly in lung cancer patients and account for approximately 30–55% in autopsy series of all patients with non-small cell lung cancer (NSCLC). Unfortunately, once metastatic brain disease develops, the cancer has already disseminated widely. The median survival of patients with brain metastases from NSCLC is approximately 1 month without treatment [1], 2–3 months when treated with steroids alone [2], and 3–6 months when treated with whole brain radiotherapy (WBRT) [3]. Because survival of patients with brain metastases is so short, quality of life and relieve of symptoms are considered the first goal of therapy. However, aggressive treatment with either surgical resection or radiosurgery has been applied with potential curative intention. Neurosurgical resection of solitary brain metastasis of different origin prolonged median survival to 3.5–8 months [4]. Subsets of patients with stage IV NSCLC and one solitary brain lesion as the only site of metastatic disease have been reported to benefit from combined neurosurgery and lung surgery [5,6]. If the decision to

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resect a single brain metastasis revealing an NSCLC may be readily taken, resection of the primary lung tumour is more controversial [7]. To define subgroups of patients who could benefit from bifocal surgery in this situation, different prognostic factors have been proposed by different authors.

In a study of Mussi and associates [5], survival was significantly higher in patients with NSCLC and metachronous metastasis who had N0 status with respect to survival in patients with N1-2 status. In case of synchronous presentation, the only variable that was significantly associated with a longer survival was the presence of squamous lung cancer ($P = 0.02$). In contrast, Bonnette and colleagues [8] observed significantly better prognosis for patients with adenocarcinomas. This was confirmed in a series presented by Granone [6], who also observed significantly better prognosis in N0 tumours compared to N1-2 tumours. Burt and associates [9] found no significant effect of the locoregional stage on survival in case of synchronous metastasis, but complete resection of the primary disease significantly prolonged survival. In Hankins' series [10], both nodal involvement (N0-1 vs N2) and radicality of surgical resection significantly impacted on the prognosis.

In summary, no clear guidelines can be derived from recent literature concerning appropriate treatment of patients with brain metastases from NSCLC. The aim of our retrospective study was to compare survival of patients with isolated synchronous and metachronous brain metastases from NSCLC after combined surgical treatment.

2. Materials and methods

2.1. Patients

From January 1994 to November 1999, 991 patients underwent surgical resection of primary NSCLC at the Department for Cardiothoracic Surgery of University Hospital of Vienna. Out of these, 32 patients underwent surgical procedures for the primary tumour and for isolated brain metastases in addition. This cohort of patients was retrospectively allocated to two groups of patients: group 1 ($n = 16$), patients with synchronous metastases, defined as being diagnosed at the same time of the primary tumour and group 2 ($n = 16$), patients with metachronous metastases diagnosed more than 2 months after the primary lung tumour.

Group 1 consisted of 8 male and 8 female patients with a mean age of 55.9 ± 9.8 years. Group 2 comprised 13 male and 3 female patients with a mean age 62.2 ± 8.9 years.

The quite low number of patients treated for metachronous metastases may be explained by variety of reasons. Some of these patients are not diagnosed with brain metastases and die from their underlying disease without developing specific symptoms; others are seen by a doctor but not referred to a specialised centre for further treatment. Only patients in a regular oncological follow up after initial lung surgery were included in this study.

In group 1, neurosurgery preceded lung resection in all cases. Median time between cerebral procedures and pulmonary resections was 27.5 days with a range of 8–110 days. In group 2, brain metastases were diagnosed after lung surgery with a median disease free interval (DFI) of 10 months (range 3–60 months). Complete re-staging excluded extracranial metastases in all patients.

Preoperative work-up included chest CT in all patients, bronchoscopy or CT-guided fine needle biopsy when applicable for histological evaluation in all patients, CT scan or sonography of the upper abdomen as a routine, cranial MRI (alternatively cranial CT) in all patients in order to exclude brain metastases and bone scan. All patients in group 1 without neurological symptoms underwent thorough preoperative evaluation including cranial MRI (alternatively cranial CT) as a routine staging measure before surgery. In patients with neurological deficits as the leading symptom due to brain metastases screening for primary malignancy revealed the diagnosis of lung cancer. Mediastinoscopy was not performed routinely, but in all patients presenting with mediastinal lymph nodes bigger than 10 mm in diameter at CT scan. PET was not available as a routine in those days. Pathologic review of lung and brain neoplastic tissue confirmed the same histological diagnosis for all patients who underwent craniotomy.

