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PLEUROPULMONARY METASTASIS WITH UNKNOWN OUTSET – DIAGNOSIS ALGORYTHM

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Abstract: *Lung metastases with unspecified starting point represent an entity with poor prognosis The group of study included 24 patients with pulmonary metastases of with occult tumors. The study was retrospective and assessed the prognosis factors correlated with the survival ratio: gender p=0.112, average age of 56.6 years good status of performance p=0.0337, average number of investigations (between 2 and 12)7.46, with an average cost on patient of 558.33 lei, pattern metastases p=0.696, histology p=0,906, groups of risk p=0.040, average survival 5.85 months. Some algorithms of diagnostic for a better management of patients with lung metastasis were studied.*

Key words: *lung metastases, occult tumors, prognosis factors.*

1. Introduction

Unspecified outset carcinomas represent a heterogeneous group of tumors which have as a joint feature the presence of metastasis without identifying the outset tumor at the moment of treatment start (3). The incidence varies between 0.5% and 15% among the tumors of the adult and between 5% and 10% for tumors in general.

Lung is the most frequent place of supradiafragmatic metastasis. Searching of the primary tumour is difficult because the metastasing pattern can be atypical (1). We expect that among patients with lung cancer, 30% - 50% of them will also have bone involvement. Only 4% of the patients with an undetermined primary tumour (which later has been proved to be lung cancer) have had also bone metastasis. Thus, the relative frequency of metastasis from a known tumour cannot be used in establishing the diagnosis. In 15% of the cases primary tumour remains unknown even when an autopsy has been performed. Among the most of the cases with unknown primary tumour at autopsy, the most frequent, the neoplasia is hidden in the lung or pancreas (9). Unknown outset metastasis prognosis is poor with an average survival length of 6 – 12 months (3).

2. Work Hypothesis

Prognosis and the treatment of patients with neoplasia are tightly related to the site of the primary tumor. Diagnosis evaluation of the unknown outset metastasis endorses, on one side, the acknowledgement of

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neoplasia and, on the other side, the search of the primary tumor. Study objectives are: defining diagnosis, evaluation of validated prognostic factors for other sites metastasis with occult tumors, evaluation of the treatment with survival assessment, as well as the assessment of cost – efficacy – benefit balance of the investigation among patients with unknown primary tumor.

3. Material

We have studied 24 patients with pleuropulmonary metastasis and unknown primary tumour at the moment of treatment initiation which were admitted to Oncologic Institute Cluj and/or Clinical Hospital of Pneumology between January 2000 and December 2005. Patients with solitary pulmonary nodule, whose pulmonary primary cancer diagnosis hasn't been ruled out, were excluded as well as the patients with any neoplasia history (even though there was a very big period of time and metastasis was unlikely).

4. Method

Patients were investigated through: anamnesis – full physical examination (including head, neck, thyroid, rectal examination, women additional have had breasts examination and gynaecological examination and men additional have had testicular examination and of the prostate); blood analysis (CBC, liver and kidney function); chest X ray (PA, side, CT thoracic and abdominal); any symptomatic area X ray. There was an analysis of the type of pulmonary metastasis: micro opacity, macro opacity, mediastinum adenopathy, pleurisy, lymphangitis. Histological type (adenocarcinoma, scuamous, lymphoma, unknown histology) has been established through: fibrobronchoscopy (with bronchi biopsy of transbronchial), ganglion biopsy, pleural biopsy, CT or echo guided transthoracic tap. We have evaluated the diagnosis cost and we established through reviewing published studies, an investigational algorhythm depending on the patient's features (age, gender, performance status, pleuro-pulmonary metastasis type, histology). Investigations' costs were calculated based on the average price of nowadays investigations. Statistic analysis included Kaplan – Maier method (SPSS soft) for survival rate and Log – Rank test for the differentiation between survival curves.

5. Results

Group distribution based on age, gender and performance status is shown in table 1.

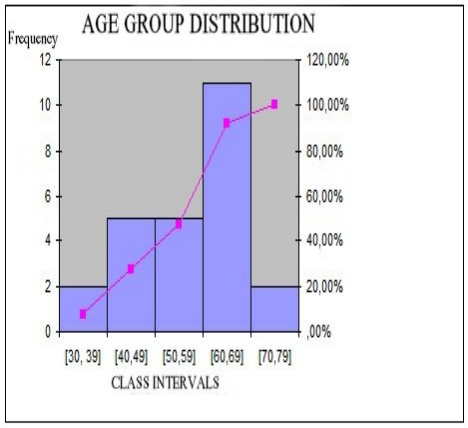

Fig. 1. *Age group distribution*

Unknown outset tumours arise more frequently in male aged 65 and more - in our batch 54% of patients without a better survival rate were men (p =0.112). Average age was 56.6 years with predominance between 60 and 69 years old. The presence of respiratory symptoms is the frequent reason of addressing to a physician. The most frequent symptoms which led to going to a physician were: dyspnoea (18), dry cough (16), thoracic pain (7), weight loss (11), asthenia (10), and fatigue (10).

