Lung Cancer Resection after Immunochemotherapy Versus Chemotherapy in Oligometastatic Nonsmall Cell Lung Cancer

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Abstract

Background Neoadjuvant immunochemotherapy is currently being tested in pivotal trials for stage I to III nonsmall cell lung cancer (NSCLC). The impact of immunochemotherapy in patients with oligometastatic disease (OMD) remains undefined. This study aimed to compare the outcomes of radical treatment after the neoadjuvant course of immunochemotherapy versus chemotherapy.

Methods We retrospectively analyzed patients with OMD who were treated with immunochemotherapy or chemotherapy combined with local ablation of metastases and radical primary tumor resection between 2017 and 2021. Group A included eight patients with immunochemotherapy; Group B included seven patients with chemotherapy. Descriptive statistical analysis included the characteristics of the patients, tumors, and outcomes.

Results There was no difference in postoperative morbidity rates between the groups ($p = 0.626$). The 30-day mortality in both groups was 0%. The median overall survival for Group A was not reached, with a median follow-up time of 25 (range: 13–35) months; the median overall survival for Group B was 26 (range: 5–53) months. In Group A, all patients remained alive; in contrast, in Group B, four patients died ($p = 0.026$). There was no local thoracic recurrence in either group. In Group B, the recurrent disease was identified significantly more often (12.5 vs. 85.75%; $p = 0.009$). The rates of complete and major pathologic response were 37.5 and 0% in Group A and 42.85 and 14.25% in Group B, respectively.

Keywords
- nonsmall cell lung cancer
- immunotherapy
- immuno-chemotherapy
- neoadjuvant therapy
- oligometastatic disease

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Conclusion Despite the small patient number and short-term results, the progression-free and overall survival in patients with OMD after local therapy for metastases and primary tumor resection following a neoadjuvant course of immunochemotherapy might be promising compared with chemotherapy.

Introduction

Currently, immunotherapy (IO) is established for use in the treatment of locally advanced nonsmall cell lung cancer (NSCLC)[1,2] and is increasingly becoming the focus of attention in the treatment of resectable NSCLC in stages I to III.[3,4]

Several studies with mostly small patient numbers have shown the feasibility of lung resection after inductive IO with tolerable morbidity rates. In most of these studies, the neoadjuvant course included two cycles of IO and was less frequently performed as immunochemotherapy (IO+ chemotherapy [CTx]).[5–9] Currently, the results of several prospective randomized trials analyzing the impact of neoadjuvant IO + CTx versus CTx in patients with resectable NSCLC are pending.[10–12]

However, the impact of neoadjuvant IO + CTx in patients with oligometastatic disease (OMD) remains undefined. This retrospective analysis aimed to compare the perioperative and oncological outcomes after a neoadjuvant course of IO + CTx versus CTx followed by local treatment for primary tumors and metastases in patients with OMD.

Patients and Methods

The Institutional Review Board approved this study, which was conducted according to the revised Declaration of Helsinki and the requirements of good clinical practice.

We retrospectively analyzed our patients treated with IO + CTx and/or CTx followed by curative-intent local treatment of all metastases and radical resection of the primary tumor between January 2017 and September 2021. According to the current definition of OMD, only patients with five or less than five synchronous metastases in a single organ were included.[13]

The standard oncological staging included regular computed tomography of the thorax, magnetic resonance imaging of the brain, and F18-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT). If PET-CT was not performed in a patient, computed tomography of the abdomen and bone scintigraphy were instead performed. Furthermore, all patients received lung and cardiac function tests, including body plethysmography, arterial blood gases, electrocardiography, echocardiography, and ergometry.

All patients were discussed in an interdisciplinary tumor conference with the participation of thoracic surgeons, oncologists, and radiotherapists to define the optimal treatment modality and to review the radiological and clinical tumor response before ablative procedures for the primary tumor and metastasis. All operations had been performed in one center. It was not always the same surgeon, but the surgery was conducted by the same team and under the same standards and conditions.

To compare the neoadjuvant treatments, we defined two groups: Group A included patients treated with IO + CTx and Group B included patients treated with CTx. The patients received two to four cycles of neoadjuvant platin-based CTx with or without additional IO. All patients underwent standard surgical treatment, including anatomic lung resection and systematic lymph node dissection in compartments, 4 to 6 weeks after systemic therapy.

