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Review Article

Current surgical management of extrapulmonary oligometastatic non-small cell lung carcinoma

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ABSTRACT

Lung cancer is one of the leading cause of mortality around the world, and it is widely known that survival is limited in metastatic lung carcinoma cases. However, in oligometastatic, non-small cell lung carcinoma cases, surgical excision of both the primary tumor and the metastatic site may yield a survival advantage in selected cases. In non-small cell lung carcinoma cases, especially after metastasectomy of brain and adrenal gland metastasis, studies in which survival advantage is reported are common in the literature, and metastasectomy is the treatment method applied to selected patient groups in brain and adrenal gland metastases. In surgical treatment of extra-cranial and extra-adrenal oligometastasis, on the other hand, there are several cases in which morbidity-free survival rates were reported after successful management. In this report, the surgical treatment results were evaluated, and the contribution of treatment methods to survival rates were investigated in extrapulmonary oligometastatic non-small cell lung carcinoma cases receiving surgical excision.

Key Words: extrapulmonary, oligometastasis, lung cancer, brain, adrenal gland, non-small cell

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Introduction

Lung cancer is a worldwide problem and the leading cause of cancer-related mortality around the world [1]. It is also the leading cause of death from cancer in both genders, accounting for approximately 26% of all cancer deaths in the United States [2]. Similarly, in Turkey, the most frequently diagnosed carcinoma is lung cancer, as well as the leading cause of cancer-related mortality [3]. Smoking is the leading prognostic factor of lung cancer; however, genetics also plays a key role [1,4].

Lung cancer consists of two main subtypes, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and the latter accounts for approximately 85% of the diagnosed lung malignancies [2,5]. Non-small cell lung cancer has several subtypes such as adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma. In addition, adenocarcinoma is the most common subtype accounting for about 40% of all NSCLC cases, followed by squamous-cell carcinoma, which accounts for about 25-30%. The gold standard treatment for NSCLC is anatomic pulmonary resection with mediastinal lymph node dissection; and complete surgical resection with en-block excision is the goal of the surgery [6].

Although the gold standard for NSCLC is en-block surgical excision, unfortunately not every patient is detected in the appropriate stage for surgery. Most of the cases are diagnosed at advanced stages, and the number of those diagnosed with metastasis is not few. At diagnosis, approximately 70% of NSCLC cases present at a locally invasive or metastatic stage [7]. The metastasis of NSCLC generally diagnosed in the brain, followed by liver, adrenal glands, and bones; however, it is also possible to observe its metastasis in almost all of the tissues of the body aside from the organs.

Metastasis is the secondary implant of a malign tumor in tissues that are distant from the primary tumor [8]. Metastasis includes several biochemical events in which biology and mechanisms are complex. Metastasis consists of steps like angiogenesis, invasion stages consisting four different phases (detachment, attachment, proteolysis, and cell migration), intra vascular phase, and extravasation [9]. In addition, metastatic pathways are classified as lymphatic metastasis, hematologic metastasis, and dropped metastasis [8]. At every stage of metastasis, several numbers of cytokines, chemokines, proteolytic enzymes, metalloproteinases and free radicals play roles [10-13]. In general, it is known that as the tumor diameter and lymphatic invasion increases, the possibility of metastasis increases. However, it was reported in some previous studies that even the tumors with low T and N status caused distant metastasis in series in which metastasectomy was applied. In the series of Mordant et al., it was reported that the diameter of the tumor was below 3 cm in 40% of the NSCLC cases that had distant metastasis and to which metastasectomy was applied; whereas only in 6% of cases, the diameter of the tumor was greater than 7 cm [14]. Similarly, it is also known that the tumors which N status is low may be metastatic. In the study by Plönes et al., 56 patients with distant metastasis were evaluated; 30 patients (53.6%) had N0 disease, 18 (32.1%) patients had N2, and one patient (1.8%) had N3 disease [15]. In another study by Mordant et al., 49% of metastatic NSCLC patients had N0 disease, and 33% of the patients had N2 disease [14].