2.2. Statistical analysis

Survival time was estimated by the Kaplan–Meier method in all patients with

1. The date of neurosurgery (groups 1 and 2) used as the starting point and the date of death or last follow-up (August 2003) as the end point;
2. The date of lung surgery (groups 1 and 2) used as the starting point and the date of death or last follow-up (August 2003) as the end point.

Comparisons of survival for univariate analysis were estimated by the log-rank test. Cox's proportional hazards model (forward stepwise procedure) was used for multivariate analysis. The results were considered significant at the 0.05 level ($P < 0.05$). All analyses were performed with the SPSS software package (SPSS version 10.0 for Windows).

3. Results

3.1. Brain metastases

3.1.1. Group 1

Eleven patients (68.8%) had neurologic symptoms before neurosurgical resection, as follows: motor deficit

(4 patients), seizure (3 patients), ataxia (2 patients), and headache (2 patients). Some patients had more than one neurologic sign.

Surgical resection of metastases was performed in 9 patients (56.2%), ablation of the lesions by stereotactic radiosurgery (SRS) in 3 patients (18.8%), both approaches used in 4 (25%) patients. Complete removal of cerebral metastases was achieved in all 16 patients. Twelve patients (75%) received postoperative WBRT; median dose was 30 Gy and ranged from 20 to 50 Gy.

- Eleven patients with one single metastasis were treated by craniotomy only ($n = 2$), craniotomy followed by whole brain radiation therapy ($n = 6$), SRS only ($n = 1$) and SRS combined with WBRT ($n = 2$).
- Three patients with two metastases were treated by craniotomy only ($n = 1$) or craniotomy plus SRS followed by WBRT ($n = 2$).
- Two patients with multiple brain metastases were treated by craniotomy plus SRS followed by WBRT.

3.1.2. Group 2

Neurologic signs were present in 14 patients (87.5%) including dizziness in 6, headache in 4, ataxia in 2, motor deficit and blurred vision in 1 case each. Similarly to Group 1, some patients had a combination of neurologic symptoms.

Cranial resection of brain metastases followed by WBRT was used in 4 cases, SRS plus WBRT in 9 cases, SRS only in 1 case and WBRT only in 2 cases. Cerebral resection was complete in 14 (87.5%) patients. In both groups, postoperative recovery was generally uncomplicated, no patient died.

- Nine patients with one single metastasis were treated by craniotomy followed by WBRT ($n = 4$) or SRS combined with WBRT ($n = 5$).
- Four patients with two metastases were treated by SRS only ($n = 1$) or radiosurgery followed by WBRT ($n = 3$).
- One patient with three metastases received SRS plus WBRT.
- Two patients with multiple brain metastases were treated by means of WBRT only. SRS in these two patients was not indicated by neurosurgeons due to the small size of lesions and good response to WBRT.

3.2. Primary site

Radical resection of primary tumour and complete mediastinal lymph node dissection was performed in 14 patients (87.5%) of group 1 and in 15 patients (93.8%) of group 2. The types of pulmonary resections are shown in Table 1. Wedge resections were performed in patients with poor pulmonary reserve. In one patient of group 1 with a sulcus superior tumour chest wall resection (ribs 1–4), laminectomy with resection of the first three thoracic neural roots and tangential resection of thoracic vertebral bodies 1–4 was performed along with an upper lobe lobectomy.

Table 1
Lung resections in 32 patients with NSCLC and synchronous (group 1) or metachronous (group 2) brain metastases

	Group 1 ($n = 16$)	Group 2 ($n = 16$)
Wedge resection	2	1
Lobectomy	8	11
Bilobectomy	1	2
Pneumonectomy	5	2

Histological findings are presented in Table 2. TN staging of the primary tumour is given in Table 3. There was no significant difference in histology of the primary tumour and local tumour stage in both groups.

