

Survival of stage I lung cancer patients with previous or subsequent primary malignant neoplasms

Oleg A Vasiljev, Vladimir P Kartchenko, Igor V Kouzmine

Moscow Research Institute of Diagnosis and Surgery, Moscow, Russia

From 1965 to 1990 2161 patients underwent the complete resection for lung cancer. In 910 cases stage I was histologically proved. pT1 – 375 (41 %), pT2 – 532 (58,7 %). There were 90,9 % cases observed more then 5 years, 60,2 % – 10 years. Ninetysix (10,6 %) patients were found to have second primary neoplasms before or after the curative treatment of stage I lung cancer. 13 (13,5 %) patients died due to subsequent primary malignancy, 17 (17 %) – of other causes. Crude 5-year survival of stage I lung cancer patients was 65 %, 10-year survival was 53 %. In the group of 96 cases with multiple neoplasms accordingly 73 and 53 %. Our data confirm that the relative probability of the second primary malignancy increases in time of monitoring after the curative surgery or the combined treatment and depends on the spread of tumor (TNM factors) in connection with indirect influence on the survival. In early lung cancer second primary neoplasms after the curative treatment do not influence formal indices of survival. The paper discusses the results of adjuvant methods of treatment in connection with multiple primaries.

Key words: lung neoplasms – mortality; survival rate; neoplasms second primary

Introduction

Every item of multiple cancer with lung primaries (MCLP) has been intensively discussed for many decades but some of them haven't been studied properly. One of the inadequately stu-

died problems is the survival of patients with early lung cancer. In the first place stage I patients have the curative treatment more frequently. Secondly, the survival is significantly longer. On the other hand, after organ-preserving surgery, a large volume of spare lung tissue with precancer changes rests the potential source of multiple growth. Moreover, there are many more possibilities for the realization of the curative surgery for the second and even third time. A repeated radical treatment is based on the certainty of pathologic determination of the new primary and the stage of its development.

The problem of MCLP plays the important role in the estimation of long-term results of

Correspondence to: Oleg A, Vasiljev, M.D., Moscow Research Institute of Diagnosis and Surgery, 117837, GSP7, Profsojuznaya str. 86, Moscow, Russia. Fax: + (095) 334-79-24, Email: DIRECTOR mniidih, MSK, SV.

The paper was presented at the 2nd Central European Conference on Lung Cancer; Ljubljana – Slovenia, April 13–16, 1994.

UDC: 616.24-006.6-036.8

radical treatment. Generally, in order to leave out the influence of MCLP on survival, this kind of patients is not included in the analysis of clinical material. But this group of patients is the most important part of treatment program and constitutes up to 10–12% of cases. At the same time, in most publications only mean duration of life in years and months was reported. According to general statistics, the crude 5-year survival of MCLP was near 30% with the consideration of all stages of the disease.

Material and methods

During the years 1965–1990 2161 patients were operated in Moscow Research Institute of Diagnosis and Surgery. Stage I of the disease was stated histologically in 910 cases. T1S – 3, T1N0 – 375, T2N0 – 532 patients. Remote results were estimated to 05.05.92 (Kaplan-Meyer method). There are 827 (90,9%) patients who have been observed for five years and 551 (60,3%) patients for 10 years. In 96 (10,6%) patients of 910 cases MCLP was detected. There are 48 patients who are still alive (Table 1). For the verification of multiple primaries generally accepted criteria were used.¹

Results and discussion

Among 234 patients with central type of cancer the incidence of MCLP was 16,2%, in peripheral (297) – 14,4% ($p > .05$). It is important to underline the similar incidence of central and peripheral multiple lung cancer. It concerns extrathoracic primaries as well. The risk of second primary in T1N0 patients is twice greater than in T2N0 patients. The difference is significant ($p < .02$) without any connection with clinico-pathologic forms of lung cancer.

Table 1. Alive after curative treatment of stage I lung cancer.

Total	No recurrence	With progr.	MCLP
415	336	29	48
100 %	81,4 %	7 %	11,6 %

The mean diameter of the primary pulmonary tumor in MCLP patients was 34 mm, in solitary lung cancer – 30 mm ($p > .05$).

The incidence of MCLP has been studied for comparison in 90 operated T1N1 – 2 lung cancer patients. In this group 6,8% of MCLP patients were found.