In diagnosing metastasis, the contribution of radiodiagnostic methods is significant, and the definite diagnosis is established in a pathologic examination. According to the doubted metastasis site, one or more of the radiologic tools such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), various scintigraphy and positron emission tomography (PET/CT) contribute to the diagnosis. Especially, a high maximum standard uptake value (SUVmax) in the doubted area in PET/CT contributes to the metastasis in cancer patients [16-18]. In detecting brain metastasis, MRI is the first radiodiagnostic tool, and must definitely be performed in routine metastasis screening of the patients with lung cancer [19]. In evaluating the bone metastasis, the superiority of whole body bone scintigraphy to PET/CT is on debate [20-22]. Although radiodiagnostic methods are guiding, the definite diagnosis of extrapulmonary metastasis is made with pathological examination. In this review, the purpose is to evaluate the contribution of the treatment of metastasis according to the implanted organ in extrapulmonary, oligometastatic NSCLC cases to overall survival, local disease-free and distant disease-free survival rates.

For this purpose, brain, adrenal gland, skeleton system (bone, muscle), and other organ involvements are examined under separate headings.

The management of extrapulmonary oligometastatic NSCLC

a. General consideration

According to the TNM International Staging System for NSCLC, 8th classification, M1b represents a single extrathoracic metastasis in a single organ, M1c represents multiple extrathoracic metastasis in one or several organs [23]. The principle treatment strategy for NSCLC patients with distant metastasis is chemotherapy as a systemic treatment [24]. Local treatment strategies, such as radiotherapy, are generally used for palliative purpose to relief cancer-related symptoms. Surgical excision of metastatic site is rarely indicated. However, survival benefit of surgical excision is controversial. In a study by Mordant et al., 94 patients with distant metastasis were enrolled between 1983-2006; brain metastasis was the most common (n = 57; 60.6%), followed by bone (n = 14, 14.9%), adrenal gland (n = 12, 12.8%), skin (n = 6, 6.4%), and liver (n = 5, 5.3%) metastasis [14]. The site of the bone metastasis was rib in seven patients, femur in two patients, vertebra in two patients, and scapula, skull, foot big toe in one each [14]. All patients underwent surgical excision for the primary tumor site, lobectomy was the common preferred type of surgery (n = 65, 69.2%) [14]. Sixty-nine (73%) metastasis was excised surgically, and in-hospital mortality reported as 7% [14]. When in-hospital mortality was excluded, 5-year survival rate was calculated as 16% with a median of 13 months [14]. According to Mordant et al., the resection of hepatic or bone metastasis was never associated with long-term survival, even when the bone metastasis was on the rib [14]. The resection of solitary cutaneous metastasis was associated with long-term survival; solitary synchronous brain and adrenal metastasis were associated with 5-year survival rates of 12 and 22%, respectively [14]. In another study by Plönes et al, 46 patients (82.1%) suffered from brain metastasis, four patients (7.1%) had adrenal gland metastasis, four patients had soft tissue metastasis (7.1%), and two patients (3.7%) had bone metastasis [15]. All patients underwent anatomical surgical excision for the primary tumor site; and for the metastasis, the resection was macroscopically and microscopically completed in all cases [15]. Analyzing the influence of metastatic site, authors found a median overall survival of 23 months for patients with soft tissue metastasis, 16 months for patients with brain metastasis, nine months for patients with adrenal gland metastasis, and only four months for patients with bone metastasis [15]. The multivariate analysis revealed that bone metastasis was the only significant parameter influencing median overall survival (p □ 0.001) [15]. In another study by Congedo et al., 53 patients with oligometastatic NSCLC were examined, and the most commonly involved organ was brain (n = 39, 73.6%), followed by adrenal gland (n = 7, 13.2%), bone (n = 3, 5.7%) and vertebrae (n = 3, 5.7%) metastasis [25]. Distant disease was completely resected in 42 (79.2%) of patients, and other patients were treated with chemotherapy and/or radiotherapy [25]. In this study, median follow-up was 28 months and 1- and 5-year survivals were 73.1% and 24%, respectively [25]. Median overall survival, local disease-free survival, and distant disease-free survival was calculated as 19 months, 72 months, and 12 months; respectively by using the Kaplan-Meier method [25].

