Non-small cell lung cancer, pleural effusion and carcinomatosis: always a criterion of inoperability?

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Abstract: Pleural carcinomatosis is detected in only 8–15% of patients with non-small cell lung cancer (NSCLC) at the moment of initial diagnosis, whilst in 40–50% of them it will be confirmed during the disease progression. In 12.5% of patients with NSCLC and malignant pleural disease (MPD), there is no evidence for distant metastases. IASLC reported that 1- and 5-year survival of patients with carcinomatous pleuritis were 36% and 2%, respectively. That is why the most of modern clinical guidelines and consensus, do not recommend routinely performing radical surgical interventions in patients with ipsilateral pleural dissemination, considering this as the IV stage NSCLC, which should be treated by conservative systemic/chemoradiation therapy (CRT). Nevertheless, it should be recognized that using only conservative methods of treatment is not always quite effective, so that various types of palliative and symptomatic surgical interventions could be used according to modern clinical recommendations. There are continuing attempts to improve the long-term results of treatment of these patients. In a number of recent publications, the usefulness of the surgical treatment including resection of the primary tumor in patients with NSCLC M1aMPD is described, with declared MS ranged from 13 to 52 months. After thorough study of available literature data we can summarize that it is impossible to make reasonable, unambiguous conclusions about the feasibility, effectiveness, safety and optimal extent of resection in this category of patients. Particularly all authors note the need to conduct randomized controlled trials taking into account the alleged high potential to use the modern combined and complex treatment methods.

Keywords: Surgery; non-small cell lung cancer (NSCLC); malignant pleural effusion (MPE); malignant pleural disease (MPD); pleural carcinomatosis; malignant pleuritis; malignant pleural nodules (MPN)

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Introduction

Lung cancer (LC) is the second leading cause among all types of oncological diseases, the first one (31%) among malignant tumors in men and represents 2/3 of all non-small cell lung cancers (NSCLC). In 55–60% of patients with locally advanced NSCLC have malignant pleural disease (MPD) and in case it is accompanied by malignant pleural effusion (MPE), this worsens the prognosis and limits treatment options. Most frequently, in the structure of LC, MPD occurs in adenocarcinomas (40%) and squamous cell carcinoma (23%). In 8–15% of cases, MPE is found at the initial diagnosis, in 40–50%—during the progression of the disease, more often it is presented

ipsilateral in 90%, less often bilateral or contralateral in 10% (1-5). However, 12.5% of patients with MPD don't have any data for distant metastases. According to many authors, 65% of patients with MPE don't survive 3 months, by 6 months 80% of them die (6-9). According to the analysis of a database of 57685 patients performed by Morgensztern *et al.* [2012], it was demonstrated that MPE without distant metastases in 9,170 (15.9%) was an independent predictor of worse survival (HR =1.76; 95% CI: 1.65–1.87, P<0.001) (6). Recently, Ryu *et al.* showed that even minimal pleural effusion (<10 mm) correlates with lower survival rates [median survival (MS) 7.7 *vs.* 17.7 months, P<0.001; HR =1.40; 95% CI: 1.21–1.62] (10). The category of NSCLC patients united by the "M1a" criteria is heterogeneous, and, according to the latest, 8th edition of the TNM classification, it includes: "separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion". The subgroup of patients with morphologically confirmed MPD is also very heterogeneous, it is indicated by many different conditions (2,5,8,11,12):

- MPE;
- Malignant pleural nodules (MPN);
- MPE + MPN.

NSCLC with MPD (M1a) is generally contraindicated for surgery, thus only a systemic exposure can affect life expectancy. Currently, therapeutic intent surgical procedures are not recommended by NCCN guidelines for management of metastatic NSCLC with pleural dissemination but they may be offered in selected patients (4,13). In the case of first time diagnosed MPE in previously untreated patients, the use of systemic chemotherapy may provide a pronounced clinical effect, including the disappearance of effusion in the pleural cavity in 30–60% of patients. Nevertheless, it should be recognized that conservative treatment may not always be effective, so that various types of palliative and symptomatic surgical interventions could be used according to modern clinical recommendations (an official ATS/STS/STR clinical practice guideline) (8,9).