There was no hospital mortality after chest surgery despite one bronchial stump insufficiency 3 months after right pneumonectomy in group 1 and one broncho-pleural fistula after upper sleeve lobectomy in group 2. The first situation was managed by re-thoracotomy, decortication, re-resection and covering of the stump with a pediculated pericardial flap. The broncho-pleural fistula presented with a prolonged airleak for 8 days and did not require any further intervention.

Five patients out of each group received perioperative platin-based chemotherapy. In group 1, two patients received induction chemotherapy and three patients had adjuvant chemotherapy. One patient of group 2 received induction as well as adjuvant chemotherapy; another 4 patients received adjuvant treatment. Decision making was based on clinical stage and made in co-operation with the oncologists.

3.3. Survival analysis

Follow-up was complete for all 32 patients for a median follow-up of 12.7 months and a range of 1.8–79.8 months. The median follow-up for groups 1 and 2 was 9.3 and 16.4 months, respectively.

3.3.1. Group 1

Recurrences developed in 11 patients (68.8%) after a median of 5 months after neurosurgery and were local cerebral in 5 (45.5%), distant bone in 1 (9%), and both local

Table 2
Histological types of primary lung tumours of 32 patients with NSCLC and synchronous (group 1) or metachronous (group 2) brain metastases

	Group 1 ($n = 16$)	Group 2 ($n = 16$)
Adenocarcinoma	13	13
Squamous cell carcinoma	1	2
Large cell carcinoma	2	–
Adenosquamous carcinoma	–	1

Table 3
Pathological staging of 32 patients with NSCLC and synchronous (group 1) or metachronous (group 2) brain metastases

	Group 1 ($n = 16$)	Group 2 ($n = 16$)
T1 N0	2	1
T2 N0	5	4
T3 N0	1	1
T2 N1	1	3
T1 N2	1	2
T2 N2	3	3
T3 N1	2	0
T4 N0	0	1
T3 N2	1	1

and distant (2 brain/bone, 1 thoracic/bone, 1 brain/intestinal, 1 brain/adrenal/liver) in 5 (45.5%). Three (33.3%) of the 9 patients who had cerebral recurrence did not receive WBRT. Five patients underwent late SRS for recurrent brain metastases, one patient had WBRT and two patients had radiosurgery plus WBRT. Two patients received local radiation therapy and one had chemotherapy for late distant recurrence.

Currently, 3 patients are alive (one with cerebral/intestinal relapse, one with cerebral/adrenal/liver relapse and one without evidence of recurrent disease) at 79.7, 69.4 and 47.8 months after neurosurgery. Of the remaining 13 patients 10 died from systemic relapse of the disease and 3 from local recurrence.

3.3.2. Group 2

Only one patient is still alive with a brain recurrence 10.5 months after neurosurgery. Three patients died from cerebral local recurrence, 12 patients from systemic neoplastic relapse.

3.3.3. Survival rates in both groups

After cerebral procedures estimated survival rates (Kaplan–Meier method) in group 1 were 37.5% (95% confidence intervals [CI], 13.8–61.2%) at 1 year, 25.0% (95% CI, 3.8–46.2%) at 2 years and 18.8% (95% CI, 0–37.9%) at 5 years; in group 2 survival rates were 31.3% (95% CI, 8.5–53.9%), 15.6% (95% CI, 0–34.7%) and 0% at 1, 2 and 5 years, respectively (Wilcoxon test, $P = 0.148$).

After lung surgery estimated survival rates were identical in group 1; for group 2 patients estimated survival rates were 62.5% (95% CI, 38.8–86.2%) at 1 year, 43.8% (95% CI, 19.4–68.0%) at 2 years and 18.8% (95% CI, 0–37.9%) at 5 years (Wilcoxon test, $P = 0.101$). Survivals after cerebral procedures and after lung surgery are shown in Figs. 1 and 2.

3.3.4. Length of survival in both groups

The median length of survival after neurosurgery was 9.3 months (range 1.8–79.8 months) in group 1 and 6.2 months (0.5–58.4 months) in group 2. There was no significant difference between groups (Wilcoxon rank-sum test, $P = 0.127$).