In other series in which less number of cases included, similar survival rates were reported. In a study by Yamaguchi et al, 23 consecutive synchronous, M1b-c, NSCLC patients were enrolled; all patients underwent curative anatomical pulmonary resection [24]. Brain metastasis was the most common (n = 13, 56.5%) followed by bone (n = 3, 13.0%). For the treatment of extrapulmonary metastasis, surgical resection was commonly preferred management method (n = 13, 56.5%) [24]. Seven patients with brain metastasis were managed without surgical interventions (whole brain radiotherapy (WBRT) and stereotactic radio-surgery (SRS)), two patients with bone metastasis were managed with radiotherapy, and one liver metastasis was managed with chemotherapy [24]. During follow-up, 17 patients experienced recurrence; three patients (17.6%) had local recurrence, 13 patients (76.5%) had distant recurrence, and one patient (5.9%) had both [24]. The median progression-free survival and 3- and 5-year progression-free survival rates in the 23 patients were 11.8 months, 21.7%, and 14.5%, respectively [24]. The median progression-free survival for patients with brain metastasis was 12.5 months and for those patients with metastasis outside the brain was 9.2 months, without statistical significance [24].

Finally, Karagkiouzis et al examined 12 extrapulmonary oligometastatic patients with NSCLC; adrenal metastasis was common (n = 6, 50%) followed by brain metastasis (n = 3, 25%), thoracic wall metastasis (n = 2, 16.7%), and diaphragm (n = 1, 8.3%) [26]. All patients underwent combined resections of the primary lung tumor and solitary hematogenous metastasis; subsequently all patients received adjuvant chemotherapy, and the median follow-up period was 13.5 months [26]. The median survival was 24.1 months, survival rates at 1- and 5-years were 73%, and 39%, respectively [26].

Although we review the literature data on extrapulmonary oligometastatic NSCLC cases we wish to include the survival study results of ipsilateral or contralateral lung oligometastasis. Tönnies et al. compared the survival rates in NSCLC cases with ipsilateral or contralateral lung oligometastasis to extrapulmonary oligometastasis [27]. It was reported that all of the 99 patients whom were included in the study received surgery both for primer lung cancer and for solitary metastasis [27]. The organ in which solitary metastasis was most commonly detected in ipsilateral or contralateral lung (n = 57, 57.6%), followed by brain (n = 21, 21.2%), adrenal gland (n = 10, 10.1%), bone (n =4, 4.0%), liver (n = 2, 2.0%), and other organs (n = 5, 5.0%) [27]. Ipsilobar metastasis was excluded from the study; and anatomical lung resection with mediastinal lymph node dissection was the common surgical procedure for the primary tumor site [27]. As the survival results, Tönnies et al. reported a 5-year survival rate of 48.5% in the patients with a solitary metastasis in the ipsilateral or contralateral lung; whereas the rate was 23.6% in patients with extrapulmonary metastasis [27].

So far, the studies in which primary lung cancer and related oligometastasis were treated with surgical procedures have been mentioned. However, it was reported in the study by Griffioen et al, surgery for lung cancer was applied only in nine of 61 lung cancer patients, and none of the 39 patients in the series of Ruysscher et al. received surgical procedures for lung cancer [28,29]. In these series, although different protocols were applied for the treatment of metastasis, the overall survival, disease-free survival, 1- and 5-year survival rates were reported to be more limited [28,29].