Evidence about surgical treatment of patients with NSCLC and MPD

It is widely known, that most of modern clinical guidelines and consensus, do not recommend routinely performing radical surgical interventions in patients with ipsilateral MPD ($M1a_{MPD}$), considering this as the IV stage NSCLC, which should be treated by conservative systemic/chemoradiation therapy (CRT). Nevertheless, there are continuing attempts to improve the long-term results of treatment of these patients using surgery as a stage of treatment with a radical, conventionally radical or palliative purpose. In most studies, that entails intraoperative diagnosed local MPNs (11,14). Also in a number of recent publications, the usefulness of the surgical treatment is described. It includes resection of the primary tumor in patients with NSCLC $M1a_{MPD}$. The success of these operations lies in the careful selection of patients, considering the functional status, degree of tumor spread, as well as a number of prognostic and predictive markers. Treatment results reached by Li *et al.* [2019] on a series of 5,513 patients with NSCLC who had MPD (76.3%, MPE; 9.5%, malignant pericardial effusion; and 4.2% MPNs), showed that patients after surgery possess better MS—20 months *vs.* 11 in a non-surgical cohort (P<0.001). Moreover, it is important to note that OS (HR =0.56; 95% CI: 0.48–0.65; P<0.001) and PFS (HR =0.60; 95 % CI: 0.51–0.70; P<0.001) was better for NSCLC patients with MPE, in compare to the group with malignant pericardial effusion (P=0.065) (15). In a study performed by Ren *et al.* [2016], 62 patients, with gross confirmation of malignant pleural dissemination, underwent resection of the primary tumor with MS of 37.3 *vs.* 17.4 months in the biopsy group (14). In the other study of these authors (n=2,217; SEER registry), an analysis was performed to compare the outcomes of surgical treatment of patients with ipsilateral MPD. Surgical group had significantly better MS compared to the group without resection—20 *vs.* 7 months; P<0.001. They also demonstrated the decrease in OS in group without resection (HR =2.136; 95% CI: 1.645–2.772; P<0.001) and PFS (HR =2.053; 95% CI: 1.568–2.690; P<0.001) (16). In a multicenter study performed by the Japan clinical oncology group in 2015, by Iida *et al.*, the authors reported about improvement in survival rates after resection of the primary tumor in patients with pleural carcinomatosis, with postoperative MS reaching up to 34.0 months and a 5-year survival rate of 29.3% (17). Ichinose *et al.* (2001; n=227) have obtained similar data on the advantage in the resection group over the control group: 3-year survival rate of 28.8% *vs.* 10.9%, and 5-year survival—14.9% *vs.* 0%, respectively (P=0.04) (11,18). In 2017, Li *et al.* reported the results of surgical treatment of 110 patients with MPNs, they demonstrated unequivocally higher survival rates in surgical group than in the control group: MS 49.0 *vs.* 29.4 months, 3-year survival 69.4% *vs.* 41.7% 5-year-old 31.7% *vs.* 19.5% (P=0.037) (19). Mordant *et al.* [2011] demonstrated that

radical surgical resection in patients with limited metastatic pleural involvement allows achieving MS up to 15 months, with a 5-year survival rate of 16.2% (95% CI: 6.9–33.6) *vs.* 0% in the exploration group (20). Yun *et al.* [2018] compared the effectiveness of CRT as the only treatment modality with surgical treatment only in the studied category of patients. In a multivariate analysis, it was shown that surgical resection was the only significant prognostic factor (P<0.01). They found that MS rate in the CRT group was 33 months, 1-year survival 88.1%, 3-years 41.1%, and 5-years 15.2%. In the surgical group, these parameters were statistically significantly higher—52 months, 91.7%, 66.7% and 42.7%, respectively (P<0.012). PFS after 6 months, 1 year and 3 years was 67.2%, 25.2% and 12.6% in the CRT group and 93.8%, 87.3% and 71.3%, respectively, in the surgical group (P<0.001) (21). In the articles published by Fukuse *et al.* and Shiba *et al.*, the authors achieved similar results, with the group of patients with NSCLC $M1a_{MPD}$ who underwent a surgical treatment, when compared with the control group has better MS rate: 37.9 *vs.* 6.2 months and 5-year survival: 14.3% *vs.* 0%, respectively (22,23). Nevertheless, some of the studies have shown the lack of benefit from surgical treatment in this group of patients. So, in a pursuant to Sawabata *et al.* [2002] there were no significant benefits of complete (R0) or incomplete (R1) resection compare to exploratory thoracotomy in patients with MPE volume less than 300 mL (24). Therefore, MS and 5-years survival for these groups were13 months and 9% for the R0 group; 34 months and 10% for the R1 group (P=0.3); and 17 months and 0% for the biopsy group (P=0.8).