Age and sex

The mean age of MCLP patients (Stage I) was 57,9 years, of others – 55,6 ($p < .005$). In patients of 60 years old and younger the incidence of MCLP was 8,3%, in an elderly group of patients – 15,3% ($p < .05$). The direct correlation of MCLP was not found but the annual relative risk of second malignant tumor was on average 2%. During postoperative monitoring of patients two picks of increasing of multiple lesions of respiratory tract in 1–2 and 4–5 years after the radical treatment were observed. The same data have been already mentioned in the literature.²

Seventeen (18%) MCLP patients were women. In the group of multiple cancer of respiratory tract patients women represent 7,1% cases. In the entire group MCLP was observed in 12% of women and in 10% of men. The difference is not significant.

So the possibility of MCLP development is connected with the stage of the lung cancer and the period of monitoring: factors with direct influence on the survival of cancer patients. The risk of a new primary tumor seems to be equal for all stages, however, the incidence of MCLP is lower due to the shorter follow-up period. The majority of new cancers would appear only a few years after the primary treatment, i.e. only after the patients with advanced tumors already died.

Localization of MCLP

In 52 (55,8%) patients the second cancer was found in lung, in 6 (6,3%) – larynx, in 4 (4,3%) – stomach, 3 (3,2%) – esophagus, 2

(2,1 %) – urinary bladder, 29 (30,2 %) – other organs. 13 (13,5 %) patients deceased of progression of the second primary, 17 (17 %) – of other cause. Eventually the common etiologic factor in most cases is cigarette smoking. Carcinogens of tobacco smoke influence on the respiratory and gastrointestinal mucosa. The secretion of harmful derivations in urinary tract supports the high level of malignant transformation of epithelium.

The influence of diagnostic methods

In 1980 the diagnostic technologies significantly ameliorated in our institution. Most of the patients were examined with echography, fibroendoscopy, CT, single photon emission CT. More frequently the needle biopsy under visualization control and surgical methods of diagnosis were practiced. So before 1980 MCLP was detected in 24 (5,5 %) of 433 patients, the next decade – in 72 (15 %) of 477 patients ($p < .001$).

The influence of treatment methods

The problem of iatrogenic etiology of MCLP remains exceptionally actual. The studies of influence of radiation therapy and chemotherapy on the risk of multiple cancer are not yet known because of synchronous action of different factors and complexity of malignant transformation of cells. However, some facts of the process is worth to analyze and find out the optimal match of treatment methods.

395 patients were operated without any other influence on malignant cells; MCLP of different localizations was found in 47 (13 %) patients. 551 patients were irradiated before or after the surgery; MCLP was observed in 49 (8 %) of them ($p > .05$). Lobectomy or pneumonectomy were practiced in 771 patients; MCLP was diagnosed in 70 (9 %). The conservative surgery (resections less than lobectomies) was carried over 141 patients; MCLP developed in 17,6 % of them ($p < .05$).

Most of organ preserving compromised lung resections were practiced on the patients already had radical treatment of malignant tumor in anamnesis. In 38 cases the second cancer was observed in organs outside the respiratory system. 13 patients radically treated 3–10 years earlier and were in complete remission when the second primary in lung was found. In most cases before operation there was no possibility to except the metastatic processes. MCLP was verified just after obtaining histologic and camnestic data.

Theoretically, chemotherapy influences the occult microlesions of second cancer. But on the other hand, it is to stimulate the malignant growth in connection with immunosuppression. In 48 cases of stage I lung cancer patients received repeated cycles of chemotherapy (cisplatin, vindesine, ethoposide and other cytostatics). MCLP was observed in 1 (2 %) case. 862 patients have not received any chemotherapy. MCLP developed in 93 (10,8 %) cases ($p < .05$). However, it is difficult to prove the role of chemotherapy in etiology of MCLP because of multiple prognostic factors that influence the survival. This problem is to be studied more properly.

Survival after radical treatment and MCLP

414 patients died, including 13 (3,3 %) patients – of second malignancy progression (Table 2). 5-year survival consistutes 65 %, 10-year – 53 %. In the group of MCLP patients these

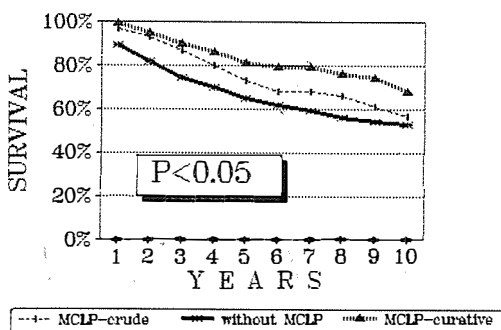


Figure 1. Stage I lung cancer. Multiple cancer with lung primary (MCLP).

indexes were 73 and 53 % respectively. Significant differences were first observed 4 years after the treatment. Relatively good results were obtained in MCLP after the curative treatment of both lesions (Figure 1). Five years lived 81 % of patients, 10 years 60 %. Long term results were not significantly influenced by methods of management, type of surgery, adjuvant irradiation or chemotherapy.