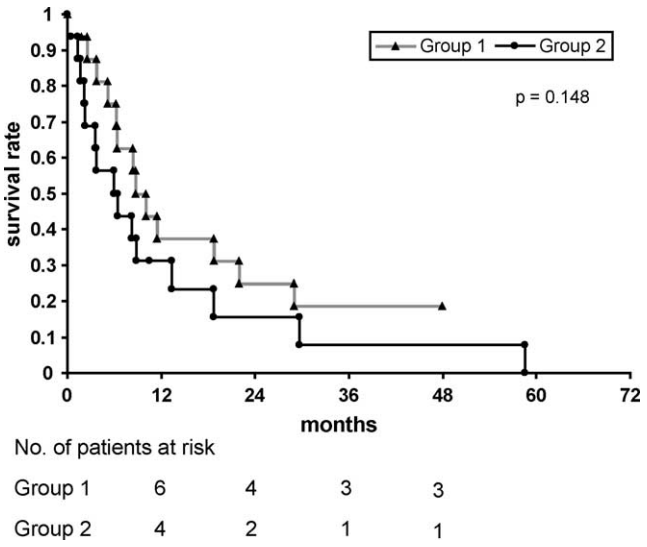

Fig. 1. Survival after neurosurgical procedure.

The median length of survival after lung surgery was 8.5 months (range 1.2–79.7 months) in group 1 and 16.4 months (range 6.4–77.3 months) in group 2. There was no significant difference between the groups (Wilcoxon rank-sum test, $P = 0.094$).

3.3.5. Analysis of potential prognostic factors

Univariate model analysis was performed in the whole cohort of patients with isolated brain metastases In the univariate model, none of the following variables influenced survival: sex (odds ratio 1.453, confidence limits 0.653–3.233), age (odds ratio 1.030, confidence limits 0.984–1.077), T stage of the tumour (odds ratio 1.076,

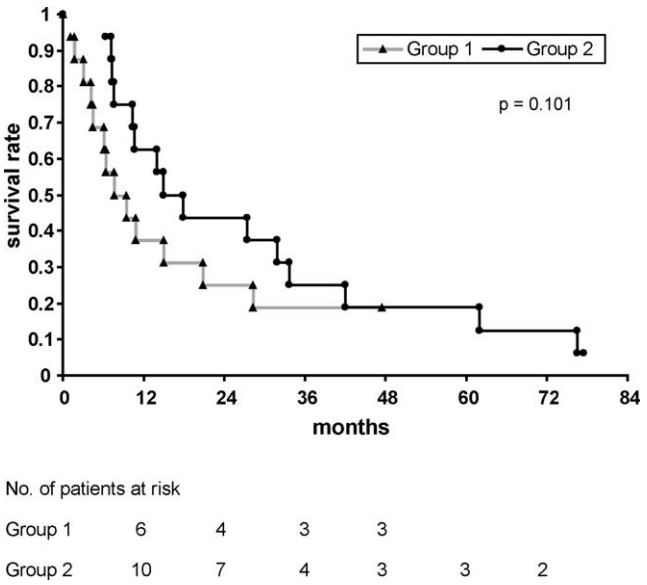

Fig. 2. Survival after lung surgery.

confidence limits 0.672–1.721), nodal status (N0 vs. N+) (odds ratio 1.382, confidence limits 0.649–2.942), timing of the metastatic lesion (synchronous vs. metachronous) (odds ratio 0.808, confidence limits 0.383–1.702), number of cerebral metastases (solitary vs. multiple) (odds ratio 1.704, confidence limits 0.777–3.738), complete resection of primary tumour (odds ratio 0.450, confidence limits 0.132–1.532) and histology (adenocarcinoma vs. other types) (odds ratio 0.717, confidence limits 0.287–1.789).

Multivariate analysis of these data using the Cox's proportional hazards model did not reveal any risk factor which significantly predicted survival. DFI did not correlate with survival of patients in group 2.

4. Discussion

The prognosis of patients with brain metastases arising from NSCLC is poor. The natural course of untreated brain metastases is a progressive neurological deterioration with a median survival time of 1–2 months [4]. Surgical removal of solitary brain metastases prolonged survival and improved quality of life [11]. Median overall survival of patients undergoing resection of brain metastases from lung cancer is 4–7.7 months [4]. Patients with metachronous brain metastases from NSCLC have significantly improved prognosis after successful neurosurgery with estimated 5 year survivals of 21–45% [10,12]. Several factors have been found to influence survival in this cohort of patients including complete resection, locoregional tumour stage and length of DFI.