Postoperative morbidity was classified according to minor and major morbidity using the Thoracic Morbidity and Mortality Classification System of Ottawa Hospital.[14] The Charlson Comorbidity Index (CCI) was retrospectively calculated from our hospital records to categorize the preoperative condition of the patients. Because a solid tumor with metastases already accounted for six points in the CCI score, we divided the patients into those with six points on the CCI and those with more than six points.

According to the findings in the pathophysiological analysis, the presence of complete and major pathologic response (MPR) were noted. A complete pathologic response (CPR) was defined as resected tumors without viable cancer cells, and a MPR was defined as $\leq$10% viable cancer cells in the tumor specimen.[15]

Overall survival was defined as the time from first treatment to the date of death or last follow-up. Recurrence-free survival was defined as the time from the first treatment to the date of first progression or recurrence. Progression and recurrence after complete treatment were diagnosed by histological confirmation or radiological criteria. The follow-up data were retrieved from the clinical data and correspondence with the attending physicians and oncologists. Follow-up was performed by thoracic and abdominal imaging quarterly for the first 2 years and later at longer intervals. Depending on the location of the metastases, additional organ-specific imaging was performed for follow-up.

Descriptive statistical analyses, cross tables and the chi-square test were used to analyze the characteristics of the patients, the tumors, and short-term and long-term outcomes. Values of p less than 0.05 were regarded as significant. All analyses were performed using SPSS 22.0 software (SPSS, Inc., Chicago, IL, United States).

Results

Patient Characteristics

In total, 15 patients fulfilled the study criteria and were included in the study: eight patients in Group A and seven

Table 1 Patients and tumor characteristics

		IOCTx *n* (%)	CTx *n* (%)	*p*-Value
Gender	Female	3 (37)	4 (57)	0.405
	Male	5 (63)	3 (43)	
Age		57 years (range: 51–73)	62 years (range: 44–72)	
ECOG	0	8 (100)	6 (86)	0.467
	1	0 (0)	1(14)	
Charlson Comorbidity Index	6	6 (75)	5 (71)	0.662
	> 6	2 (25)	2 (29)	
ASA score	2	0 (0)	3 (43)	0.077
	3	8 (100)	4 (57)	
Preoperative FEV1		70% (range:59–79)	73% (range:68–87)	
Former smoking status	Yes	6 (75)	6 (86)	0.554
	No	2 (25)	1 (14)	
Number of metastases	1 >1	6 (75) 2 (25)	4 (57) 3 (43)	0.427
Localization of metastases	Brain	3 (37)	4 (57)	0.555
	Lung	2 (25)	2 (29)	
	Bone	2 (25)	0 (0)	
	Extrathoracic lymph node	1 (13)	1 (14)	
Histology	Adeno	7 (88)	4 (57)	0.351
	Squamous	1 (12)	2 (29)	
	Other	0 (0)	1 (14)	
PD-L1 score	0	3 (37)	–	
	1–49	5 (63)	–	
	≥ 50	0 (0)	–	

Abbreviations: CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; IO, immunotherapy; PD-L1, programmed death-ligand 1.

patients in Group B. There were no patients in the study period with OMD and neoadjuvant treatment who could not be operated on. The median patient age of the whole cohort was 58 years (range, 44–73 years), with a median age in Group A of 57 years (range, 51–73 years) and in Group B of 62 years (range, 44–72 years). Sex distribution was not significantly different between the two groups ($p = 0.405$). Regarding the preoperative constitution of the patients, there was no significant difference in the preoperative CCI ($p = 0.662$), American Society of Anesthesiology score ($p = 0.077$), Eastern Cooperative Oncology Group status (0.467), or former smoking status (0.554). The median preoperative forced expiratory volume in 1 second was 70% (range, 59–79%) in Group A and 73% (range, 68–87%) in Group B (►**Table 1**). Besides one patient in Group B, all patients underwent PET-CT before surgery.

Tumor and Treatment Characteristics

The predominant tumor histology in both groups was adenocarcinoma (Group A: 87.5%; Group B: 57.15%). The histology and mutation status of the primary tumor are listed in ►**Table 2**. The synchronous metastases in Group A were localized in the brain in three patients, in the bones in two patients, in the lung in two patients, and in an extrathoracic lymph node in one patient. Additionally, in Group B, the most common metastasis localization was the brain in four patients, followed by the lung in two patients and an extrathoracic lymph node in one patient. There was no significant difference in the groups between single metastasis and multiple synchronous metastases ($p = 0.427$; ►**Table 1**). Besides one patient in Group A who declined the third cycle of systemic therapy, all patients in the study had three to four cycles of systemic therapy. The exact systemic treatments and ablative therapy of the metastases are listed in ►**Table 3**.