b. The management of brain oligometastasis of NSCLC

The most frequent organ metastasis of lung cancer is in the brain; and in most of the series, brain metastasis ranks the first among extrapulmonary metastasis [14,15,24-30]. For this reason, every patient with pathologically proven lung carcinoma and for whom a pulmonary resection is planned should be examined in terms of a possible brain metastasis .At present, the best tool for the diagnosis of brain lesions is Magnetic Resonance Imaging (MRI) [19,31]. Computed Tomography of the brain underestimates the magnitude of intracranial metastases, and accuracy is poorer than MRI [19]. The treatment modality is on debate in NSCLC cases with brain oligometastasis, and the clinical reports published in this field may be guiding for us in the efficiency of the treatment methods and their effectiveness. The review of literature is demonstrated that different treatment approaches were applied for different case groups by several authors. Whole brain radiotherapy (WBRT), cranial metastasectomy, and stereotactic radio-surgery (SRS) or combinations of these modalities are the treatment options for brain metastasis. In addition, there are different groups of patients with brain metastasis like those with a brain metastasis synchronous with the primary tumor or those with brain metastasis that develops months or years after successful management of the primary tumor.

In a study by Antuna et al., 71 patients with brain metastasis from NSCLC underwent surgical metastasectomy, and 80.3% of cases had solitary brain metastasis [32]. Complete resection was achieved in 90.1% of cases; however, 15.4% of the cases had complications such as intracranial hematoma, neurologic deficits, hydrocephalus, and pneumothorax [32]. The average survival after brain surgery was 20.4 months; the survival rate was 45.1% in one year, 22.5% in two years, 14.1% in three years, and 8.5% in four years [32]. Antuna et al. did not find any significant difference to affect survival rates such as size or number of the metastases [32]. In another study by Yuksel et al., 28 patients with solitary brain metastasis at the time of diagnosis underwent surgical resection to sites, brain metastasectomy and primary lung tumor [33]. Yuksel et al. followed-up the patients for 23.6 months and reported the overall survival rates were 79% in one year, 42% in two years, and 8% in five years; these survival rates were better than those reported by Antuna et al. [33]. Yuksel et al concluded NSCLC with resectable solitary cranial metastasis, low locoregional stage, without mediastinal lymph node involvement, without any extrathoracic spread would mostly benefit from consecutive complete resection of both tumors, and were supposed to have a better survival [33].

Brain metastasectomy is also an efficient method in the treatment of recurrent metastases for NSCLC. In a study by Bae et al., 86 patients had post-operative brain metastasis as the initial recurrence after complete pulmonary resection [34]. The median follow-up time after the initial lung resection was 24.0 months (range: 2-126 months); median overall post-recurrence survival was 11 months [34]. Seventy-nine of the patients (91.9%) were symptomatic at the time of recurrence, 50 patients (58.1%) had multiple metastases, and 62 (72.1%) patients received systemic chemotherapy for brain metastasis [34]. Surgical metastasectomy was preformed to 17 of the patients (19.8%); however, the rest of the patients were treated with either SRS or WBRT or combination of treatment modalities [34]. An initial lung lesion of adenocarcinoma, non-pneumonectomy patients, a disease-free interval of longer than 10 months from the initial lung resection, solitary brain metastasis, and a size of less than 3 cm for the brain lesion, were reported as positive factors for post-recurrence survive [34].

With the increasing experience in Stereotactic Radio-Surgery applications, it was reported with increasing frequency and success rates in brain metastasis [35-38]. In a study by Harris et al., 126 patients with cranial metastasis due to several tumors were treated with SRS and the most common (50%) tumor histology was NSCLC, followed by breast cancer (12.7%) [36]. However, patients with breast cancer had the longest median survival time of 9.2 months; the median overall survival time for all patients was 5.8 months [36]. Similarly, Abacioglu et al. reported series of 100 patients with brain metastasis from NSCLC; 78 of the patients were received WBRT prior to or after gamma knife radio-surgery, 26 patients had surgical removal of metastasis [35]. Local tumor control was achieved in 95% of the lesions and median overall survival for all patients was 9 months from the date of radio-surgery and 14 months from the diagnosis of brain metastasis [35]. Bai et al. compared the survival times between the patients underwent brain surgery as primary treatment and the patients received SRS [38]. Of 76 patients, 54 patients (71.1%) received SRS, 22 patients (28.9%) underwent brain surgery [38]. The overall survival for patients treated with SRS and brain surgery were 12.6 months and 16.4 months, respectively (p=0.08) [38]. In this series, 21 patients (27.7%) underwent primary tumor resection; however, they did not experience a significantly improved overall survival compared to those who did not undergo lung resection. The overall survive of the patients who underwent lung resection was 16.4 months compared to those who did not undergo lung resection was 11.9 months (p=0.46) [38].