Low performance status (4 or 3) was present in 75% of the patients. The performance status is determined based on the presence of symptoms and the tolerance to effort. If for performance status one can establish two classes such as low (when performance status is 2 or 3) and fair (good) (when is 0 or 1), then this performance status becomes a prognostic factor for the survival rate. Through Kaplan – Maier we obtain a significant p value for Log – Rank test, $p=0.0337<<0.05$.

Batch repartition based on age, gender and performance status Table 1

Age		Gender		Performance status	
30 – 40	8%	M	54%	unknown	4%
40 – 50	21%			1	21%
50 – 60	21%				
60 – 70	42%	F	46%	2	54%
70 – 80	8%			3	21%

Metastases diagnosis was established based on chest X – ray PA, LL and CT to all patients. Patients have had on chest X – ray: multiple opacities spread among both lungs, lymphangitis image or image of pleurisy of unknown aetiology. The patients with solitary pulmonary nodules or unique opacities whose primary pulmonary aetiology was not ruled out were excluded, wheather the patients were smokers or not. Patients presented most frequently micro nodular metastasis pattern (46%), macro nodular metastasis (21%), lymphangitis carcinomatosa (4%) and serohemorrhagic pleurisy (29%). To confirm the pulmonary metastasis diagnosis additional investigations were performed one hand to acknowledge the neoplasia diagnosis and on the other hand to elucidate the outset. Fibrobronchoscopy being an invasive investigation was able to be performed only at 14 patients.

General appereance and low performance status did not allow to perform fibrobronchoscopy to all patients. Confirmation was obtained only in 50% of the cases through: pleural biopsy (2), malignant cytology (3), fibrobronchoscopy with biopsy (2), with bronchial brushing (3) or transbronchial biopsy (1), peripheric ganglion biopsy (1). Lymphangitis carcinomatosa and a part of the multiple metastasis haven't had a histopathological confirmation and impaired general feeling with low performance status did not allow open thoracothomy od thoracoscopy to be performed.

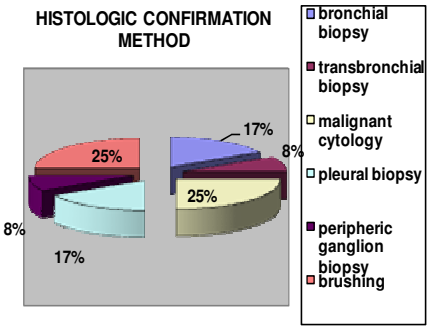

Fig. 2. *Histological confirmation methods*

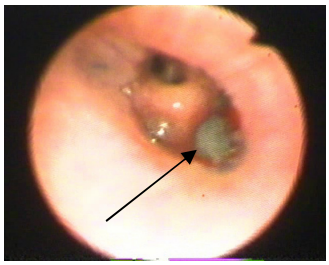

Fig. 3. *Endobronchial metastasis (unknown aetiology batch*)

Our study has discovered a significant number of unknown histology (50%) followed by the presence of adenocarcinoma (unknown histology includes all the cases which the cancer commission – formed by an oncologist, radiologist and a pneumologist – established as being metastasis based on X- ray, CT or at histopatology examination there were onla malignant cells or they had only cytology).

Table 2

Prognostic factors – favourable, unfavourable for unknown outset pulmonary metastasis

Prognostic factors	Favourable	Unfavourable
Histology	Low differentiated, squamous	Adenocarcinoma
Gender	Women	Men
Performance status	1–2	3–4
No. of metastasis	< 3	≥ 3
Alkaline phosphatase	Normal	High
Metastasis site	Axillary lymph nodes	Cerebral, hepatic

In studied group histologic type was not a prognostic factor for survival (p=0.906), although it was observed that there is a different survival rate based on the histological type (patients with adenocarcinoma have had a survival interval of 9 months, patients with squamous adenocarcinoma have had an average survival interval of 6 months and those with low differentiated carcinoma have had an average survival interval of 3.25 months; the unknown histologic type have had an average survival interval of 8.2 months).