Table 2. Causes of death after treatment of stage I lung cancer

Total Smal	Compli- cations	Progress	Second tumor	Non- cancer
414	45	323	13	33
100 %	10,9 %	78 %	3,1 %	8 %

The best remote results were registered in women suffering from MCLP. The five year survival was 94 % and in solitary lung carcinoma 73 %. The most probable explanation of this contradiction are peculiarities of second cancer; in most case there were genital diseases with a relatively favourable prognosis.

The problem of survival emerged during the analysis of long term results of localized lung cancer and monitoring of patients with relatively good prognosis. We haven't found any special reports on the statistical features of multiple lung cancer.

Similar data were obtained in the analysis of 1510 cases of localized breast cancer including 157 patients with multiple primary lesions that were detected before or after the curative treatment. The period of observation was 20 years. The 10-year survival in the group of multiple primaries (exceptionally cancer deaths considered) was significantly higher than in the one of a solitary tumor. The results were not correlated with histologic type of cancer, treatment methods, type of surgery or other prognostic factors.³

Authors couldn't properly explain the results of their study. An attempt to consider the pathogenetic mechanisms associated with anti-tumor defence of the patient, to discuss the role of lymphatic nodes in biologic suppression of malignant growth or morphometric features of

multiple tumor nodes didn't look rather convincing.

The most possible cause of relatively high survival in multiple malignancy was introduced by R.C. Margoese.⁴ The convincing explanation of the apparent contradiction was connected with the patient's selection in the observation groups. As a rule among patients with solitary cancer the cases with assured better prognosis of one of the tumor localizations were collected. The mean survival is to be rather long for the second primary appeared or detected.

For the more appropriate analysis of the MCLP patient's survival we have to use the other methodological approach to statistical development of the data. It is to be multivariate analysis with regard to the time of appearance of the second tumor as a covariant of the dependance and distribution of different prognostic factors depending on the patient and tumor. Of course the statistical estimation must be designed with consideration to the noncancer lethality and lost patients.

We haven't realized yet the profound analysis of the remote results of the MCLP study. The most important purpose of our report is the estimation of influence of MCLP on the formal indexes of survival of the stage I lung cancer patients.

So we have the impression that MCLP does not significantly influence the long term results of treatment of stage I lung cancer. It seems the most possible cause of relatively high survival after the primary curative surgery in this group is the priority of the appearance of new malignant disease with patients being observed for a long time (selection phenomena).

Conclusions

1. The relative risk of MCLP increases with the time of monitoring after the curative surgery and generally correlates with the stage of primary lung cancer in connection with the indirect influence on the period of observation.

2. In the case of the early detection of MCLP and principle set up on radical treatment of

both diseases, every new malignant tumor does not significantly impact the formal survival of stage I lung cancer patients.

3. The adjuvant irradiation of curatively treated patients does not produce the essential influence on the incidence of MCLP respiratory and extrathoracic localization and does not correlate with the long term results.

4. The influence of the modern chemotherapy (neoadjuvant including) could not be definitely proved. But according to our limited experience (without randomization) we could assume that chemotherapy decreases the risk of second primary cancer with stage I lung cancer patients.

References

1. Martini N, Melamed M. Multiple primary lung cancers. *J Thorac Cardiovasc Surg* 1975; **70**: 606–12.
2. Razzuk MA, Rockey M, Urschell HC, Paulson DL. Dual primary bronchogenic carcinoma. *Ann Thorac Surg* 1974; **17**: 434–43.
3. Peloquin A, Poljicak M, Falardeau M, et. al. Survival of breast cancer patients with previous or subsequent neoplasms. *Canad J Surg* 1992; **35**: 481–85.
4. Margolese RG. Survival of breast cancer patients with previous or subsequent neoplasms. *Canad J Surg* 1992; **35**: 476–80.