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Surgical Treatment in Oligometastatic Lung Cancer

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ABSTRACT
Lung cancer is the primary cause of cancer-related deaths across the world. About four fifths of lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC), and diagnosis can be established only at the advanced stage of disease in 70% of these patients. Among NSCLC patients, who have a maximum of five metastatic lesions which are suitable for radical therapy with local treatment (surgical resection, radiotherapy or both) to achieve long-term survival are considered to be at the oligometastatic disease stage. In this study, we examined the surgical treatment practices and their results in oligometastatic NSCLC patients. Medical literature in the thoracic surgery and oncology network was reviewed, and studies, cases, and meta-analysis studies that included surgical treatment practices in oligometastatic small cell lung cancer treatment and their results were examined. A discussion was made by also analyzing the survival data in light of the literature studies and available guidelines. The most common treatment option in oligometastatic NSCLC patients is surgical metastasectomy. The use of this method especially in patients with metastasis isolated in the contralateral lung, brain and adrenal glands has been widely accepted. For patients that are classified as M1b stage in the international guidelines, aggressive local treatment is recommended on metastatic and primary areas. If patients with multiple metastatic regions have between two to five independent metastases, then systemic chemotherapy must be applied. Long-term disease control and even improvement is possible in these patients with ablative treatment of the primary tumor and metastases.
Keywords: Lung cancer, oligometastasis, surgery

INTRODUCTION

Lung cancer is the primary cause of cancer-related deaths across the world. According to EUCAN (European Countries), 409,911 new lung cancer cases were diagnosed in Europe in 2012, with almost 80% being non-small cell lung cancer (NSCLC) cases (1). In about 70% of the patients with NSCLC, the disease is at the advanced stage when diagnosed, and these patients are not considered eligible for curative treatment. Traditionally, all metastatic NSCLC patients have been grouped under a single category (Stage IV) using TNM classification under the M identifier.

Electronic and printed literature was used when planning this review. In Internet searches performed by using the key words "non-small cell lung cancer", "oligometastasis" and "surgical treatment", studies were found on various databases. Among these studies, the research studies, collected works and meta-analyses including patients at a stage where surgical treatment can be applied were selected.

CLINICAL AND RESEARCH CONSEQUENCES

Non-small cell lung cancer and the Oligometastatic Disease Stage
In the eighth version of the lung cancer TNM classification, the M category of the International Association for the Study of Lung Cancer (IASLC)'s staging was revised. It was recommended to continue to group the patients with pleural/pericardial effusion, contralateral/bilateral lung nodules, contralateral/bilateral pleural nodules, or the combination of these parameters under the M1a category. However, single metastatic lesion in a single distant organ was advised to be assigned to the M1b category. It was stated that patients who had multiple lesions in an organ or multiple lesions in multiple organs must be re-classified as M1c category. Thus, the first step was taken towards the having a definition for a reasonable oligometastatic disease stage in NSCLC in the future (2).

The concept of oligometastatic condition was first used by Hellman and Weichselbaum (3) in 1995, and refers to the group consisting of patients with a limited number of metastases in number and location. This stage is an intermediate condition between local limited and disseminated metastatic cancers.

The number of metastases for it to be considered as an oligometastatic condition varies. Such variance might be from a single metastatic lesion in a single organ to multiple metastatic lesions in multiple organs (4). However, the most commonly accepted criterion for it to be considered oligometastatic is the presence of a maximum of five metastatic lesions, which are suitable for radical therapy with local treatment (surgical resection, radiotherapy or both) to achieve long-term survival.

The most important prognostic factor for oligometastatic disease is the condition of the primary tumor. Patients with uncontrollable primary tumor seem to have a worse prognosis compared to patients with primary tumors that are under control.

Oligometastases are seen relatively commonly. Single metastasis was reported in 7% of the metastatic lung cancer cases. In a study, Parikh et al. (4), performed an analysis on 725 patients with Stage IV NSCLC, and 186 (26%) patients were found to be at the oligometastatic disease stage (≤5 lesions) during the diagnosis. The disease was limited to a single lung in 81% of cases, and a single metastatic lesion was found in 51% of the patients. Compared with patients who had multiple lesions, patients with

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oligometastatic disease were found to have a longer median overall survival (OS) (17 months vs. 14 months).

The International Association for the Study of Lung Cancer (IASLC) found that 225 (22%) of 1025 metastatic patients with NSCLC had a single metastatic lesion. It also stated that there were prognostic differences between patients with multiple metastatic lesions in a single organ and those with multiple lesions in multiple organs (2). The most common location of the single lesion in NSCLC is the bone tissue, followed by the brain, adrenal glands and liver.

The most common option selected as treatment in oligometastatic condition is surgical metastasectomy (55%) (5). However, use of less invasive, ablative techniques such as stereotactic radiosurgery (SRC) has increased remarkably during recent years.