The average number of investigations that have been performed to a patient was of 7.46 with an interval between 2 an 12 to identify the primary tumour site. Average cost per ratient was of 558. 33 lei.

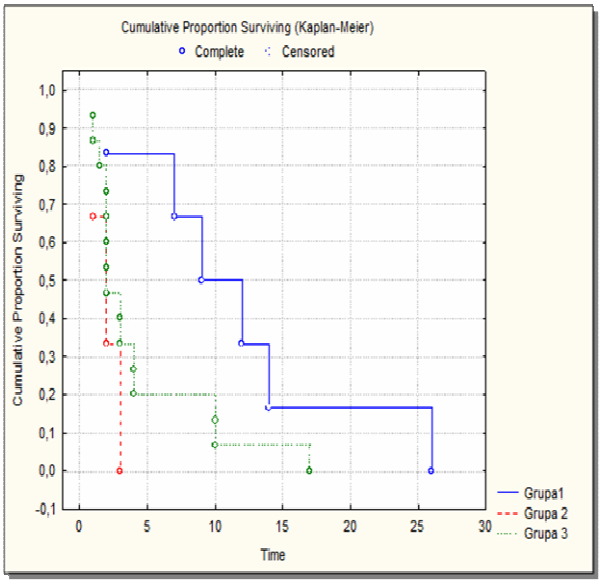

Fig. 4. *Survival based on risk groups*

Carcinomas with unknown outset are a heterogenous group of tumours which have as a common clinical feature the presence of metastases without being able to discover the primary tumour at the moment ot therapy start. The discovery of the primary tumour was made in 38% of the cases and those were located as it follows: lung, liver, ovary and uterus. We have evaluated retrospectively the most important prognostic factors bound to influence survival among other published studies.

Risk groups. We observed for the patients with multiple metastasis different survival rates. Thus, for patrients with pulmonary and bone metastasis 10 years survival rate was of 33% and the average was of 5.5 months. The presence of pulmonary metastasis classifies the patient as having an unfavourable prognosis. We tried to evaluate if dividing this last type of patients into another 2 batches there is an influence regarding the survival rate:

Group 1: patients with good performance status and less than 2 metastasis,

Group 2: patients with low performance status and less than 2 metastasis,

Group 3: patients with low performance status and more than 2 metastasis. Following this division, survival rate was influenced in these risk groups ($p=0.040<0.05$).

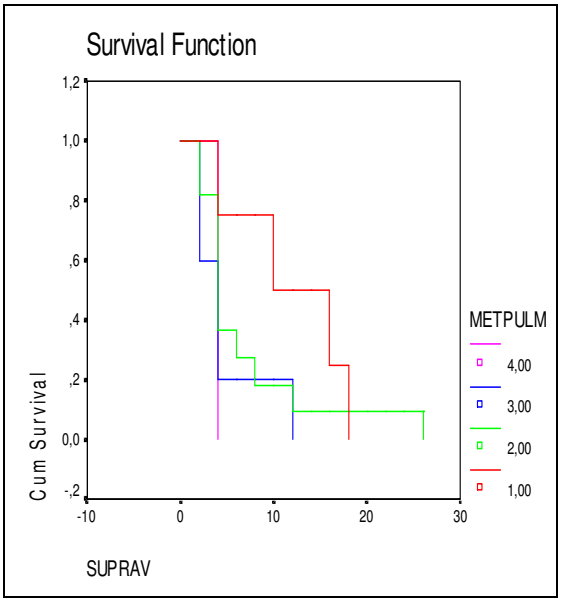

Fig. 5. *Survival rate in patients with unknown outset pulmonary metastasis based on pulmonary metastasis type (- pleurisy, - micro opacity, - macro opacity, - lymphangitis)*

The patients were treated with chemotherapy or only for symptoms those with low performance status. Treatment response was monthly evaluated. In our group no patient went into complete remission. A small number had a partial remission 21% and the rest had an unfavourable evolution with death in 3.76 months. Partial response to treatment singnificantly influence survival $p=0.003<0.05$. For the four types of pulmonary tumours the time line was

determined as well as the 5, 7 months survival rates. For type 1 pulmonary metastasis (pleurisy) 2 months survival rate was 75%, 8 months survival rate was 50% and 14 months survival rate was 25%. The average survival was 14 months. In type 2 pulmonary metastasis (micro opacity) 2 months survival rate was 36%, 4 months survival rate was 27%, 8 months survival rate was 18%, 12 months survival rate was 9%, 24 months survival rate was 9% and average survival was 3.4 months. In type 3 pulmonary metastasis (macro opacity) 8 months survival rate was 20% and the average survival was 2.5 months. Lymphangitis carcinomatosa has a survival of 1 month.