The resection of the primary tumor was performed in Group A (six lobectomies, one sleeve lobectomy, and one segmentectomy) and in Group B (six lobectomies and one bilobectomy) (►**Table 3**). In both groups, a median of 32 lymph nodes (range, 12–60) was removed per patient and according to the criteria of systematic lymph node dissection.

Short- and Long-Term Outcomes

All patients in Group A had an R0-resection; in Group B, six patients had an R0-resection, and one patient had an R1-

Table 2 Histology and mutation status of the primary tumor

	Histology	EGFR	ALK	Ros-1	RAS	B-RAF	Other	PD-L1 (TPS)
1	Adenocarcinoma	WT	Negative	Negative	Exon-2 G12C Mutation	WT	Negative	1
2	Adenocarcinoma	WT	Negative	Negative	u	WT	u	0
3	Adenocarcinoma	WT	Negative	Negative	WT	WT	PIK3CA/ TP53	5
4	Adenocarcinoma	WT	Negative	Negative	Exon-2 c35.G Mutation	WT	Negative	0
5	Adenocarcinoma	WT	Negative	Negative	u	Negative	u	0
6	Adenocarcinoma	WT	Negative	Negative	WT	u	u	40
7	Adenocarcinoma	WT	Negative	Negative	Exon-2 G12C Mutation	u	Negative	2
8	Squamous cell cancer	u	u	u	u	u	u	10
9	Squamous cell cancer	WT	u	u	u	u	u	–
10	Adenocarcinoma	u	u	u	Exon-2 G12C Mutation	WT	Negative	–
11	Large cell neuroendocrine	WT	Negative	Negative	WT	WT	Negative	–
12	Squamous cell cancer	WT	u	u	u	u	u	–
13	Adenocarcinoma	del15	Negative	Negative	WT	WT	Negative	–
14	Adenocarcinoma	WT	Negative	Negative	u	WT	KEAP1 / TP53	–
15	Adenocarcinoma	WT	Negative	Negative	WT	WT	PIK3CA/ TP53	–

Abbreviations: ALK, anaplastic lymphoma kinase; B-Raf, B-RAF Proto-oncogene; iEGFR, Epidermal Growth Factor Receptor; RAS, Rat Sarcoma Virus; ROS-1, receptor tyrosine kinase-1; TPS, Tumor proportion score; u, unknown; WT, wildtype.
Note: White background: Group A; gray background: Group B.

resection of a primary tumor in the left lower lobe associated with tumor invasion of the descending aorta. An adjuvant postoperative radiotherapy with 60 Gy was performed on this patient. Regarding the pathologic response rates, 37.5% of the patients treated with IO + CTx (Group A) had a CPR and none had an MPR; the CPR and MPR rates in Group B were 42.85 and 14.25%, respectively (►**Table 4**).

There was no difference in postoperative morbidity ($p = 0.626$) or 30-day mortality (0%) between Groups A and B. The postoperative minor and major morbidity rates were 12.5 and 25% in Group A and 28.58 and 0% in Group B, respectively (►**Tables 3** and **4**). The median overall survival for Group A was not reached, but the median follow-up time was 25 months (range, 13–35); in Group B, the median overall survival was 26 months (range, 5–53). All patients in Group A were still alive; in contrast, four patients in Group B died ($p = 0.026$; ►**Table 4**).

Group B patients suffered significantly more often from recurrent disease ($p = 0.009$). There was no local thoracic recurrence in either group. Only one patient in Group A suffered from a local recurrence of brain metastasis and an additional distant metastasis (12.5%). In Group B, six patients suffered from recurrence (85.75%). In total, four local recurrences at the initial metastatic side and two distant metastases occurred. The median progression-free survival in Group A was not reached, while in Group B, it was 8 months (range, 3–12; ►**Table 4**).