On the other hand, Patchell et al. recommended whole brain radiotherapy after a complete metastasis surgery to avoid recurrences [39]. In a study by Patchell et al., 95 patients who had single metastasis to the brain that were treated with complete surgical resection were enrolled; and the patients were randomly assigned to treatment with post-operative WBRT (n = 49) or no further treatment group (n = 46) with median follow-up of 48 and 43 weeks, respectively [39]. The recurrence of tumor anywhere in the brain was less frequent in the radiotherapy group than in the observation group [39]. Only 9 patients (18%) of 49 patients in the radiotherapy group had recurrence compared to 32 patients (70%) of 46 patients in the observation group (p □ 0.001) [39]. Postoperative radiotherapy prevented brain recurrence at the site of the original metastasis and at other sites in the brain (p □ 0.001) [39]. Similarly, Chung et al. also advised WBRT after resection of brain oligometastasis due to NSCLC [40]. According to Chung et al. WBRT seems to enhance intracranial control [40]. However, according to the series of Abacioglu et al., opposite to this option, an addition of WBRT did not have any effect on overall survival [35].

c. The management of adrenal gland oligometastasis of NSCLC

The adrenal gland is a common site of metastasis due to the presence of multiple pathways of blood supply. Adrenal metastasis is often confined with the adrenal capsule, offering more opportunities to obtain en-block adrenalectomy. The histories, symptoms, and diagnostic methods of the NSCLC patients with brain oligometastasis may be different from the NSCLC patients with adrenal oligometastasis. A significant rate of the metastatic NSCLC cases may be diagnosed with brain metastasis, and these cases are directed to Thoracic Surgery Clinics after brain metastasectomy [8]. However, adrenal metastasis is generally detected accidentally during distant metastasis screening, and the cases diagnosed NSCLC after pathological examination of the adrenalectomy material is uncommon [8]. The value of adrenal metastasectomy for oligometastatic NSCLC cases; which patient group will benefit from metastasectomy; the contribution of the surgery to survive are still on debate in the literature.

In a study by Raz et al., 37 patients with isolated adrenal metastasis from NSCLC were identified; and 20 patients (54.1%) underwent complete adrenalectomy and lung resection compared with non-surgical group [41]. None of the non-surgical group patients had resection of their primary lung cancer. Raz et al. tried to determine the reason why adrenal resection was not part of the treatment for the group of patients managed non-operatively [41]. Patients did not undergo adrenalectomy owing to suspicion of N2 disease, medical comorbidities, or patient preference [41]. The five-year overall survival was 34% for patients treated operatively and 0% for patients treated non-operatively (p □ 0.05) [41]. Among patients treated with adrenalectomy, patients with ipsilateral metastasis had a 5-year survival of 83% compared with 0% for patients with contralateral metastasis (p □ 0.05) [41]. Patients without mediastinal nodal disease had a 5-year survival of 52% compared with 0% for patients with mediastinal nodal disease (p □ 0.05) [41]. Raz et al. concluded surgical resection of isolated adrenal metastasis from NSCLC provides a survival benefit in selected cases compared with non-operative management [41].