5. Discussion

Unknown outset pulmonary metastasis represents a low number of cases among all cases of admitted neoplasia patients. In our study 54% of patients were men congruent with the literature. Issing reported among 167 cases the presence of 71.3% men (5). Stephan Culine has found the presence of 82% men (3). Our study shows that gender is not statistically important and does not influence survival (p=0.112). Age distribution analisys has revealed a predominence among patients aged 56 to 64 with an average age of 56.6 years and did not influenced survival. Roland Bugat reported a bimodal distribution with a first peak at 55 years old and the second peak at 65 years old with an average age of 65 years (2). Our study has revealed also the predominance of tumours with an unknown histology followed by adenocarcinoma which is congruent with the literature and histology has not significantly influenced survival (5.97 months survival). Levine argues that the discovery of the primary tumour allows an increase of survival rate of just 0.5% from 11% to 11.5%. Steckel et. al. haven't revealed survival rate's increase and no improvement of the quality of life in patiens whose primary tumour was discovered (6, 7, 13). In case of discovery of the primary tumour localized at breast or ovary the survival was of 48 months (11). The cost of the investigational balance is low among breast an ovary site in women and prostate site in men (13). In men the increase of tumour markers is sugestive and helps the diagnosis. Other markers like CEA, CA 19 – 9, CA 125, CA 15 – 3 had low prognostic and diagnosis value (11). David Mitzerstates also observed the lack of sensibility and sensivity of the markers and concluded that though, intuitively, a marker panel may be helpful to establish the origin of the tumour, their value is not conclusively (8). Lenzi concluded that if a potential curative malignancy is excluded the extensive expence is little justified for the diagnosis (13). Stephan Culine stated in his study that one third of the patients hava a low performance status and he deemed to be a unfourable prognosis factor ($p<0.0001$) (3,10). Kirsten deemed that performance status, multiple sites of metastasis and a loss of weight over 10% may constitue independent pronostic factors for survival (12). In our study performance status is the only prognostic factor which statistically influence survival (p=0.033).

Unfortunately we were not able to discover specific subtypes that could receive a specific treatment with a favourable prognosis. Hainsworth J. D. reported that only 40% of the patients can be included into subtypes with specific treatment. Empiric treatment is applied at 60% of the patients. Patients with low performance status and multiple organ metastasis have an average survival of 1 month. Survival of the most patients is not based on treatment except those with cervical ganglion metestasis derived from unknown neoplasia from head and neck,

patients vith lymphoma or those with germinal neoplasia (4). Van der Gaast reported among different prognostic subtypes different survival:

- Good prognosis (performance status 0 and alkaline phosphatase less than 1.25 times ULN);
- Intermediate prognosis (performance status ≥1 and alkaline phosphatase ≥125) average survival 10 months and 4 years survival rate of 15%;
- Poor prognosis (performance status ≥1 and alkaline phosphatase ≥1.25 times ULN) with average survival 0f 4 months and no survivor over 14 months (10).

Survival rate among patients with unknown outset pulmonary metastasis was as low as 85% at 3 months, under 20% at 12 months and 1.54% at 23.6 months.

6. Conclusion

Unknown outset pulmonary metastasis is a rarely clinical syndrome in oncology with a poor prognosis. These patients with multiple site metastases, with extensive disease and frailness body at the moment of diagnosis benefit only of symptomatic treatment. Studies report a low rate of response to chemotherapy without influencing the survival rate (3 – 4 months), in our study a survival rate of 5.86 months. Only the identification of those patients with a treatable disease may be able to improve prognosis and the survival period of time. The only statistically significant prognosis factor was the division into risk groups based on performance status and the number of metastatic sites, as a sign of dissemination $p=0.040<0.05$. The search of primary tumor, even with excesive costs, has not always been very successful, only a low number of cases (per patient cost is 583.33 RON at 7.46 investigations per patient). Routine radiographic or endoscopic examination of organs without symptoms is not enought. The benefits of establishing the diagnosis at any cost, with consumption of time and resource in patients with extensive disease are minimal. Pulmonary metastasis had known histology in 50% of the cases without an evidence of a difference in survival between groups with known and unknown histology (5.75 respectively 5.95) with $p=0.906> 0.05$. Patients in critical condition, with rapid tumour progression, sometimes with imminent local complications need rather more therapeutic interventions than diagnosis evaluation. Survival rate at patients with unknown outset pulmonary metastasis was lower towards other sites. Thus, we have obtained a 3 months survival rate of 58%, 1 year survival rate of under 20% and 23.6 months survival rate of 1.54%. This evolution is due to erly dissemination (suggested by the absence of primary tumour symptoms), aggressivity of the primary tumour and due to the unpredictable metastasis way. The improvement of prognosis in these patients can be achived only through increasing the sensitivity and specificity of the image (spiral CT with rapid detection of volume modifications, PET, MRI), improvement of endoscopy alongside the increase of specificity of pathologic examination. Newer tests of imunohistochemistry, histochemistry as well as the extension of investigations at chromosomes anomaly (cytogenetics, molecular biology, cellular culture) may be useful to diagnose the primary tumour.