Discussion

Currently, there are several studies comparing IO + CTx with CTx as a neoadjuvant therapeutic concept in operable NSCLC stage IB-IIIA.[10–12,16] The impact of neoadjuvant IO + CTx and ablation therapy for primary tumors and metastases in patients with OMD is currently undefined. However, the overall survival in these patients after ablative therapies is still heterogeneous,[17] and particularly, synchronous OMD compared with metachronous OMD seems to be a negative prognosticator for survival.[18] Nevertheless, a meta-analysis of patients with synchronous OMD showed improved survival after radical treatment, including local therapy for primary tumors as well as for metastases, compared with patients without additional local therapy.[19] Recently, published retrospective multicenter analyses including surgery have also demonstrated promising survival rates.[20,21]

The randomized KEYNOTE-407 study comparing placebo plus CTx and pembrolizumab plus CTx in patients with metastatic squamous NSCLC showed a significant improvement in overall survival in the pembrolizumab group, with a median overall and median progression-free survival of 17.1 and 8 months, respectively.[22] It remains unclear whether these positive effects are transferable to the OMD setting, but they might be showing the therapeutic impact of IO in the management of metastatic NSCLC.

However, in patients with OMD, synchronous metastases seem to be a negative prognosticator compared with metachronous metastases,[18] but curative-intent treatment, including local ablation of metastases and radical surgery of the primary tumor, improves overall and progression-free survival.[19,23]

By definition, patients with metastatic tumors already have an elevated CCI and, thus, an increased risk of postoperative morbidity and mortality after NSCLC resection.[24]

Table 3 Patient and outcome overview

	Age (years)	Localization of the primary cancer	Localization of the metastases	Neoadjuvant therapy (number of cycles)	Type of resection	Morbidity	Progression free survival (months)	Survival (months)
1	53	Right upper lobe	Brain	Cisplatin/Pemetrexed/Pembrolizumab (4)	Lobectomy	–	9	28
2	51	Left upper lobe	Bone	Carboplatin/Pemetrexed/Pembrolizumab (3)	Extrapleural Lobectomy	–	–	25
3	56	Right lower lobe	Brain	Cisplatin/Pemetrexed/Pembrolizumab (4)	Lobectomy	Major	–	25
4	51	Right lower lobe	Bone	Cisplatin/Pemetrexed Pembrolizumab (2)	Sleeve Lobectomy	Minor	–	22
5	59	Right upper lobe	ELN	Carboplatin/Pemetrexed/Pembrolizumab (3)	Lobectomy	Minor	–	13
6	71	Left upper lobe	Lung	Cisplatin/Pemetrexed/Pembrolizumab (4)	Segmentectomy	–	–	35
7	58	Left lower lobe	Brain	Cisplatin/Pemetrexed/Pembrolizumab (4)	Lobectomy	–	–	34
8	73	Right upper lobe	Lung	Carboplatin/Paclitaxel/Pembrolizumab (4)	Lobectomy	–	–	12
9	72	Left lower lobe	Lung	Carboplatin/Paclitaxel (3)	Lobectomy + angioplasty	Minor	12	29 ([a])
10	48	Right upper lobe	Brain	Cisplatin/Vinorelbine (3)	Lobectomy	–	10	53 ([a])
11	63	Left upper lobe	ELN	Cisplatin/Etoposid (4)	Lobectomy	Minor	12	12 ([a])
12	66	Right lower lobe	Lung	Cisplatin/Gemcitabine (3)	Bilobectomy	–	5	17 ([a])
13	44	Left upper Lobe	Brain	Cisplatin/Pemetrexed (4)	Lobectomy + angioplasty	–	7	26
14	58	Left upper lobe	Brain	Carboplatin/Pemetrexed (4)	Lobectomy	–	3	29
15	62	Right upper lobe	Brain	Cisplatin Vinorelbine (3)	Lobectomy + Chest wall	–	–	5

Abbreviations: CR, complete remission; Cy, cyber knife; ELN, extrathoracic lymph node; R, resection; Ra, radiation therapy.
Note: White background: Group A; gray background: Group B.
[a]Dead.

Table 4 Short- and long-term outcomes

		IOCTx n (%)	CTx n (%)	*p*-Value
Pathologic response	Complete	3 (37)	3 (43)	0.405
	Major	0 (0)	1 (14)	
	No	5 (63)	3 (43)	
Morbidity	No	5 (63)	5 (71)	0.626
	Minor	2 (25)	2 (29)	
	Major	1 (12)	0 (0)	
30-dmortality	No	8 (100)	7 (100)	1.000
	Yes	0 (0)	0 (0)	
Recurrence	No	7 (88)	1 (14)	0.009
	Yes	1 (12)	6 (86)	
Median progression free survival (months)		NR	8 (3–12)	
Still alive	Yes	8 (100)	3 (43)	0.026
	No	0 (0)	4 (57)	
Median overall survival (months)		NR	26 (5–53)	

Abbreviation: NR, not reached.