In a study by Ma et al., 75 patients with adrenal metastasis underwent adrenalectomy, the most common primary tumor was renal cell carcinoma (n = 26), followed by NSCLC (n = 23), and hepatocellular carcinoma (n = 12) [42]. The 5-year survival rate was 6.1%, the local recurrence rate was 5.3%, and the median survival was 24 months [42]. Ma et al. compared the median estimated survival of patients who underwent adrenalectomy to those who did not undergo any operations for adrenal metastasis and to whom adjuvant therapies were carried out [42]. The median estimated survival of the non-operation group and open operation group were nine months and 22 months, respectively [42]. Patients who suffered metastasis from renal cell carcinoma had the most favorable outcome (median survival was 36 months), whereas, patients with NSCLC was the worst group (median survival was 13 months) [42]. Although the contribution of adrenalectomy to survive was demonstrated in various studies, there are some studies claiming this process does not have any contribution to survive in oligometastatic NSCLC cases. According to Huang et al. adrenalectomy does not improve survival rates of patients with solitary adrenal metastasis in NSCLC [43]. Huang et al. identified 22 NSCLC patients with solitary adrenal metastasis; 10 of these patients had adrenalectomy, and 12 were treated by non-surgically [43]. The median survival was 11 months and 1-year survival rate was 51.4% for all 22 patients [43]. There was no significant survival difference between patients who underwent primary and metastasis resection and those treated conservatively [43]. Moreno et al. reported adrenal metastasectomy for oligometastatic NSCLC had lower survive rates when compared to the metastasectomy applied to other tumors, especially for renal cell carcinoma [44]. Moreno et al. studied adrenalectomy for solid tumor metastasis of several tumors; NSCLC was the most frequent tumor type (n = 148, 46.7%), followed by colorectal carcinoma (n = 43, 13.6%), renal cell carcinoma (n = 37, 11.7%), breast cancer (n = 11, 3.5%), and melanoma (n = 11, 3.5%) [44]. Adrenal metastasis were synchronous in 73 patients (23.0%), isolated adrenal metastasis occurred in 234 patients (73.9%) [44]. Patients with renal cell carcinoma showed a median survival of 84 months, patients with colorectal carcinoma showed a median survival of 29 months, and patients with NSCLC showed a median survival of 26 months (p □ 0.05) [44]. Also, patients with metachronous adrenal metastatic disease showed a median survival of 30 months compared with 23 months in patients with synchronous adrenal metastatic disease (p □ 0.05) [44]. Howell et al., on the other hand, reported shorter median survival rates for the NSCLC cases to whom adrenalectomy was performed [45]. In the series of Howell et al., the median survival rate was 17 months in NSCLC cases with adrenal metastasectomy (n = 31, 50%), and the median survival rate was 47 months in the group which received adrenalectomy for other carcinomas (n= 31, 50%) (p □ 0.05) [45]. However, there are some other studies reporting longer median survival rates when compared with these series. Solaini et al. demonstrated the results of 37 adrenalectomies in 34 patients, patients with NSCLC (n = 15) had a median survival of 63 months and disease-free survival of 35 months [46]. According to Solaini et al., the concurrent resection of the adrenal metastasis with the primary tumor was the only factor influencing disease-free survive [46].

Laparoscopic adrenalectomy surgery is one of the methods performed frequently in the surgical excision of adrenal metastases. Tonyali et al. examined survival analyses following laparoscopic adrenalectomy for solitary metastasis of lung cancer [47]. In this series, 13 patients underwent 15 laparoscopic adrenalectomy, and the mean estimated survival in the patients with metachronous adrenal metastasis was lower than in those with synchronous adrenal metastasis (33.1 ± 5.4 vs. 33.2 ± 7.5 months, respectively) [47]. The estimated survival in the patients with contralateral metastasis was higher than those with ipsilateral metastasis (43.7 ± 7.6 vs. 24.1 ± 4.8 months, respectively) [47]. In total, ten patients had NSCLC and three had SCLC; and the estimated survival in the patients with NSCLC was higher than in those with SCLC (33.9 ± 5.7 vs. 24 ± 4.2 moths, respectively) [47]. None of the differences were significant; and the estimated overall survival was 33.4 ± 5.2 months [47]. Beside those studies, some other series in which small groups of patients were evaluated, also offers adrenalectomy in selected NSCLC patients who have good performance status and with minimal local nodal involvement from primary tumor [48,49]. Adrenalectomy for metastatic NSCLC patients is associated with low morbidity and may offer a chance for long-term disease-free survival.