The influence of T- and N-status on the results of surgical treatment in NSCLC patients with MPNs

In the eighth edition of TNM classification, the major changes are associated with T-status and its influence on the long-term results. However, speaking of the surgical treatment of patients with MPD, most authors showed that the T-status did not significantly affect overall survival (11,17,18,21,25,26).

Almost all the works, we have included in the publication, indicate an unequivocal correlation between the condition of regional lymph nodes and the long-term results of treatment of patients in the studied category (3,11,14,16-18,26-30).

In individual studies, the pathological N-factor was not a statistically significant survival factor among patients in the resection group (N1-3: P=0.53, 0.73, 0.12, respectively) (21).

According to Mordant *et al.* [2011] and Dai *et al.* [2016], the N0/N1 status is an independent predictor of better survival. The analysis of survival evaluating the entire cohort showed that patients without metastases in the lymph nodes had better PFS (P<0.001) than patients with N1 (20,27).

Li *et al.* also found that surgical treatment was not beneficial for patients with N3 (15). Morgensztern *et al.* [2012] and Xu *et al.* [2016] showed that as higher was N-stage, as lower was survival rate after resection of the primary tumor (6,29). Dr. Okamoto and colleagues [2012] demonstrated that MS for patients with N0–1 status (33.7 months) was better than with N2–3 (24.1 months; P<0.003) (26).

Iida *et al.* and Ren *et al.* showed that N0-N1 status is an independent predictor of better overall survival (14,16).

The effect of the type of the pleural and pericardial involvement to the results of surgical treatment of patients with NSCLC and MPD has not been fully studied, and the obtained data are not similar. After surgical treatment, a significant part of patients with resectable $M1a_{MPD}$ tumor spread demonstrates long-term results comparable to the M0 group, in contrast to unresectable ones, that probably mean direct dissemination into the pleura and local rather than metastatic disease (27,31). This mechanism was described in the classification of visceral pleura invasion (VPI) proposed by Hammar in 1988 (32).

According to Chikaishi *et al.* [2017], survival rates in the cM0 and $pM1a_{MPD}$ group are quite comparable with those in pM0 group (33). Tumor pleural lesions could be either massive or limited and they are not always accompanied by effusion. According to Li *et al.* [2019] the group of patients with malignant pleural dissemination had better MS compared with the group with pericardial effusion (P<0.001) (15). Iida *et al.* showed that in patients with a combination of MPE and malignant pleural nodes (MPE + MPN), the prognosis was significantly worse than in patients with only MPE or MPN, 5-year survival rate was 16.2%, 37.6% and 34.5%, respectively. There were no significant prognostic differences between MPE and MPN, as other studies have shown (17,26,31). According to Kodama *et al.*, 3-, 5-, and 10-years overall survival directly correlated with the nature and the degree of incidence of the tumor process along the pleura, the worst prognosis was for the combination of MPN + MPE (P=0.0001–0.0029) (31).

Dr. Liu and colleagues [2015] found that patients with MPE had worse 5-years survival rate than patients with MPN (12.5% *vs.* 30.6%, P=0.069) (34). In a multivariate

analysis Ren *et al.* found that MPN is a more favorable prognostic factor than MPE (HR: 3.409, P=0.001) (14,16).

On the other hand, the analysis performed by Fukuse *et al.* demonstrated that patients with MPE after surgery had significantly better results compared to patients with only MPN and with the combination of MPE + MPN (HR =3.24; 95% CI: 1.26–8.35; P=0.015): MS 58.8 months, 10 months (P=0.0001) and 19.3 months (P=0.019), regardless of other factors (22).

In a study of treatment results, performed by Shiba *et al.* [2001] there were no significant differences in 5-years survival between microscopic and macroscopic pleural lesions (23).

The influence of the tumor histological structure on the results of surgical treatment of patients with NSCLC M1a$_{MPD}$ with MPD

Most researchers agree that adenocarcinomas are more likely to disseminate to the pleura than other types of LC (4,6,35). According to the study by Ichinose [2000] among 227 patients with pleural dissemination, the best 5-years survival rate was for lung adenocarcinoma 14.5% *vs.* 9.1% in compare to all other types of NSCLC (P<0.001) (11,18).