Nevertheless, in our study, even in these patients, no increased morbidity after neoadjuvant IO + CTx compared with neoadjuvant CTx was identified. The recently published morbidity rates after neoadjuvant IO + CTx or IO followed by NSCLC resection were between 39 and 50%.[7,8] Additionally, the morbidity rate of 37.5% and the mortality rate of 0% of the IO + CTx group in our study are comparable to rates after neoadjuvant IO in other tumor stages or even in patients with advanced-staged NSCLC without neoadjuvant treatment.[16]

Additionally, a newly retrospective multicenter analysis including surgery showed a median overall survival of up to 40 months and 5-year survival rates of 36%.[20,21] In our study, the median overall survival in Group A was not reached, at a median follow-up time of 25 months (range, 13–35 months); in Group B, the median overall survival was 26 months (range, 5–53 months). All patients in Group A were still alive; in contrast, four patients in Group B had died.

Bott et al described an "increased occurrence of inflammation and/or dense adhesions in either the fissure or surrounding hilar and mediastinal nodal stations" after neoadjuvant IO for locally advanced stages of NSCLC, which potentially led to an increased conversion rate of thoracoscopy to thoracotomy.[8] These results show that particularly in patients with neoadjuvant therapy, including IO, the intraoperative accessibility of the central anatomical structures, such as veins, arteries, and bronchus, and of lymph nodes is limited by extensive fibrotic changes (►**Figs. 1** and **2**). Furthermore, inflammation and fibrosis of lymphatic tissues are well known as potential reasons for skipping lymph node metastases. In addition, the frozen section examination by the pathologist might be complicated, and therefore, tumor cells could be overseen. As a consequence, extensive fibrosis potentially leads to tumor understaging. In summary, all of these aspects underline the importance of systematic lymph node dissection in compartments for achieving exact pN staging[25] and for reducing the risk of local recurrence. The avoidance of local and distant recurrence is, in our opinion, two cornerstones for good long-term outcomes after radical surgery. The anatomical lung resections in our study were in all patients performed combined with a systematic lymph node dissection, with attention given to an en bloc dissection of the lymph nodes with the surrounding fat tissue. This approach is in our opinion essential to prevent local recurrence and to achieve proper lymph node analysis. On average, 32 lymph nodes were removed per patient in our study. Consequently, during the short-term follow-up, no patient experienced local

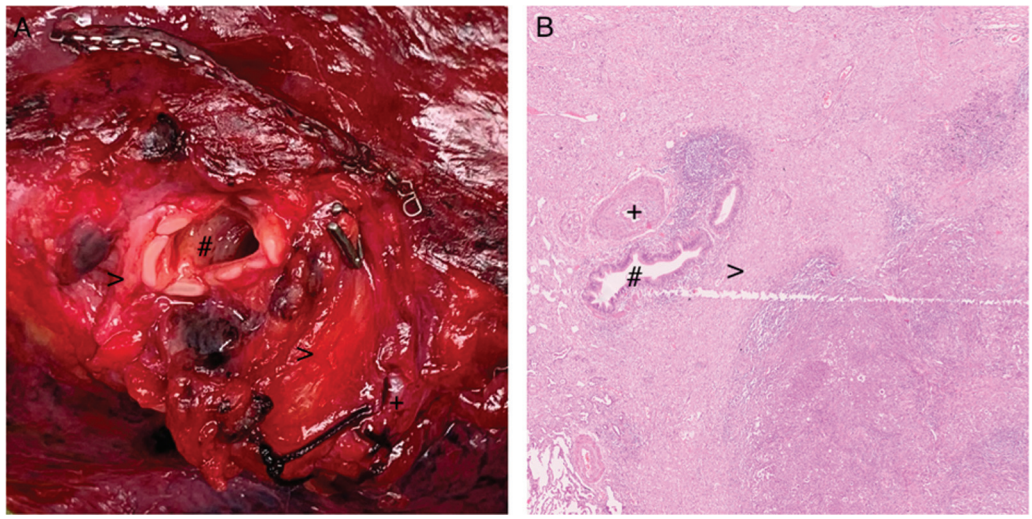

Fig. 1 (**A**) Resected lung hilum showing the bronchus (#) and the vein (+) surrounded by fibrotic and reactive tissue (>) after IO + CTx. (**B**) Microscopic image of a bronchus (#) and a vessel (+) surrounded by fibrotic and reactive tissue (>) after IO + CTx.