If there is metastasis isolated in contralateral lung, brain and adrenal glands in NSCLC patients, metastasectomy is performed. Sometimes, patients with metastasis isolated in other sites, such as bone, liver, etc. have also been treated with surgery, however the number reported in the literature is quite low (6). In a retrospective analysis of 99 NSCLC patients with synchronized single metastasis treated with curative surgery (primary tumor surgery and metastasectomy), 5-year OS was found to be 38% (7). Good prognostic factors for OS are a lack of mediastinal node involvement (the median OS in patients with and without involvement was 40 and 10 months, respectively, p = 0.015), limitation of metastases only to lungs, and the absence of non-lung pulmonary metastases (5-year OS 48.5% vs. 23.6%, respectively) (7).

In a study by Ashworth et al. (8) performed in 2014, the metastasis rates in NSCLC patients were found to be as specified in the below Table 1.

Oligometastatic Lesions in the Brain and Surgery

Lung cancer is the main cause of brain metastasis in cancer patients, and constitutes the primary focus in 63% of all patients with brain metastasis (9, 10). Such metastases are seen in 30-50% of NSCLC patients and they are the phenomena that can emerge in the early period during the natural course (11). In the past, brain metastases were associated with weak prognosis. Among these patients, the treatment of both the primary tumor and brain metastases for aggressive purposes is recommended in patients with a good Karnofsky Performance Scale (KPS) score who can undergo resection or receive radiotherapy in both areas.

Table 1. Metastasis rates on organs in NSCLC patients Ashworth et al. (8)

Oligometastasis Site	N (%)
Brain	269 (36)
Lung	254 (34)
Adrenal Gland	98 (13)
Bone	64 (9)
Liver	18 (2)
Lymph Node	18 (2)
Other	59 (8)

In NSCLC patients with synchronous brain metastases who received radical therapy for metastases and primary tumors, the median OS was 5.2-64.9 months and 1-year OS was 22-95% (6). When radical therapy was not performed on the primary tumor, survival was observed to decrease. Arrieta et al. (11) examined the results of the treatment of primary tumor in the breast and metastasis in the brain with concurrent radiotherapy in 30 NSCLC patients who had brain metastasis during diagnosis and had no metastasis findings in other areas. All patients were in the RPA class II, and there was N2-3 node involvement in 47% of them. Median survival without progression and OS were 8.4 and 31.8 months, respectively. The 1 and 2-year OS rates were 71.1% and 60.2%, respectively. Three-year OS was found to be significantly superior in patients with N0-N1 stage of the disease, compared to those with N2-N3 stage of the disease (60% vs. 24%, respectively; p=0.038)

Sakamoto et al. (12) reported that metachronous brain metastasis developed in 3.2% of NSCLC patients after surgery for primary tumor. Post-relapse survival results were not very good.

In a recent study, median survival time after lung resection was found to be 25 months for these patients and the OS rate was 79.1%, 38.6% and 22% in 1 year, 3 years and 5 years, respectively. Survival duration was found to be only 11 months after the treatment of brain metastasis (13).

Oligometastatic Lesions in the Adrenal Glands and Surgery

The adrenal gland is one of the areas where metastasis is common in NSCLC. Even though adrenal gland metastases are generally seen in patients with metastasis in other distant regions, metastatic NSCLC has been reported to be solitary adrenal gland metastasis in 4-20% of cases. The effectiveness of computerized tomography (CT) in imaging the adrenal involvement is limited, because adrenal growth is a benign lesion in significant portion of cases. Magnetic resonance (MR) and positron emission tomography (PET) can be helpful in distinguishing incidental the benign adenoma from the adrenal metastases. However, as the treatment and prognosis of the patient depend on the benign or malignant nature of the lesion, histologic confirmation is recommended.

Traditionally, adrenalectomy (firstly open surgery, and laparoscopic in the later period) has been the type of therapy used in treatment of adrenal metastases; however, the use of stereotactic body radiotherapy (SBRT) for treatment purposes has increased remarkably during recent years.

Recently, in a study by Barone et al. (14) performed on 2298 patients with NSCLC, adrenal metastasis was reported in 1.6% "37" of the patients. 13.5% "5" of these patients were reported to have bilateral adrenal metastasis. When 37 patients with adrenal metastasis were examined in terms of OS, and cases with bilateral metastasis (11 months), ipsilateral (27 months) and contralateral metastasis (29 months) were compared, OS was shown to be significantly worse in patients with bilateral metastasis. In this study, adrenalectomy was performed on 18 of 37 patients with adrenal metastasis. The median overall life expectancy of these patients who underwent adrenalectomy was 31 months (3-year OS 48% and 5-year OS 29.3%) while the median OS was found to be 13 months in medical treatment areas only.

Oligometastatic Lesions in the Liver and Surgery

Aggressive treatment for the liver metastasis of colorectal cancer is a recognized method, and has been shown to increase OS (a 5-year OS rate of 30-60%) (15, 16). However, NSCLC-related liver metastases are more rare cases compared to other regions, and cases in which the single metastasis area is the liver are particularly rare. When metastases on the liver were compared to metastases of other areas such as the brain or bone, they were shown to be associated with worse survival (17, 18).