In publication by Liu *et al.* [2015], it was shown that, among all other forms of NSCLC, adenocarcinomas demonstrated better 5-years survival rate—32.3% *vs.* 25.4%, (P=0.07). An additional factor, the authors determined was the smoking status, which significantly reduces this index—18.6% *vs.* 40.3% in non-smokers (P=0.006) (34).

In the article published by Chiang *et al.* (n=5,321; 2017), the authors presented the results of surgical treatment of lung adenocarcinomas in patients with intraoperatively founded pleural effusion. The 5-years survival rate was 30.2%, and MS in the surgical group was significantly higher than in the control group—35.3 *vs.* 17.0 months (P<0.001) (25).

Analysis performed by Chikaishi *et al.* [2017] showed less long-term indicators for squamous types of NSCLC (33). According to other authors, there were no differences in survival rate considering the histological type of the tumor (15,20,26).

Influence of the operational volume on the results of surgical treatment of patients with NSCLC M1a with MPD

As far as is known, anatomical lung resections are optimal for surgical treatment in the early stages of NSCLC, and show the best long-term results. In a study of Li *et al.* (n=5,513; 2019), it was found that lobectomy leads to significantly longer overall survival compared to sublobar resections or physical methods of tumor destruction with a MS of 50 months *vs.* 13 and 10 months, respectively (P<0.001) (15). In a study published by Liu *et al.* in 2015, in the group of limited resections there was a tendency towards a better 5-years survival than in the group with standard operations (31.4% *vs.* 16.3%; P=0.067) (34). The results acquired by Okamoto *et al.* [2012] indicate that pneumonectomy in patients with pleural dissemination is associated with a much lower MS compare to the group with smaller operational volume (12.8 *vs.* 26.1 months, respectively, P=0.0018) (26).

According to Ren and Yun, the MS rate after lobectomy is 35 and 45 months, respectively, and there was no significant difference in survival between anatomical and sublobar resections, that was also shown in several other studies (14,16,21,28). Jin, Yamaguchi and Yokoi on small series estimated the efficiency of extrapleural pneumnectomies and showed a MS of 18, 32.1, 34 months, respectively (36-39). From the article published by Iida *et al.* [2015], it is known that 5-years survival in patients with pleural dissemination and macroscopic R0 resection, 5-years survival reached 37.1%, while in groups with macroscopic R1-2 resection and diagnostic thoracotomy, it was significantly lower—22.7% and 12.2% (P=0.009 and P<0.001), respectively (17).

Ichinose *et al.* also reported the benefits of macroscopically R0 resection with 5-years survival rate of 17.9% (11,18). Yun *et al.* [2018] conceive that R0 resection is not possible in patients with pleural dissemination. In their study, macroscopic R2 resection was not a statistically significant survival factor (P=0.53) (21). It is implicit in article by Ren *et al.* [2016]—that there was no significant improvement in survival during parietal pleurectomy compared with partial pleural resection or systematic mediastinal lymphatic dissection (MS 31.1 *vs.* 36.1 months, P=0.533) (14,16). Similar data were obtained by a number of other authors (16,17,38,40,41).

Almost all authors showed an improvement in local control (11,17,18,36-44). According to Yun, the absence of local progression after 3 years was observed in 71.3% of patients in the resection group *vs.* 12.6% in the control group (P<0.001). On the contrary, the frequency of distant metastases between the two groups did not significantly differ (P=0.9) (21). Yamaguchi *et al.* [2015]

reported a frequency of progression in the form of distant metastases in 88.9% of patients undergoing extrapleural pneumonectomy (39).

Influence of CRT in patients with NSCLC M1a with MPD

According to Migliore *et al.* [2015], pleural chemoperfusion can increase the 1-year survival rate in patients with MPNs from 0.8% to 54.7% with MS 20 *vs.* 6 months in the control group. A meta-analysis of 20 articles devoted to this topic showed that this method allows increasing MS up to 27 months (45).

In 2015, Yamaguchi *et al.* performed a research in which patients with NSCLC and MPNs underwent induction CRT followed by surgery (pleural resection) and subsequent chemoperfusion with Cisplatin. The OS rate in 1, 3, and 5 years were 100.0%, 33.3% (95% CI: 2.5–64.1%) and 22.2% (95% CI: 0.0–49.4%), respectively (39). According to Arrieta *et al.* [2019], the median of progression-free survival in the similar research was 15.9 months, and the 5-year OS was 37.1% (1). By performing a technique described by Go *et al.* [2015], representing the combination of removal of the primary tumor with resection of the affected pleura, chemoperfusion with cisplatin and pleurodesis with the OK-432 medication, MS up to 18 months, with an overall 5-years survival rate of 22.2% were reported (28). Most authors have used systemic therapy in their studies, but the effect on long-term results did not receive wide coverage.