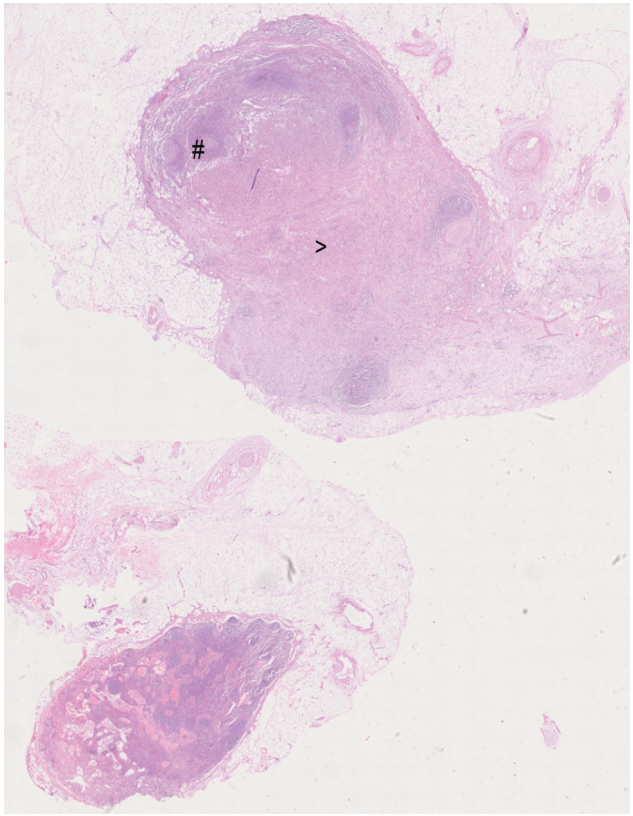

Fig. 2 Microscopic image of a dissected necrotic lymph node with residual lymphoid tissue (#) and fibrotic tissue (>) after IO + CTx.

recurrence. In addition, patients in Group A suffered less often from recurrent metastases (12.5 versus 85.75%; $p = 0.009$). The most frequent recurrences of the whole study population appeared at the locally treated distant metastases.

According to the literature, a systematic review including 49 studies of patients with OMD treated with locally ablative therapies showed a median progression-free survival of 12 months.[17] These results were recently confirmed by two multicenter studies including patients with synchronous OMD treated with radical surgery with a median progression-free survival of up to 11 months.[20,21] Bauml et al found a promising progression-free survival of 19.1 months after treatment with pembrolizumab followed by local ablation.[26] To date, only one patient in Group A suffered from recurrent disease at a median follow-up time of 25 months.

Regarding the CPR and MPR following IO, our results were comparable to the data reported in the literature. The study of Román et al. showed an MPR rate of 19.5% and a CPR rate of 63.4% after neoadjuvant IO + CTx in patients with stage IIIA NSCLC.[7] In general, MPR rates of 40.5 to 56.7% and CPR rates of 15 to 33% for neoadjuvant IO in locally advanced NSCLC have been described.[16] Furthermore, a recently published multicenter study including 13 NSCLC patients with OMD identified a CPR rate of 54% after neoadjuvant IO with or without additional CTx.[27] One reason for the slightly lower CPR rate of 37.5% in our patients might be the lower PD-L1 score (►**Table 2**). However, the lack of a 100% remission rate further supports the use of curative-intent resection of the primary tumor and the ablative procedures of metastasis and might lead to a reduced risk of thoracic recurrence.

Conclusion

As a study limitation, the retrospective data analysis of a small patient number should be noted. However, the study demonstrates the feasibility of lung cancer resection after neoadjuvant IO + CTx in patients with synchronous OMD. Although the number of included patients was small, the progression-free survival and overall survival in patients after neoadjuvant IO + CTx might be promising compared with patients after neoadjuvant CTx alone. Regardless of these promising results, further studies with larger case numbers and matched outcomes are required to define the potential superiority of IO + CTx as a neoadjuvant course in patients with synchronous OMD in the future.

Note

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Conflict of Interest

M.S. receives honoraria AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens and research grants from AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens. All other authors declare no conflict of interest.

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