Surgical resection followed by whole-brain radiotherapy has become the standard management practice in highly selected patients with solitary metachronous brain metastases without extracranial disease. However, appropriate treatment of lung cancer with synchronous brain metastases is judged controversially.

Different reports have shown considerably worse results after resection of synchronous brain metastases [5,13]. Five-year survival rates of only 5–10% with a median survival of less than 10 months have been reported for patients treated by means of neurosurgical resection alone [14]. To improve the outcome in these patients Andrews and associates [15] proposed surgical resection of the primary lung tumour besides resection of the brain metastases. Patients who underwent resection of the primary NSCLC had a median survival of 25.7 months compared with 9.1 months in patients who did not undergo resection of the primary tumour.

Synchronous brain and lung resection series are generally very small. Torre and associates [16] reported a series of 27 patients with single brain metastases from NSCLC. Out of these, 21 had synchronous lesions and underwent combined surgery. The overall 5-year survival rate was 15%, and the mean survival time was 26 months. Similar results with bifocal surgery and WBRT have been presented by Rossi et al. in a study including 40 patients with single brain lesions. Survival at 1, 2 and 5 years were 35, 25 and 12.5%, respectively, [13].

Addressing prognostic factors in patients with NSCLC and single brain metastases Mussi and associates [5] found that the only variable associated with a significantly longer survival was squamous cell histology ($P < 0.02$). The 5-year survival rate of a subgroup of 15 patients with synchronous presentation was 6.6% with a median survival of 18 months. In contrast, in a multicenter study of Bonnette and colleagues [8] only adenocarcinoma histology was associated with a significantly better prognosis compared to those with squamous cell carcinomas ($P = 0.019$). The survival rates of 103 patients with synchronous lesions (99/103 single metastases) were 56% at 1 year, 28% at 2 years and 11% at 5 years with a median length of survival of 12.4 months. Series of Granone [6] and associates confirmed significantly better survival in subgroups of patients with histological diagnosis of adenocarcinoma and with N0 primary tumours. Among 20 patients after bifocal surgery for histologically different primary tumours of the lung and single synchronous brain metastases survival analysis showed values of 95% at 1 year, 47% at 2 years and 14% at 3 years (median survival time was 23 months).

Other authors have addressed locoregional tumour stage of the primary as prognostic factor. In a report of Billing and colleagues [14], the presence of thoracic lymph node metastases (N1 or N2) significantly affected 5 year survival ($P = 0.001$). In a group of 28 patients with synchronous brain metastases from NSCLC survival at 1, 2, and 5 years was 64.3, 54.0, and 21.4%, respectively, with a median survival of 24 months. The authors conclude that a selected group of patients with synchronous brain metastases from NSCLC without nodal involvement may benefit from bifocal surgery. Torre and associates [16] also obtained better results in patients without lymph node metastases at thoracotomy and in patients with supratentorial metastases.

In Burt's series [9], 185 consecutive patients underwent resection of brain metastases from NSCLC, of whom 65 were synchronous. There was no significant difference in survival between patients with synchronous and metachronous lesions. In a subgroup of 32 patients with synchronous metastases who had complete pulmonary resections survival rates were 71, 16, and 16% at 1, 5, and 10 years, respectively (median survival time was 21 months). In contrast, survivals of patients with incomplete resections were 40, 4, and 0% at 1, 5, and 10 years, respectively (median survival time was 10 months). In multivariate analysis not locoregional stage but complete resection of the primary disease significantly prolonged survival in the subgroup of patients with synchronous metastases ($P = 0.002$).

Although, it is intuitively apparent that some patients will benefit from aggressive treatment of brain metastases it remains unclear which patients should be treated and how. The majority of published series have analysed the outcome of patients with one single brain metastasis. Cerebral lesions

are often multiple and usually single localisations do not exceed 30% of the cases [1,6]. It is obvious that only patients in whom both synchronous brain metastases and primary tumour can be completely resected may be considered candidates for curative treatment. The number of brain metastases may not play a role as long as the number is small (≤ 3), and they can all be completely resected as has been demonstrated by several retrospective studies in patients treated for palliation [17].