According to the literature, adjuvant chemotherapy/CRT in the absence of contraindications and sufficient functional reserves can increase 5-years survival rate in this category of patients. According to Yun, an improvement in 5-years survival rate is associated with the usage of adjuvant therapy (47.2% *vs.* 23.1%, P=0.01) (21). Other authors have showed similar results (11,18,25). In a majority of works, the biology of the tumor, the presence of driver mutations, and treatment with targeted drugs are not appropriately sanctified. Moreover, Shiba *et al.* in 2001 revealed a significant effect of the tumor proliferation index on the prognosis of patients after surgical treatment, and showed that low Ki-67 was an independent prognostic factor for better 5-years survival rate (28.6% with Ki-67 <10% *vs.* 4.1% with Ki-67 ≥10%, P<0.0001) (23). It should be taken into account that in most studies that showed improved survival rate in adenocarcinomas with pleural carcinomatosis, the targeted therapy was used (16,33). There is quite convincing evidence of a possible correlation between the EGFR mutation and the incidence of MPE (25,35). Moreover, the analysis of the tumor cell genome revealed a correlation of other activating mutations (KRAS, PIK3CA, BRAF, MET, EML4, ALK and RET) with the MPE frequency rate, which may affect the choice of treatment (5,35).

Authors from Taiwan Chi-Lu Chiang *et al.* have demonstrated that EGFR-TKI therapy can convincingly increase MS to 111.1–123.3 against 18.6–22.1 months (P<0.001). In patients with driver mutations, there is no advantage in the long-term results of the surgical stage of treatment, that's why, conducting molecular-targeted therapy in these patients may avoid surgical intervention. Surgical treatment provided better OS in patients with wild-type EGFR, or in patients with unknown EGFR status and without EGFR-TKI treatment (P=0.003) (25). The appearance of immunotherapy should be definitely heeded, due to the high expectations of it for treatment of NSCLC, especially in patients with stage IV NSCLC (46). In none of the researches of surgical treatment of MPD, the expression level of PD-L1was studied and so was not described the use of checkpoint inhibitors.

In most publications, 30-day mortality after the surgical stage was in the interval of 0.3–1.2% (16,20,28,31,34,39). Authors from France described a 16% intrahospital mortality in these patients (20). The frequency of postoperative complications according to the literature is 6.2–34% (16,20,21,36).

Significant prognostic factors

The study of the relationship of long-term results of treatment of patients with $M1a_{MPD}$ with MPNs, with various factors described above, allowed us to conclude that the long-term results and the choice of management for these patients are affected by: (I) age (P=0.001); (II) female gender (P<0.001); (III) N status (P<0.001); (IV) morphological structure (adenocarcinoma P<0.001) and the presence of driver mutations (P<0.001); (V) degree of pleural dissemination (P<0.001); (VI) the radicality of the resection R0-1 (P=0.045); (VII) ECOG status (P<0.001); (VIII) expression level of Ki-67 (P<0.001); (IX) tumor differentiation degree (P<0.001).

Conclusions

It should be noted that any of modern clinical guidelines do not recommend routinely performing radical

surgical interventions in patients with ipsilateral MPD. Nevertheless, there are continuing attempts to improve the long-term results of treatment of these patients using the full surgical stage with a radical, conditionally radical or palliative purpose.

After thorough study of available literature data we can summarize that at present most authors agree that it is impossible to make reasonable, unambiguous conclusions about the feasibility, effectiveness, safety and optimal volumes of surgical interventions in this category of patients. Particularly all authors note the need to conduct urgent randomized controlled trials taking into account the alleged high potential to use the modern combined and complex treatment methods. It is obvious that an individual approach is necessary then choosing the management for patients with NSCLC and malignant tumor nodules. Along the same lines, we may barely in mind the most significant prognostic and predictive factors, such as: one-sided nature of pleural involvement, local tumor spread (lack of signs of hematogenous and lymphogenous metastasis, N-status), gender, age, sufficient functional reserves, morphological structure, the presence of driver mutations, the risk of pneumonectomy and the occurrence of postoperative complications.

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