The discovery of high specificity and low toxicity chemotherapeutic agents as well as the identification of action mechanisms and newer classes of tumour therapy (such as targeting chromosomes) may change the future of these patients with unknown primary tumour and unfavourable treatment response, also. More likely these disease derives from non

– small lung cancer, pancreatic cancer and gastrointestinal cancer – tumors whose curative treatment hasn't yet been discovered and whose prognosis is poor.

References

1. Briasoulis, E., Kalofonos, H., Bafaloukos, D., Samantas, E., Fountzilas, G., Xiros, N., Skarlos, D., Christodoulou, C., Kosmidis, P., Pavlidis, N.: *Carboplatin Plus Paclitaxel in Unknown Primary Carcinoma: A Phase II Hellenic Cooperative Oncology Group Study.* In: JCO, 2000: p. 3101-3107
2. Bugat, R.: *Standards Options et recommandations 2002 pour la prise en charge des patients a theints de carcinomas de site primity inconnu (rapport abrégé).* In *:* Bulletin du Cancer; nr.12, 2003.
3. Culine, S., Kramar, A., Saghatchian, M., Bugat, R., Lesimple, T., Lortholary, A., Merrouche, Y., Laplanche A., Fizazi K.: *Development and Validation of a Prognostic Model to Predict the Length of Survival in Patients With Carcinomas of an Unknown Primary Site.* In: JCO, 2002, p. 4679-4683.
4. Vito, V.: *Cancer Metastasis* 1998. *Principles of Molecular Cell Biology of Cancer.* Philadelphia. Lippincott. p.134-148.
5. Issing, W.J., Taleban, B., Tauber, S.: *Diagnosis and management of carcinoma of unknown primary in the head and neck.* In: Eur. Arch. Otorhinolaryngol. 2003, No. 8, p. 43-436.
6. Kirsten, F., Nee Chi, C., Learg, J.A., Alan, N.G.: *Metastatic Adeno or Undifferetiated Carcinoma from a Unknown Primary site Natural History and Guidelines for Identification of Treatable Subsets*. In: Q J Med 1987, p. 143-161.
7. Lenzi, R., Hess, K.R., MC Abbruzzese, M.C., Raber, M.N., Ordonez, N.G., Abbruzzese, J.L.: *Poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown origin: favorable subsets of patients with unknown-primary carcinoma*? In: JCO 1997, p. 2056-2066.
8. Mintzer, D.M. at al.: *Cancer of unknown primary Changing Approaches – A multidisciplinary Case presentation froam Joan Karnell Cancer - Center of Pennsylvania Hospital.* In: The Oncologist 2004, vol. 9, p. 330-338.
9. Pentheroudakis, G., Briasoulis, E. and Pavlidis, N.: *Cancer of Unknown Primary Site: Missing Primary or Missing Biology?* In: Oncologist 2007, No. 12, p. 418 – 425.
10. Rades, D., Kuhnel, G., Wildfang, I., Borner, A. R., Schmoll, H. J., Knapp, W.: *Localised Disease in cancer of unknown primary (CUP).The value of positron emission toography (PET) for individual therapeutic management.* In*:* Annals of Oncology 2001, No. 12, 1605-p. 9-16.
11. Roney, J., Texid, A., Rossel, R., Abad Esteve, A., Solans, R., Carles, J.: *Carcinoma of unknown origin. Diagnostic study of 48 cases and its clinical yield*. In: Med Clin. 1989, p. 201-206.
12. Van Der Gaast, V., Verweij, J., Planding, A.S., Hop, W.C., Stater, G.: *Simple prognostic model to predict survival in patients with undifferentiated carcinoma of unknown primary site*. In: JCO. 1995, p. 1720-1725.
13. Varadhachary, G.R., Abbruzzese, J.L., Lenzi, R.: *Diagnostic strategies for unknown primary cancer.* In: Cancer 2004, No. 1776, p. 85.