Moreover, technical aspects of a radical resection of cerebral metastases seem to be of minor impact on the outcome. Although, completed randomised studies comparing SRS vs. craniotomy are absent, many trials demonstrated comparable results of these approaches in terms of survival, local control, morbidity, and mortality. SRS has been proposed for cases when surgical resection by craniotomy is not feasible due to localisation, number or size of metastases and potential for postoperative neurologic compromise [18].

One could expect, that patients presenting with synchronous brain metastases from NSCLC suffer from a more aggressive disease compared to those with sequential brain lesions occurring after a certain DFI. In some author's experience, the synchronous presentation of lung cancer and brain metastasis represents a negative prognostic factor [5,19,20].

In the present study, none of the analysed parameters such as sex, age, nodal status, timing of metastatic lesions, number of cerebral metastases, complete resection of primary tumour and histological type had impact on survival. Multivariate analysis confirmed these results. There was no statistically significant difference between groups concerning survival after lung surgery as well as after cerebral procedures. Once brain metastases have developed length of survival of patients with NSCLC is a median of 6–9 months. However, a few patients benefit from bifocal surgical treatment and may survive up to 80 months. The value of these data is limited mainly by the small single-institution clinical experience; patients were selected for treatment by clinical criteria and underwent heterogeneous procedures administered in a non-random fashion.

Long-term survival may be more determined by other prognostic variables and depend on genetic characteristics of the tumour and the individual. The identification of reliable predictors of survival is mandatory for the definition of subgroups of patients who could benefit from a bifocal surgical approach. Kiss et al. [21] reported that DNA ploidy level in brain metastasis was related to patient survival. At the time being, there is no sufficient knowledge to envisage different behaviours of tumours presenting similar histological characteristics. The hope lies in the development of appropriate molecular markers; until then it seems not justified to exclude patients with synchronous brain metastases from combined surgery.

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Appendix A. Conference discussion

Dr A. Jilaihawi (*Glasgow, UK*): Those patients who presented with synchronous tumours, did they have symptoms of brain metastases or do you CT scan of the brain every patient with lung cancer?

Dr Getman: Not all these patients were symptomatic. Approximately 80% of this group of patients had symptoms.

Dr Jilaihawi: So you don't do brain CT for every patient with lung cancer?

Dr Getman: We do CT as a part of normal staging.

Dr Jilaihawi: Is it a routine procedure?

Dr Getman: It is a routine procedure.

Dr Jilaihawi: Do you think that's economical, because Aberdeen did a study 20 years ago where he only found 4% of patients who present with lung cancer have brain mets. Do you think you could scan everybody with lung cancer?

Dr Getman: I don't think so.

Dr A. Turna (*Istanbul, Turkey*): Did you perform mediastinoscopy in those patients and do you believe that mediastinoscopy has a role in selecting patients in order to select more convenient patients to have an increased survival?

Dr Getman: Yes, it's a normal tactic in our department to perform mediastinoscopy in cases of suspected N2 disease. If we diagnose N2 disease with verification by means of mediastinoscopy, the patient receives neoadjuvant chemotherapy, and therefore the median interval between neurosurgical procedures and lung resections was 27.5 days and ranging up to 110 days.

Dr J. Furak (*Szeged, Hungary*): In Hungary we have a national multicenter study about these topics and we have two times more patients than you, so its over 60.

Can you mention the survival in different stages of the lung cancer, I mean stage I, II, IIIA, because we have an interesting survival curve.

Dr Getman: We have performed univariate as well as multivariate analysis and we tried to analyze N0 versus N1 or 2 disease as potential prognostic factors, but in the univariate analysis we have not received any confirmation. So, the stage was not a prognostic factor in our study.

Dr P. De Leyn (*Leuven, Belgium*): The completeness of the resection of both the lung and the metastasis is of crucial importance. If you have a patient with a synchronous lesion in the brain and in the lung, would you first operate on the brain and then the lung, or would you do it the other way around?

Dr Getman: In all cases of this group, the first operation was neurosurgical resection.