d. The management of skeletal system oligometastasis of NSCLC

The metastasis of NSCLC could be detected in many bone tissues in the body. Vertebrae, ribs, and iliac wings come to the forefront in which metastasis detected in the first order [50]. In a study by Tsuya et al., the most common site of skeletal metastasis due to NSCLC was the vertebrae in 50% of patients, followed by the ribs (27.1%), ilium (10%), sacrum (7.1%), and femur (5.7%) [51]. As mentioned in the "general considerations" section, excision of the bone metastasis in oligometastatic NSCLC cases have limited contribution to survival rates. The resection of bone metastasis was generally not associated with long-term survival, even when the bone metastasis was on the rib [14,15]. Additionally, the prognosis was worse in patients with metastasis to the appendicular bone than in patients with metastasis only on an axial bone [52]. In a study by Plönes et al., the worst median overall survive was detected in patients with bone metastasis and the multivariate analysis revealed bone metastasis was the only significant parameter influencing median overall survival (p □ 0.001) [15]. In the series of Yano et al., three of the four cases with diagnosed bone metastasis and metastasectomy was performed did not survive, the patients were deceased in the 8th, 32nd, and 58th months, and the survivor case was in the 95th month without disease [53]. However, there are several studies reporting satisfactory survival rates after metastasectomy of bone oligometastasis [54-56]. In a study by Murakami et al., six cases had total en-block spondylectomy due to spinal canal and vertebral metastasis, and four cases were still alive for more than three years [54]. In another report by Hirano et al., two NSCLC cases had bone oligometastasis in the fibula and femur, surgical excision was performed both for the primary tumor site and bone metastasis, and the patients were still alive for more than five years [55]. In another case series by Zhao et al., five patients underwent synchronous lung cancer resections and solitary bone metastasectomies, the progression-free survive of the patients was 13.2 ± 7.7 months [57]. Zhao et al. concluded lung tumor resection with bone metastasectomy is a safe method in selected cases [57].

Aside from the bony counterpart of the skeletal system, NSCLC metastasis may be diagnosed in the muscles [58-61]. In the literature, these patients were mostly reported as case reports, and some reports declared long-term survive rates after metastasectomy from muscles. In a case report by Santini et al., a solitary muscle metastasis after resection of lung cancer was presented, and 24 months after surgical excision and chemotherapy, the patient was alive without disease [61]. Hence, the authors concluded more aggressive treatment modalities might be considered for selected patients with solitary muscle metastasis [61].

e. The management of extra-cranial, extra-adrenal, and extra-skeletal system oligometastasis of NSCLC

Aside from the brain, adrenal glands, muscle and bone tissues, NSCLC may cause metastasis in any organs or tissues in the body. The detected metastatic organs and tissues of NSCLC were reported as abdominal organs such as spleen, stomach, small intestine, colon, rectum, pancreas, omentum; and retroperitoneal organs such as kidneys and ureters; the breast, thyroid gland, internal ear, spinal channel, and skin [56,62-75]. In a case report, Tomita et al. presented two cases of isolated renal metastasis for NSCLC [62]. Both cases had anatomical pulmonary resection for primary lung tumor [62]. Subsequently, case one had a mass in the right kidney, was diagnosed as metastasis of NSCLC, and underwent right nephrectomy. Six months after nephrectomy, the patient reported as doing well without sign of recurrence [62]. A hypodense mass was detected in the right kidney in the second case, and this case also underwent a radical nephrectomy. One year after surgery, this patient was also disease-free without recurrence [62]. In oligometastatic NSCLC, there were some other reports in which better survival rates than previously mentioned cases were reported for kidney oligometastasis. In a report by Adamy et al., five patients underwent nephrectomy due to lung carcinoma metastasis [63]. One of the patients was deceased at 19 months after metastasectomy, and the other four patients had survival rates between 5-39 months [63].