In most of the NSCLC patients with liver metastasis, surgery is contraindicated due to the number and distribution of extrahepatic diseases. Information about the effectiveness of liver resections for metastases in NSCLC is limited, with a low number of cases published, and therefore an apparent bias is likely to occur (6). However, long-term survival was found to be unexpectedly high in patients who underwent liver resection in these studies (>60 months in some cases) (19-22). An OS rate that was higher than expected in these patients probably arose from the failure to make the patient selection with care, and therefore it did not reflect the overall NSCLC population with liver metastasis.

Oligometastatic Lesions in the Lungs and Surgery

The median survival duration for patients with intrapulmonary metastatic disease (56 months, 95% CI, 37.2-74.8; p=0.001) was found to be better compared to the median survival duration expected for patients with extrapulmonary metastasis (18 months; 95 CI, 8.5-27.5) (7). Metastases are more often seen in the lungs on the same side (23). When synchronous single contralateral lesion is diagnosed, bilateral staged lobectomy is performed in most patients, and long-term survival is achieved (5-year survival duration: 45%). This therapeutic strategy is suggested as the likelihood of the presence of two independent primary tumors is high (23, 24).

In a study performed by Okubo et al. (25) in Japan in 2009 on 76 patients with NSCLC diagnosis and pulmonary metastasis that was resected, 5-year survival was 79.6% and 41.6% for patients with synchronous metastasis on the same or different lobe, respectively. In patients with relapsing pulmonary metastases, 5-year survival was found to be 34.8%. The presence of multiple pulmonary metastasis and mediastinal node metastasis in patients were reported to be other important factors affecting survival. No significant difference was observed between ipsilateral and contralateral metastases in terms of OS.

Similarly, in a study where surgical resection was performed for multiple lung cancer with synchronous ipsilateral (n=27) or contralateral (n=28) metastasis, no significant difference was found between the two groups in terms of 5-year survival (27% vs. 43%). Mediastinal node involvement was reported to be a negative prognostic factor for survival. Five-year survival was found to be 57% and 0% for patients without lymph node metastasis (n=25) and with lymph node metastasis (n=18), respectively (26).

In another retrospective analysis, including 66 patients for whom full resection was performed on synchronous pulmonary malignant lesions, median OS was 25.4 months and five-year survival rate was 38% (27).

Based on these findings, as survival was shown to be lower in patients that were thought to have Stage IV disease and treated with palliative systemic treatment, consideration of surgical resection was recommended even in patients with contralateral lung oligometastasis who did not have lymph node involvement or distant metastasis findings, as suggested by a pre-operative comprehensive study (28). Similarly, 2-year OS was 33-84%, and local control was 51-96% in patients with lung metastasis that were treated with SBRT (6).

Oligometastatic Lesions in the Parietal Pleura and Surgery

Pleural involvement is seen at a rate of 8-15% in lung cancer (29). If there is pleural effusion in patients with suspected lung cancer, firstly thoracentesis and malignant effusion must be distinguished. Such distinction is important in terms of staging of the disease, and might change the treatment pursued in some patients (30).

There are varying views in the literature about the role of surgery in these patients, especially the effects of extrapleural pneumonectomy (EPP), on the local disease control and survival of patients. Some studies on EPP for NSCLC patients have claimed that surgery is not beneficial for survival in patients who have malignant pleural effusion and/or pleural nodules (31, 32).

However, in the study performed by Isik et al. (33) between January 2009 and December 2011 on 19 patients with metastatic malignant pleural effusion (MPE), patients were treated with localized hyperthermic perfusion chemotherapy (HIPEC) after surgical interventions, such as pleurectomy/decortication and/or lung resection (Group 1). The control group of this study consisted of patients who underwent talc pleurodesis (Group 2), video-assisted thoracoscopic surgery (VATS) in the treatment of metastatic MPE, and pleurectomy/decortication (Group 3) between June 2007 and June 2008. Patients in the control group received systemic chemotherapy for the treatment of metastatic MPEs following these treatments. The median survival lengths in Group 1, 2 and 3 were 15.4, 6, and 8 months, respectively. One-year survival was found to be at a rate of 54.7%, 0.6% and 0.8% in group 1, 2 and 3, respectively. Operative mortality was not observed in this study. As a result, it was reported that HIPEC treatment combined with cytoreductive surgery appeared to be a promising treatment option for patients with metastatic MPE.

CONCLUSION

Patients with oligometastatic status having a limited number of lesions (generally between 1-5) have a better prognosis compared to those with polimetastatic disease, despite the heterogeneity in its definition, and the retrospective methodology used in many studies. Long-term disease control and even improvement can be achieved in these patients with ablative treatment of the primary tumor and metastases. In many lung cancer guidelines, there are treatment recommendations for this patient sub-group. The guidelines of the European Society for Medical Oncology recommend systemic therapy and radical local therapy (high dose radiotherapy or surgery) for Stage IV patients with one to three metastases in the diagnosis. Additionally, the NCCN Guidelines 3.2017 suggest that aggressive local therapies on metastatic and primary areas for patients classified as M1b Stage (a single metastatic area only) under the 8th version of the lung cancer staging system recommended by IASLC. If patients with multiple metastatic regions have between 2-5 independent metastases, then systemic therapy must be applied.

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