There are several studies reporting successful survival rates for metastasis in other abdominal organs aside from the kidneys [70,76]. In a study by Fujiwara et al., nine patients with gastrointestinal metastasis due to NSCLC underwent surgical excision. After pulmonary resections of the patients, gastrointestinal metastasis was observed in the small intestine (n = 4), colon/rectum (n = 4), and stomach (n = 1) [76]. Gastrointestinal surgery was performed in five patients; the median survival after the diagnosis of gastrointestinal recurrence was 10.8 months [76]. Three patients who underwent surgery for gastrointestinal metastasis survived for more than 2 years without recurrence [76]. However, there are also some other studies reporting limited survival rates with the surgical management for solitary abdominal metastasis after anatomic resection and/or chemotherapy for NSCLC treatment. Matsuda et al. described three NSCLC cases, first one received anatomical pulmonary resection for treatment of NSCLC, and four months later she was diagnosed to have a metastasis around the stomach [70]. She underwent a laparotomy with surgical excision of the metastatic site. However, she succumbed to recurrent disease eight months after the resection for metastasis [70]. The other two cases received chemotherapy and radiotherapy for NSCLC; and several months later, both were diagnosed with omental metastasis, and surgical excision of metastasis was performed to both cases [70]. Subsequently, both cases received chemotherapy and were reported without recurrence eighth and 20th months after surgical excision for metastasis [70]. The pancreatic metastasis of NSCLC was also reported in the literature, and it was discussed in some case reports that metastasectomy could contribute to survival. In a case report by Wilson et al., surgical resection of pancreas for NSCLC metastasis improves survival of patient [68].

Aside from the abdominal organs, the other organ metastases treated surgically are uncommon and reported as case reports. In these case reports, the management strategy of the primary lung tumor and metastatic site show differences. For this reason, there is no consensus on the management protocols of these cases. As case reports and series are presented, the missing points in this field will be covered, and management protocols will be clarified in the treatment of oligometastasis of several organs in NSCLC cases.

As a conclusion, patients with M1b-c Stage IV metastatic NSCLC are generally believed to have an incurable disease. However, some M1b-c Stage IV NSCLC patients who have extrapulmonary oligometastatic disease are able to achieve longer survival by receiving curative intent pulmonary resection with mediastinal lymph node dissection and surgical treatment of distal metastasis. In many of the series, it is observed that different treatment modalities applied for the treatment of oligometastatic NSCLC cases. For example, some authors chose the management strategy of firstly neoadjuvant treatment is applied, then lung surgery is performed, and subsequently metastasis surgery may be applied. However, some other authors designed the treatment protocol as firstly performing metastasis surgery and later lung surgery. In addition, in many of the series, chemotherapy, radiotherapy, and radio-surgery might be applied as the treatment for metastasis in addition to surgical procedures, and all of the cases evaluated in the same series. A consensus has not been made on oligometastatic NSCLC patients in the literature due to reasons such as the scarcity of the cases, the differences in the patient selection criteria between the studies, and non-homogeneity of the study groups. It is documented that the survival advantage of metastasectomy surgery in the brain and adrenal gland oligometastasis is better than that in the metastasis in other organs. Additionally, the importance of selection of patients, and the essentiality of performing metastasectomy surgery to the selected patient groups are important points which emphasized in almost all of the studies. Among the criteria that must be considered in selecting patients, the most important ones are the good performance status of patients, the primary tumor being controlled or controllable, metastatic lesion that may be resected, and long survival expectations. In the treatment of oligometastatic NSCLC patients, multidisciplinary approach and coordination between teams are of great importance, and there must be a consensus in selecting proper patients that might benefit from surgical treatment.

In extrapulmonary oligometastatic NSCLC patients, aggressive surgical treatment of the metastatic lesion and primary tumor allows acceptable long-term survival advantages in selected patient groups when a successful local control is ensured.

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